METHODS FOR TREATING CONDITIONS AND DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

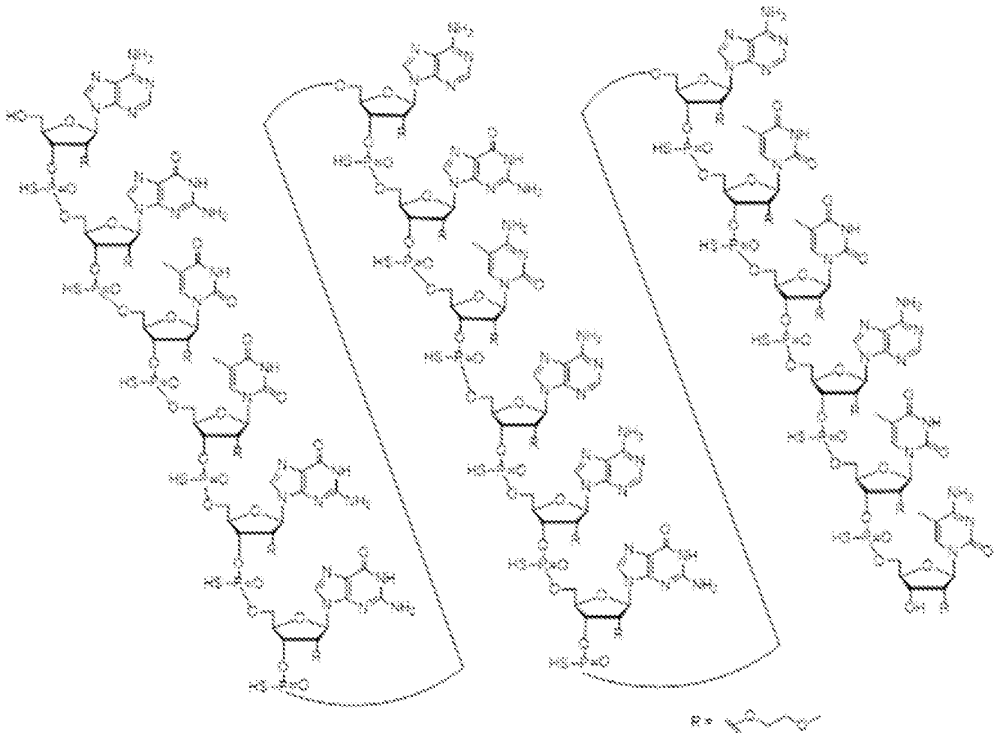
[0001] This application claims the benefit of U.S. Provisional Application No. 63/569,003, filed March 22, 2024, U.S. Provisional Application No. 63/691,797, filed September 6, 2024, U.S. Provisional Application No. 63/728,013, filed December 4, 2024, and U.S. Provisional Application No. 63/751,196, filed January 29, 2025, each of which applications is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Nervous system disorders are often associated with channelopathy, characterized by the disturbed function of ion channels that mediate neuronal excitability, neuronal interactions, and brain functions at large. Mutations in the *SCN1A* gene, which is part of the *SCN1A-SCN2A-SCN3A* gene cluster that encodes alpha-pore forming subunits of the neuronal voltage gated sodium channel, can result in expression of $Na_V1.1$ protein (also termed as "$Na_V1.1$") with reduced functions as compared to a wild-type $Na_V1.1$ protein, reduced expression of $Na_V1.1$, or both. Mutations in *SCN1A* gene are associated with development of a number of diseases and conditions, such as Dravet Syndrome (DS) (Miller, *et al.*, 1993-2015, GeneReviews, Eds. Pagon RA, *et al.* Seattle (WA): University of Washington, Seattle, Bookshelf ID: NBK1318, and Mulley, *et al.*, 2005, Hum. Mutat. 25: 535-542).

SUMMARY

[0003] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

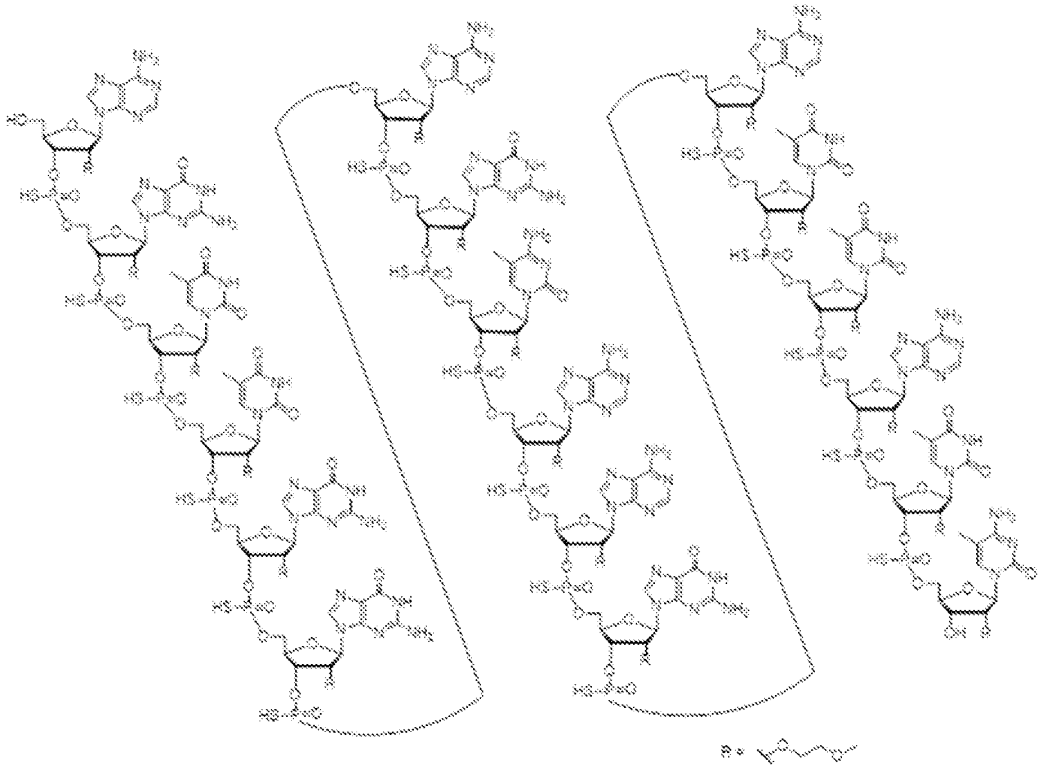
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and a first maintenance dose following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the first maintenance dose independently contains the compound at an amount of from about 25 to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and the first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose.

[0004] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

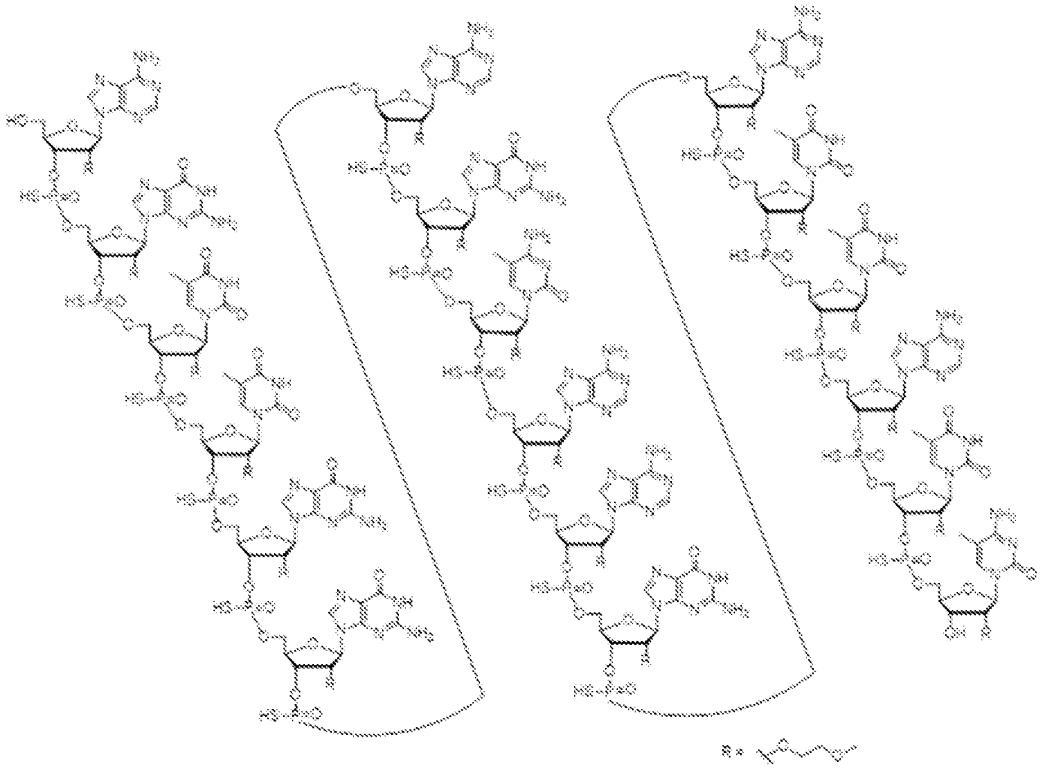


(I), or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and a first maintenance dose following the third loading dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the first maintenance dose independently contains the compound at an amount of from about 25 to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose,

and the first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose.

[0005] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



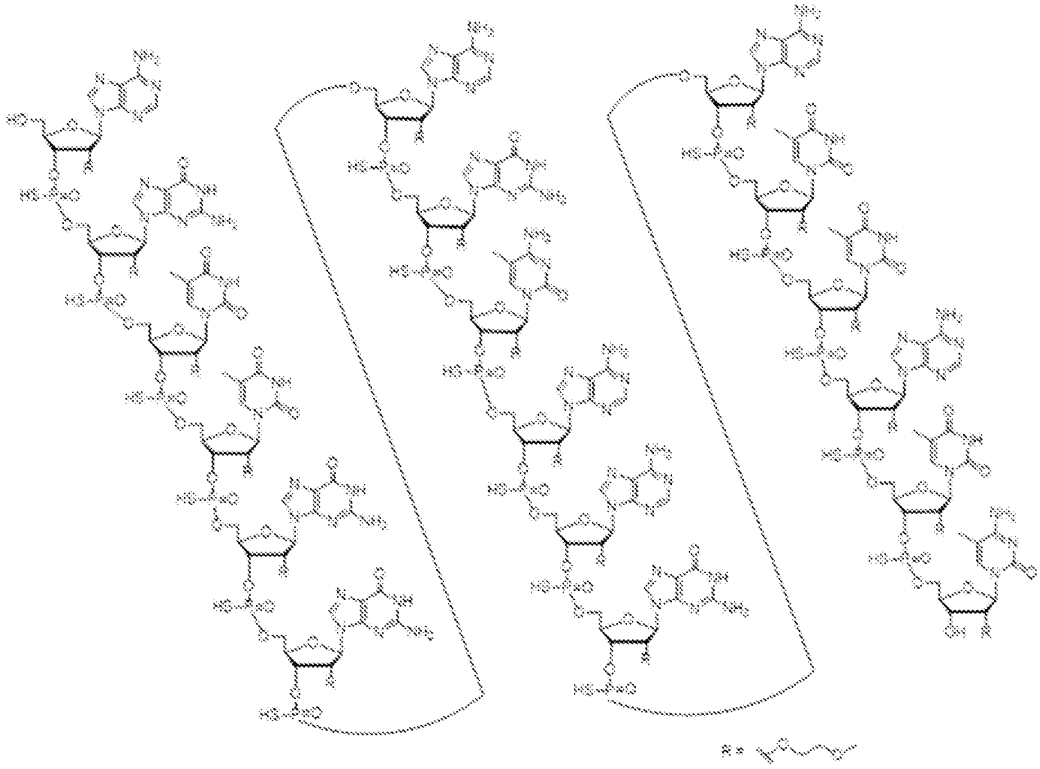
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day (±7 days) of treatment, (b) 4 months (±7 days) after the second loading dose, or (c) 16 weeks (±7 days) after the second loading dose.

[0006] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



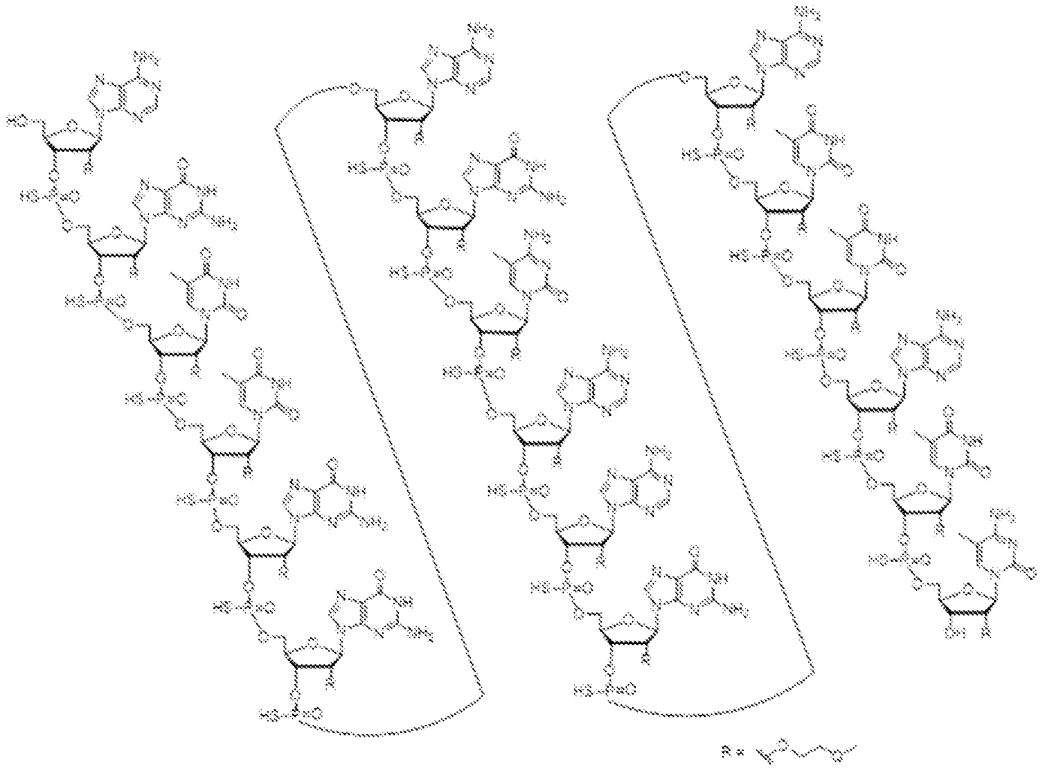
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises: administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day (±7 days) of treatment, (b) 1 month (±7 days) after the second loading dose, or (c) 4 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0007] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



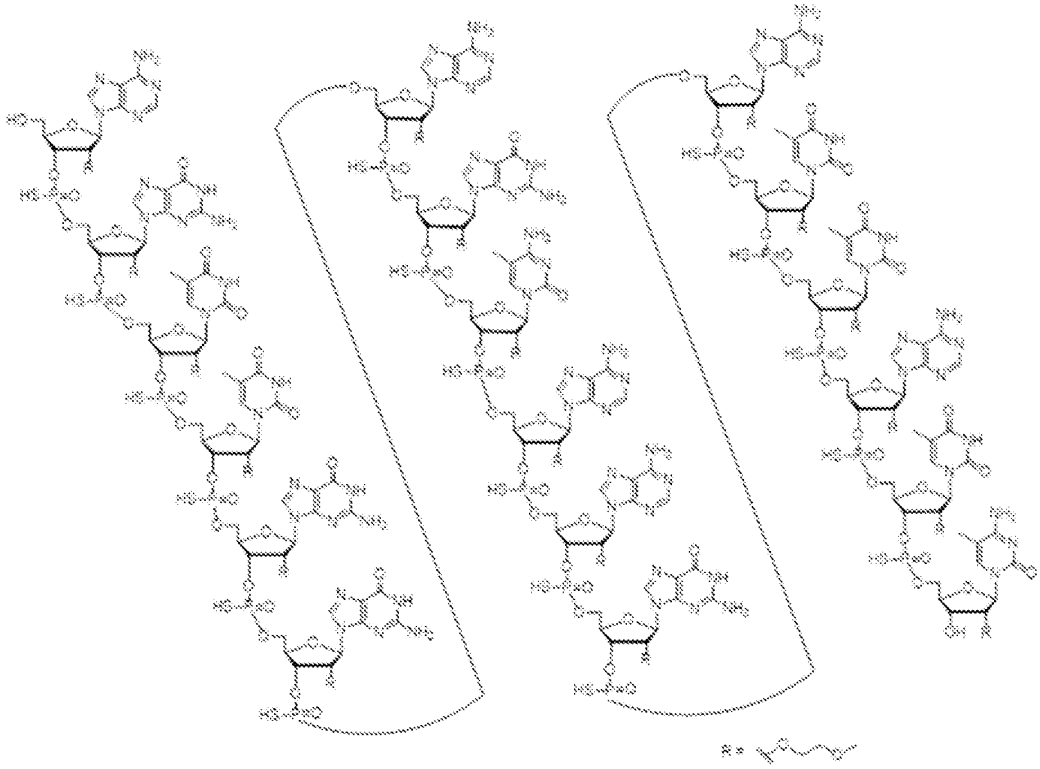
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day (±7 days) of treatment, (b) 4 months (±7 days) after the second loading dose, or (c) 16 weeks (±7 days) after the second loading dose.

[0008] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



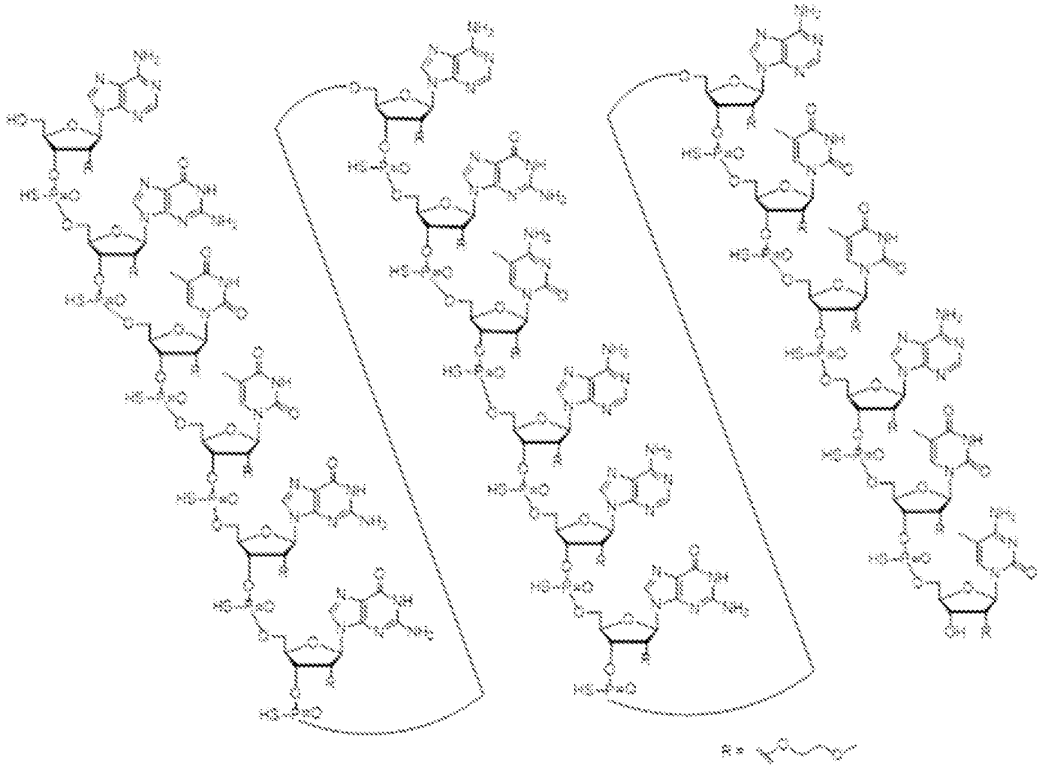
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day (±7 days) of treatment, (b) 4 months (±7 days) after the second loading dose, or (c) 16 weeks (±7 days) after the second loading dose.

[0009] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

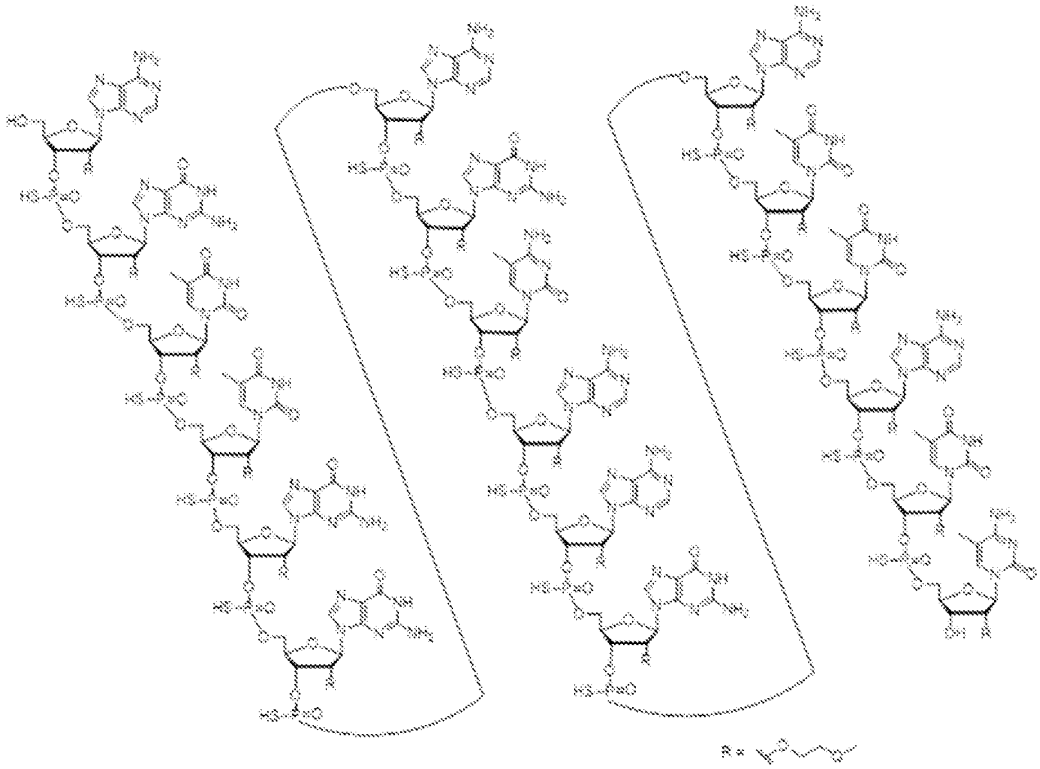
administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day (±7 days) of treatment, (b) 1 month (±7 days) after the second loading dose, or (c) 4 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0010] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

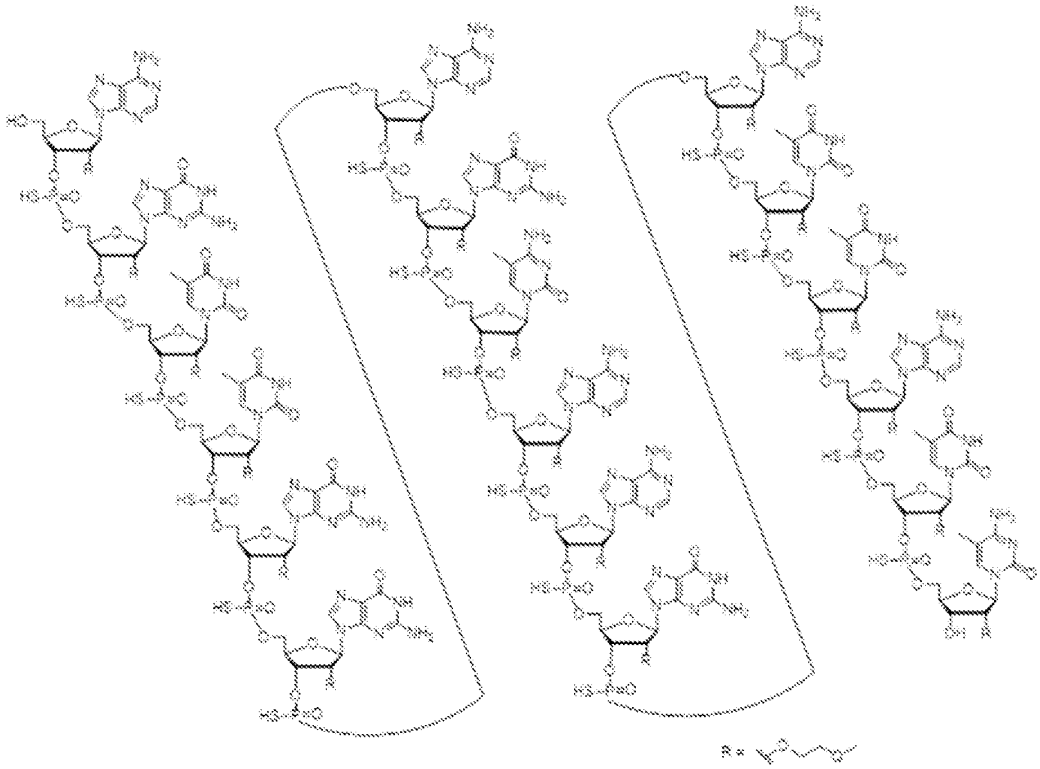
administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day (±7 days) of treatment, (b) 2 months (±7 days) after the second loading dose, or (c) 8 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0011] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

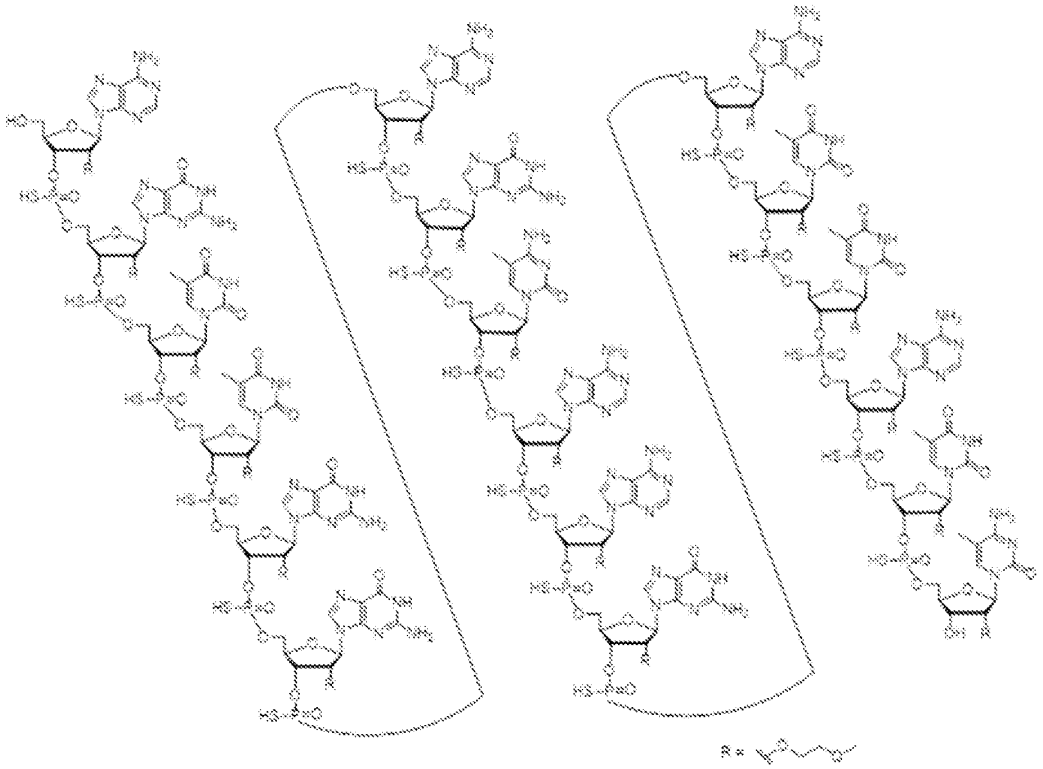
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day (±7 days) of treatment, (b) 1 month (±7 days) after the second loading dose, or (c) 4 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0012] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

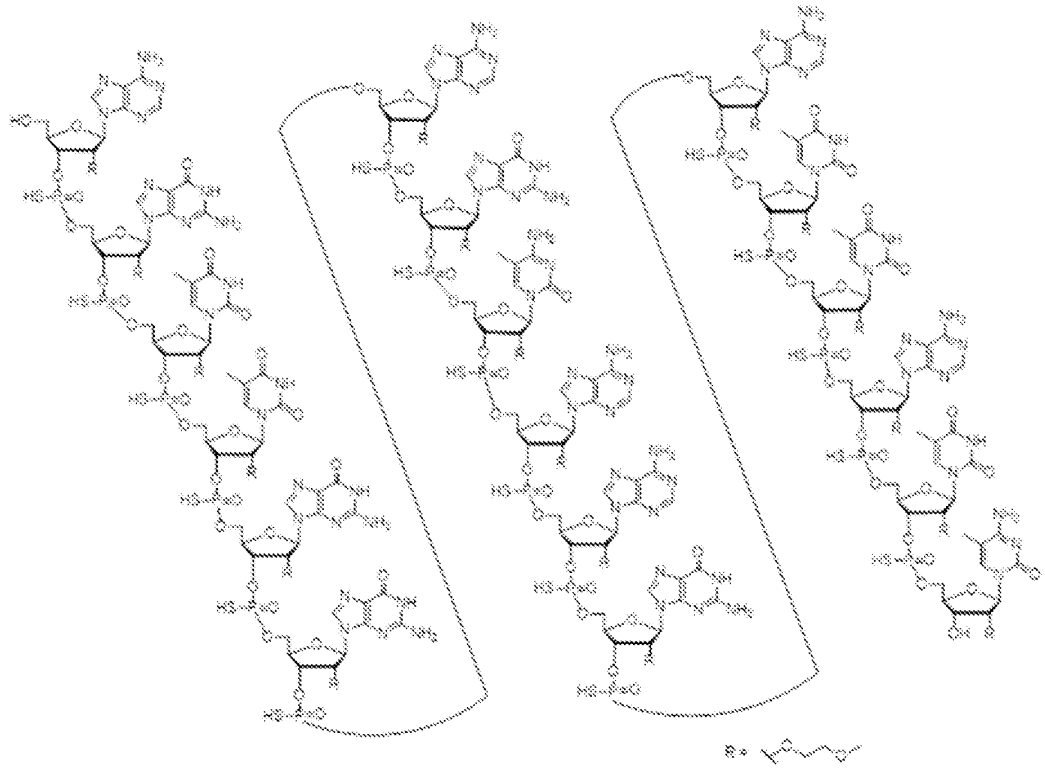
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day (±7 days) of treatment, (b) 1 month (±7 days) after the second loading dose, or (c) 4 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0013] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

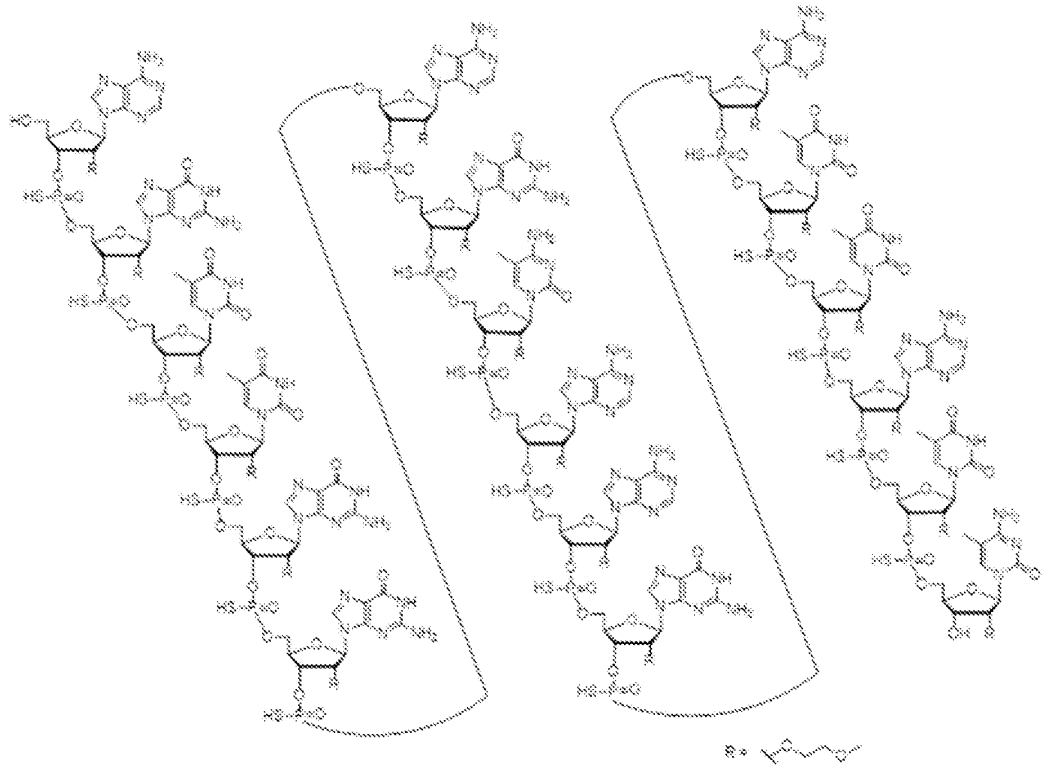
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day (±7 days) of treatment, (b) 2 months (±7 days) after the second loading dose, or (c) 8 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0014] Provided herein, in some aspects, is a dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

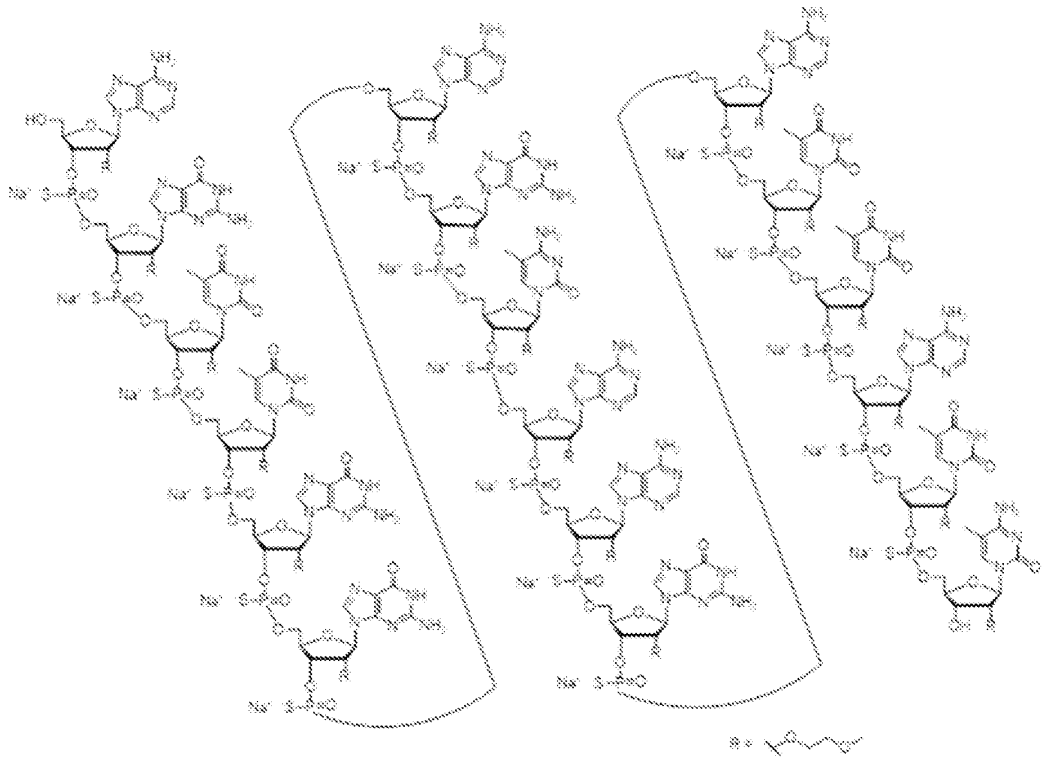
administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day (±7 days) of treatment, (b) 2 months (±7 days) after the first loading dose, or (c) 8 weeks (±7 days) after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day (±7 days) of treatment, (b) 2 months (±7 days) after the second loading dose, or (c) 8 weeks (±7 days) after the second loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day (±7 days) of treatment, (b) 4 months (±7 days) after the third loading dose, or (c) 16 weeks (±7 days) after the third loading dose.

[0015] In some embodiments, the dosing regimen further comprises administering to the human subject one or more maintenance doses after the first maintenance dose is administered. In some embodiments, each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of from about 25 to about 100 mg. In some embodiments, each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of about 45 mg. In some embodiments, each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of about 70 mg.

[0016] In some embodiments, the compound has the following structure:



(II) (the compound also referred to as "Compound-A" or "ASO-1" herein).

[0017] In some embodiments, the first loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

[0018] In some embodiments, the first loading dose contains the compound at an amount of about 30 mg. In some embodiments, the first loading dose contains the compound at an amount of about 70 mg.

[0019] In some embodiments, the first loading dose contains the compound at an amount of about 45 mg. In some embodiments, the first loading dose contains the compound at an amount of about 50 mg. In some embodiments, the first loading dose contains the compound at an amount of from 25 mg to about 35 mg. In some embodiments, the first loading dose contains the compound at an amount of from 35 to 50 mg. In some embodiments, the first loading dose contains the compound at an amount of from 45 to

70 mg. In some embodiments, the first loading dose contains the compound at an amount of from 50 to 70 mg. In some embodiments, the first loading dose contains the compound at an amount of from 60 to 80 mg. In some embodiments, the first loading dose contains the compound at an amount of from 30 to 45 mg. In some embodiments, the first loading dose contains the compound at an amount of from 25 to 40 mg. In some embodiments, the first loading dose contains the compound at an amount of from 35 to 45 mg. In some embodiments, the first loading dose contains the compound at an amount of from 40 to 55 mg.

[0020] In some embodiments, the second loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

[0021] In some embodiments, the second loading dose contains the compound at an amount of about 30 mg. In some embodiments, the second loading dose contains the compound at an amount of about 70 mg. In some embodiments, the second loading dose contains the compound at an amount of about 45 mg. In some embodiments, the second loading dose contains the compound at an amount of about 50 mg. In some embodiments, the second loading dose contains the compound at an amount of from 25 mg to about 35 mg. In some embodiments, the second loading dose contains the compound at an amount of from 35 to 50 mg. In some embodiments, the second loading dose contains the compound at an amount of from 45 to 70 mg. In some embodiments, the second loading dose contains the compound at an amount of from 50 to 70 mg. In some embodiments, the second loading dose contains the compound at an amount of from 60 to 80 mg. In some embodiments, the second loading dose contains the compound at an amount of from 30 to 45 mg. In some embodiments, the second loading dose contains the compound at an amount of from 25 to 40 mg. In some embodiments, the second loading dose contains the compound at an amount of from 35 to 45 mg. In some embodiments, the second loading dose contains the compound at an amount of from 40 to 55 mg. In some embodiments, the second loading dose contains same amount of the compound as the first loading dose.

[0022] In some embodiments, the third loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

[0023] In some embodiments, the third loading dose contains the compound at an amount of about 30 mg. In some embodiments, the third loading dose contains the compound at an amount of about 70 mg. In some embodiments, the third loading dose contains the compound at an amount of about 45 mg. In some embodiments, the third loading dose contains the compound at an amount of about 50 mg. In some embodiments, the third loading dose contains the compound at an amount of from 25 mg to about 35 mg. In some embodiments, the third loading dose contains the compound at an amount of from 35 to 50 mg.

In some embodiments, the third loading dose contains the compound at an amount of from 45 to 70 mg. In some embodiments, the third loading dose contains the compound at an amount of from 50 to 70 mg. In some embodiments, the third loading dose contains the compound at an amount of from 60 to 80 mg. In some embodiments, the third loading dose contains the compound at an amount of from 30 to 45 mg. In some embodiments, the third loading dose contains the compound at an amount of from 25 to 40 mg. In some embodiments, the third loading dose contains the compound at an amount of from 35 to 45 mg. In some embodiments, the third loading dose contains the compound at an amount of from 40 to 55 mg. In some embodiments, the third loading dose contains same amount of the compound as the first loading dose.

[0024] In some embodiments, the first maintenance dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

[0025] In some embodiments, each maintenance dose of the one or more maintenance doses independently contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

[0026] In some embodiments, each maintenance dose of the one or more maintenance doses is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

[0027] In some embodiments, each maintenance dose of the one or more maintenance doses contains same amount of the compound. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 30 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 45 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 70 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 55 to 70 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 55 to 75 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 55 to 80 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 40 to 70 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 40 to 75 mg. In some

embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 40 to 80 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 65 to 90 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 65 to 95 mg. In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from 65 to 100 mg.

[0028] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains same amount of the compound as the first loading dose or the second loading dose.

[0029] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains same amount of the compound as the first loading dose, the second loading dose, or the third loading dose.

[0030] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a higher amount of the compound than the first loading dose or the second loading dose.

[0031] In some embodiments, the first maintenance dose or each maintenance dose of the one and more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% higher than the amount in the first loading dose or the second loading dose.

[0032] In some embodiments, the first maintenance dose or each maintenance dose of the one and more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg higher than the amount in the first loading dose or the second loading dose.

[0033] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a higher amount of the compound than the first loading dose, the second loading dose, or the third loading dose.

[0034] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% higher than the amount in the first loading dose, the second loading dose, or the third loading dose.

[0035] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg higher than the amount in the first loading dose, the second loading dose, or the third loading dose.

[0036] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a lower amount of the compound than the first loading dose or the second loading dose.

[0037] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% lower than the amount in the first loading dose or the second loading dose.

[0038] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg lower than the amount in the first loading dose or the second loading dose.

[0039] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a lower amount of the compound than the first loading dose, the second loading dose, or the third loading dose.

[0040] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% lower than the amount in the first loading dose, the second loading dose, or the third loading dose.

[0041] In some embodiments, the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg lower than the amount in the first loading dose, the second loading dose, or the third loading dose.

[0042] In some embodiments, the second loading dose is administered from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5 weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks, from 6 weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the first loading dose.

[0043] In some embodiments, the second loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks after the first loading dose.

[0044] In some embodiments, the second loading dose is administered about 6 weeks after the administration of the first loading dose. In some embodiments, the second loading dose is administered about 7 weeks after the administration of the first loading dose. In some embodiments, the second loading dose is administered about 8 weeks after the administration of the first loading dose. In some embodiments, the second loading dose is administered about 9 weeks after the administration of the first loading dose. In some embodiments, the second loading dose is administered about 10 weeks after the administration of the first loading dose.

[0045] In some embodiments, the third loading dose is administered from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5 weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks,

from 6 weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the second loading dose.

[0046] In some embodiments, the third loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks after the second loading dose.

[0047] In some embodiments, the third loading dose is administered about 4 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 5 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 6 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 7 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 8 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 9 weeks after the administration of the second loading dose. In some embodiments, the third loading dose is administered about 10 weeks after the administration of the second loading dose.

[0048] In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks apart from each other. In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 6 weeks apart from each other. In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 7 weeks apart from each other. In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 8 weeks apart from each other. In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 9 weeks apart from each other. In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 10 weeks apart from each other.

[0049] In some embodiments, the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12

months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the second loading dose.

[0050] In some embodiments, the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the second loading dose.

[0051] In some embodiments, the first maintenance dose is administered about 8 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 12 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 16 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 20 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 4 months after the second loading dose. In some embodiments, the first maintenance dose is administered about 6 months after the second loading dose. In some embodiments, the first maintenance dose is administered about 9 months after the second loading dose. In some embodiments, the first maintenance dose is administered about 12 months after the second loading dose.

[0052] In some embodiments, the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the third loading dose.

[0053] In some embodiments, the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the third loading dose.

[0054] In some embodiments, the first maintenance dose is administered about 8 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 12 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 16 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 20 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 4 months after the third loading dose. In some embodiments, the first maintenance dose is administered about 6 months after the third loading dose. In some embodiments, the first maintenance dose is administered about 9 months after the third loading dose. In some embodiments, the first maintenance dose is administered about 12 months after the third loading dose. In some embodiments, the one or more maintenance doses consist of one maintenance dose.

[0055] In some embodiments, the one or more maintenance doses comprise at least two maintenance doses, and wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the dose immediately preceding the respective maintenance dose.

[0056] In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the dose immediately preceding the respective maintenance dose.

[0057] In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 8 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 12 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose

of the one or more maintenance doses other than the first maintenance dose is administered about 16 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 20 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 4 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 6 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 9 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 12 months after the dose immediately preceding the respective maintenance dose.

[0058] In some embodiments, the one or more maintenance doses consist of two maintenance doses. In some embodiments, the one or more maintenance doses consist of three maintenance doses. In some embodiments, the one or more maintenance doses consist of four maintenance doses. In some embodiments, the one or more maintenance doses consist of five, six, seven, eight, or more maintenance doses. In some embodiments, the one or more maintenance doses comprise more than three maintenance doses.

[0059] In some embodiments, the one or more maintenance doses are administered over a lifetime of the human subject. In some embodiments, the method or the dosing regimen comprises administering the one or more maintenance doses to the human subject until an indication that a most recent maintenance dose is not tolerated by the human subject. In some embodiments, the one or more maintenance doses are administered to the human subject over a period of at least one year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35, years, 40 years, 45 years, 50 years, 55 years, or 60 years.

[0060] In some embodiments, each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg.

[0061] In some embodiments, each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 70 mg.

[0062] In some embodiments, each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 70 mg.

[0063] In some embodiments, each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose

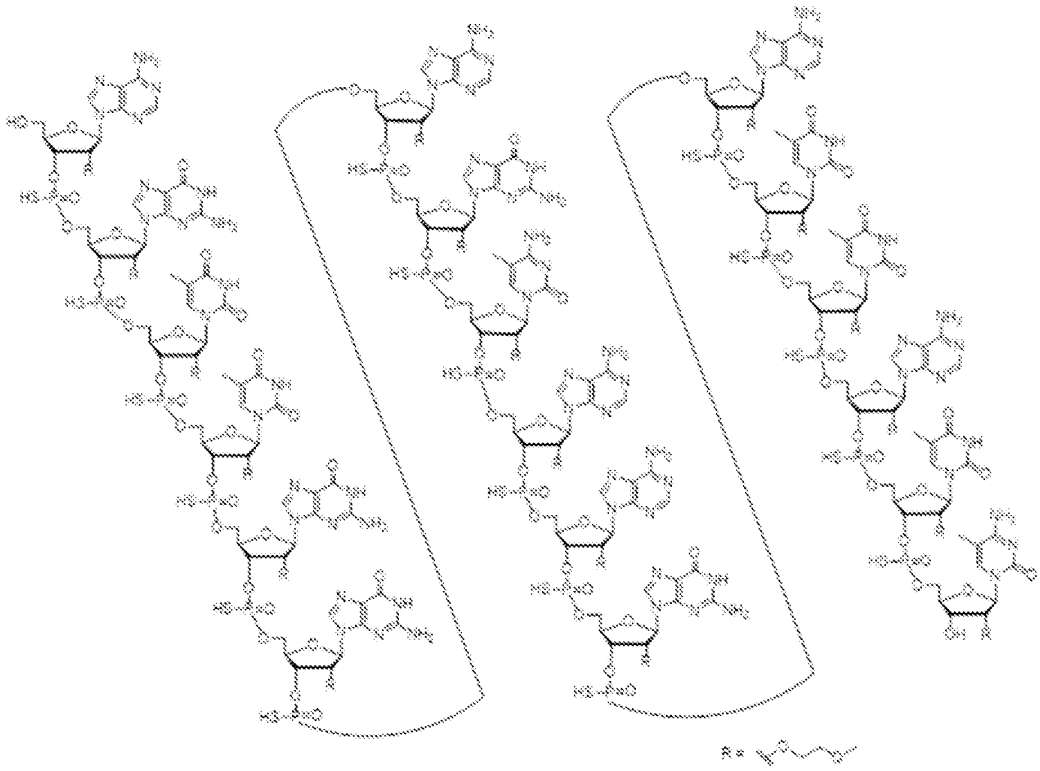
and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg.

[0064] In some embodiments, the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose of the after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0065] In some embodiments, the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0066] In some embodiments, the one or more maintenance doses are administered at a same dose frequency or a substantially same dose frequency.

[0067] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

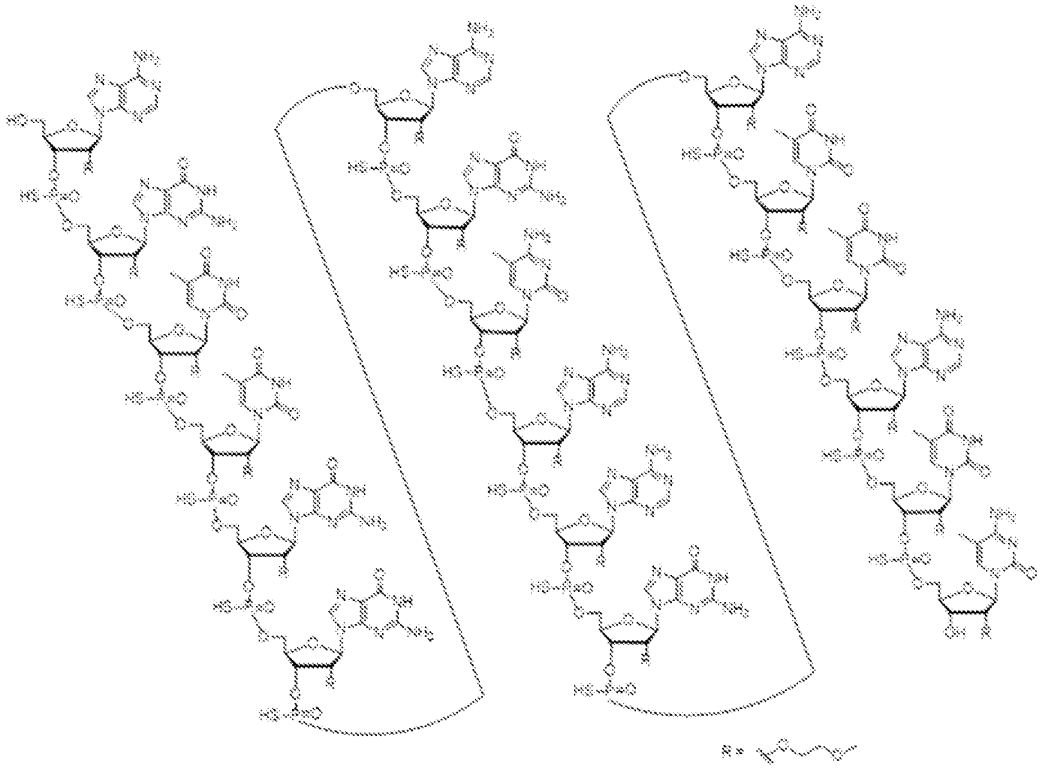
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0068] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

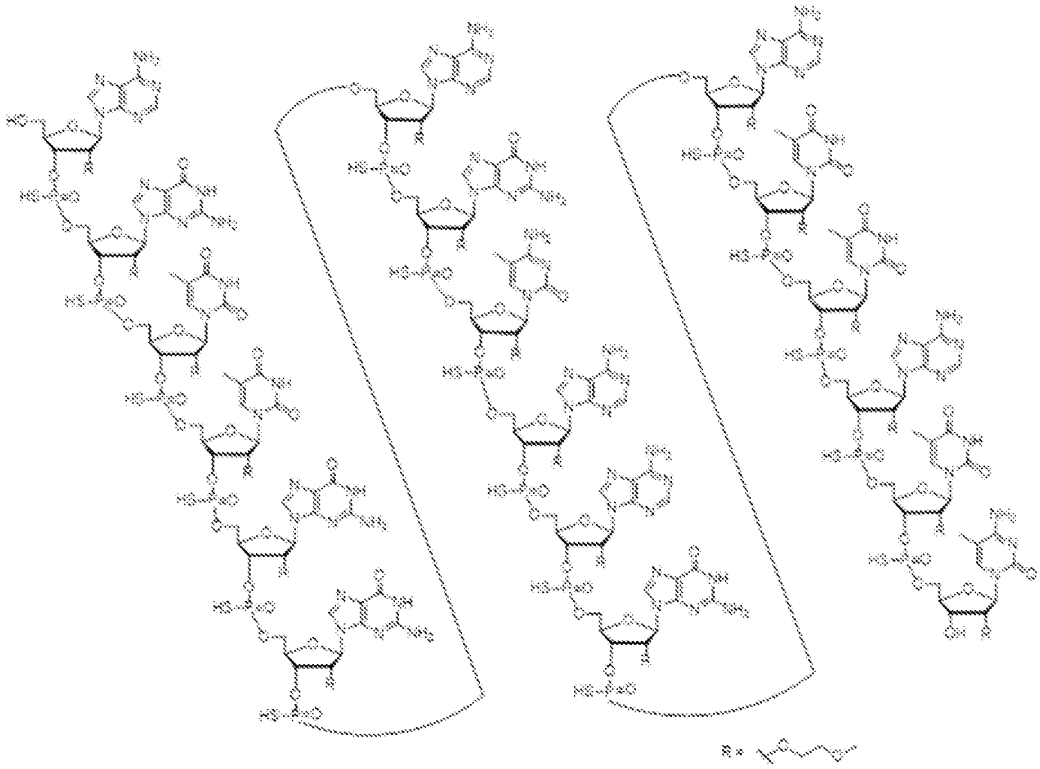
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0069] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

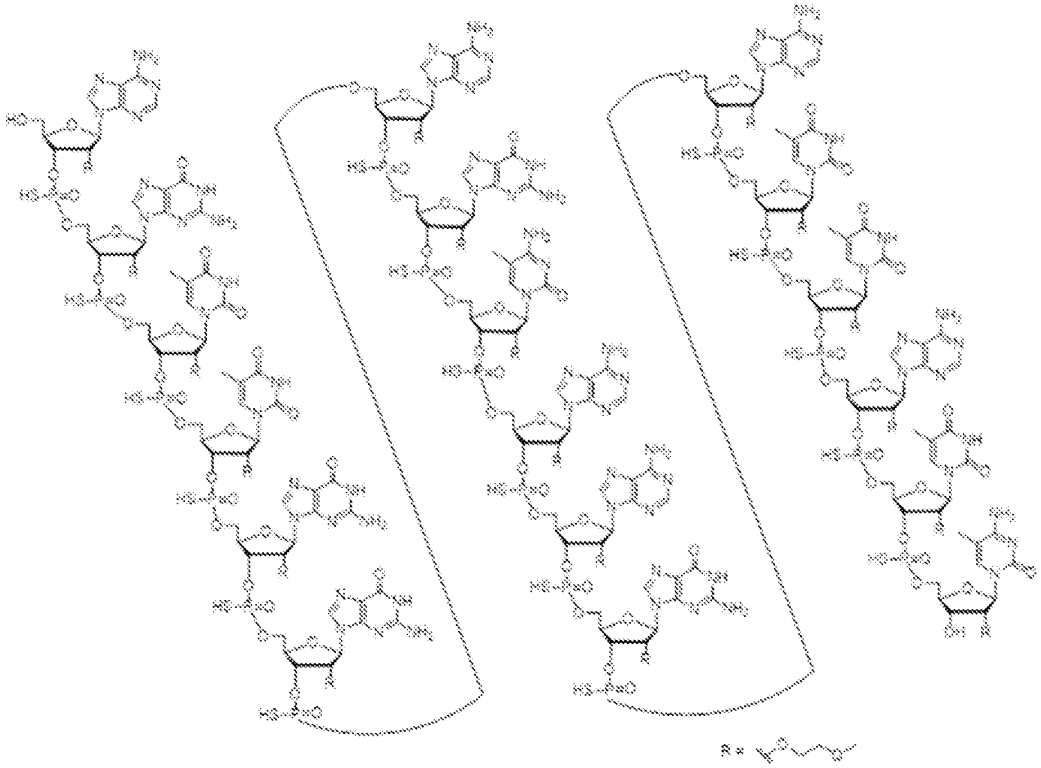
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0070] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0071] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 30 mg.

[0072] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 45 mg.

[0073] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 50 mg.

[0074] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 60 mg.

[0075] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 70 mg.

[0076] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg.

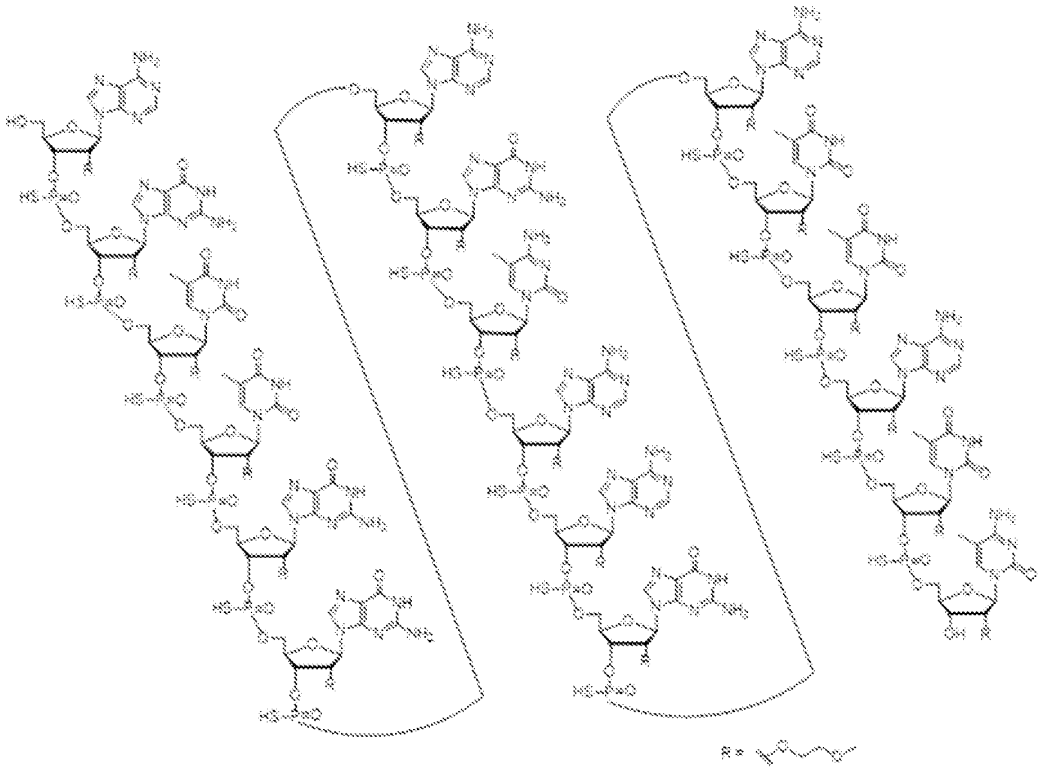
[0077] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg.

[0078] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.

[0079] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.

[0080] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.

[0081] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

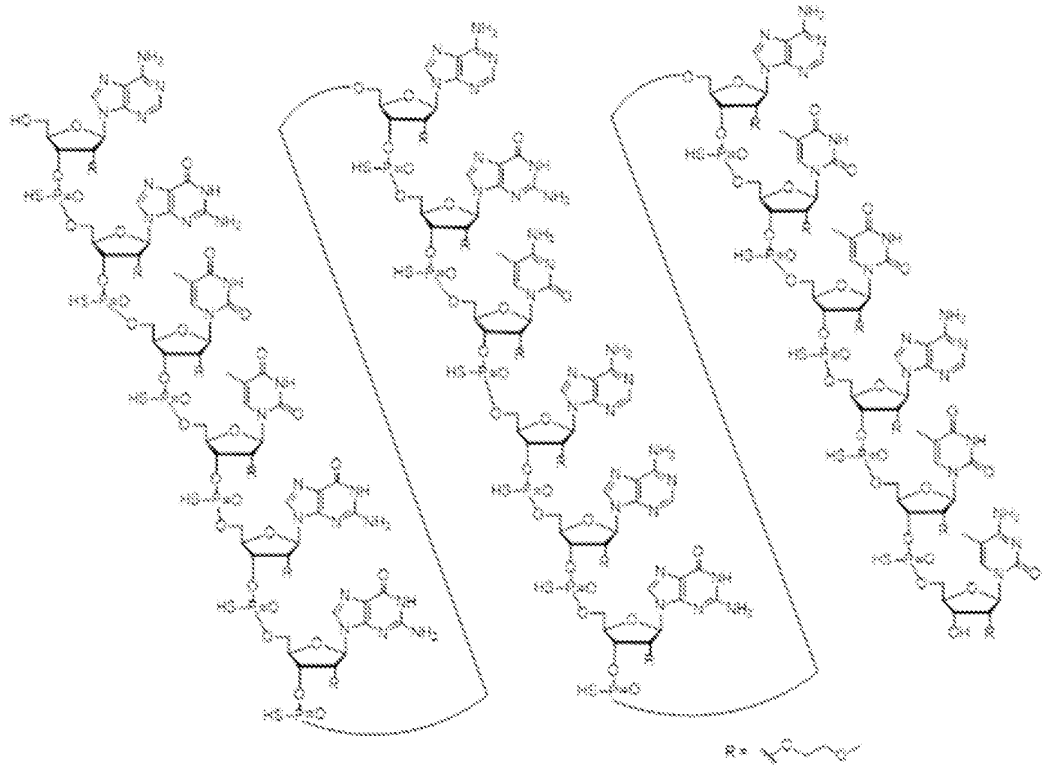
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0082] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

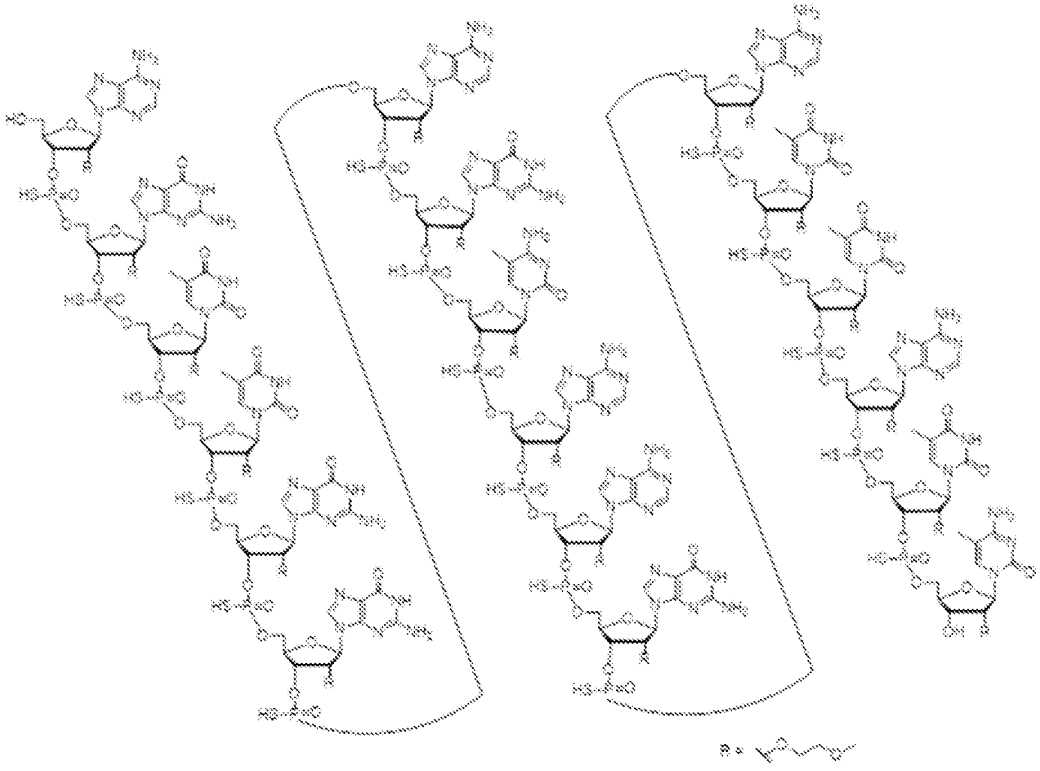
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0083] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

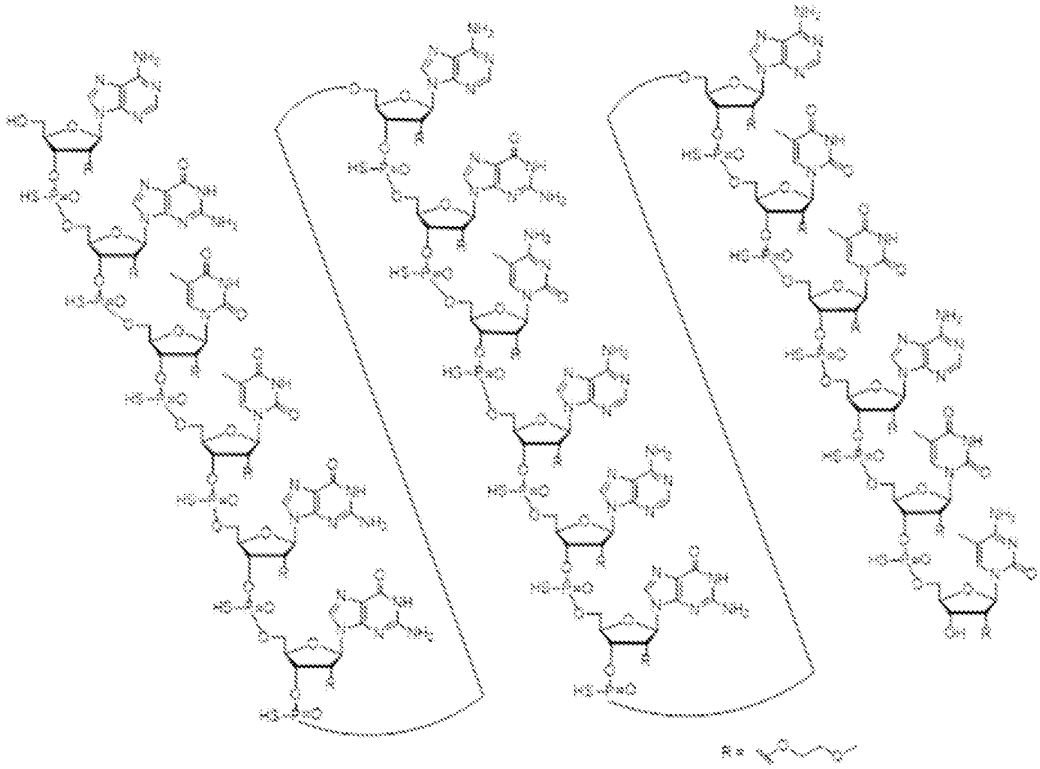
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0084] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

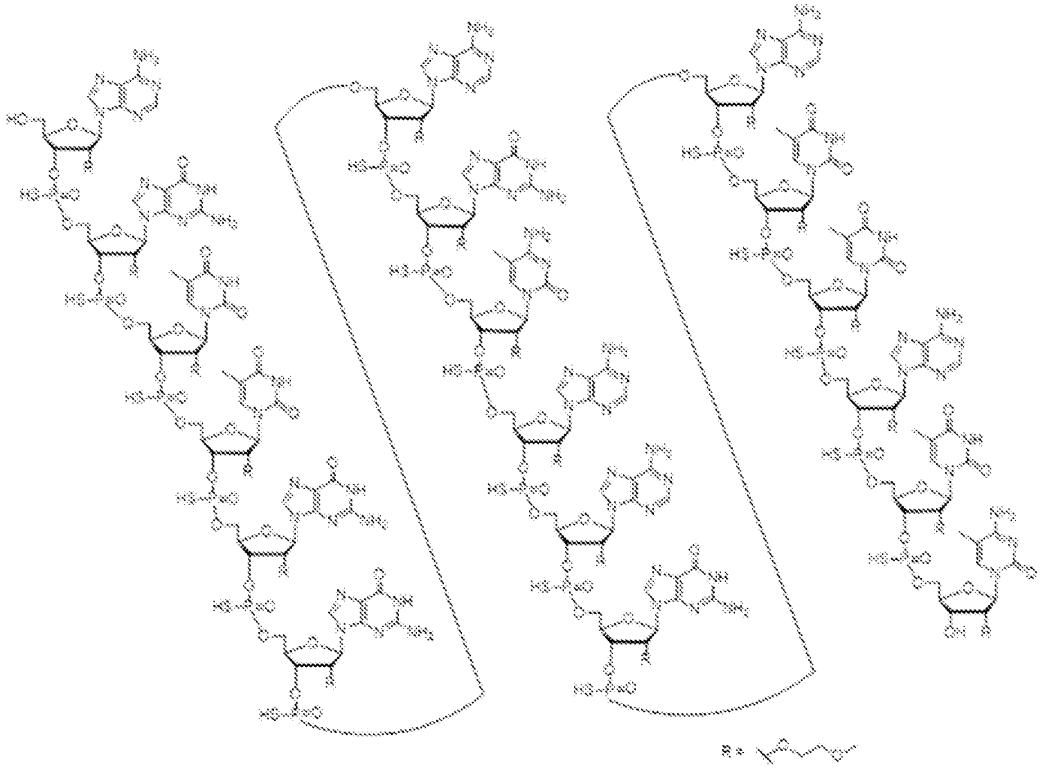
wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 6 months after the third loading dose, and each maintenance after the first maintenance dose is administered

independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0085] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

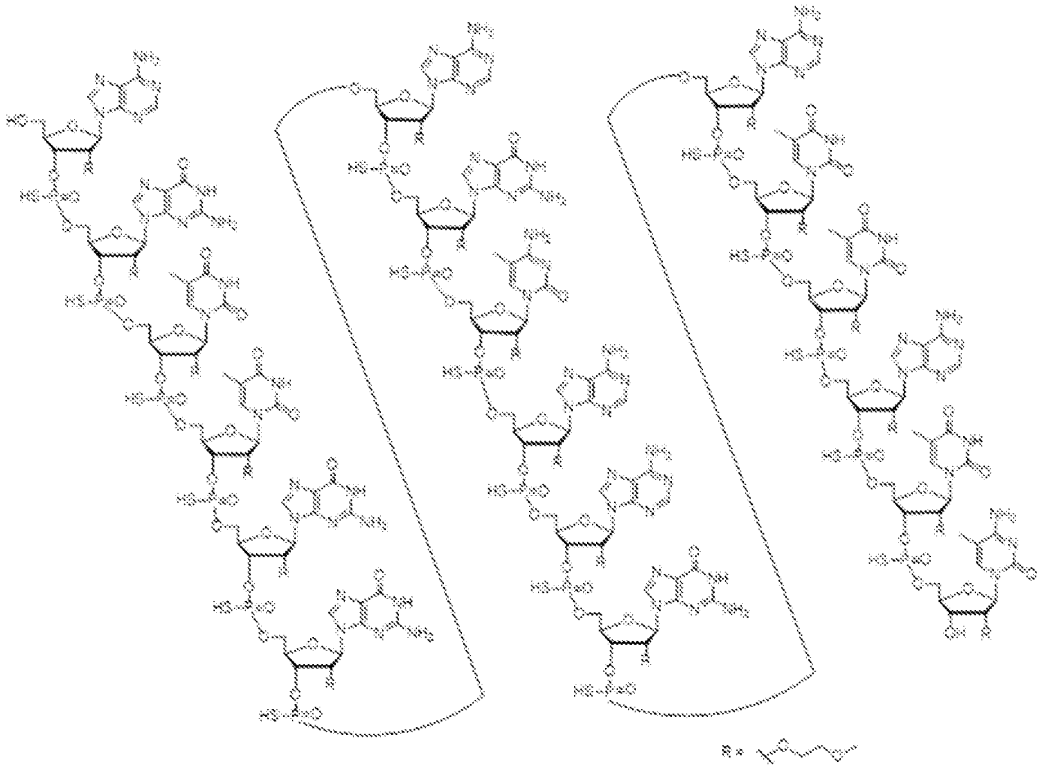
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0086] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

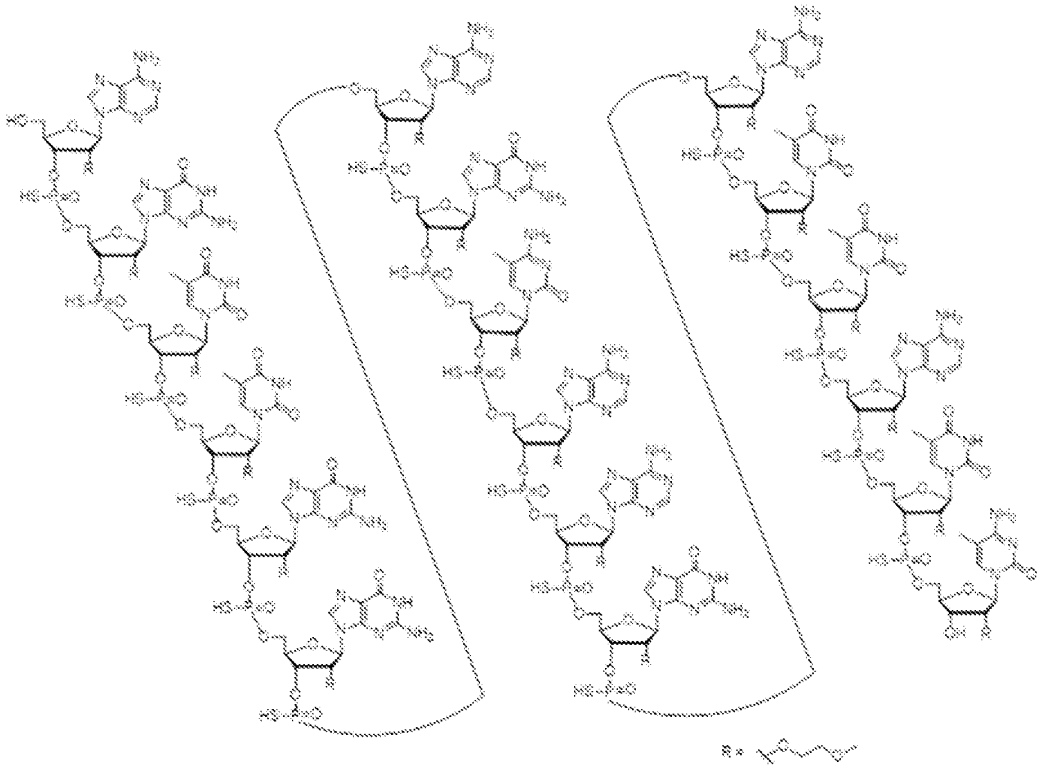
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0087] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

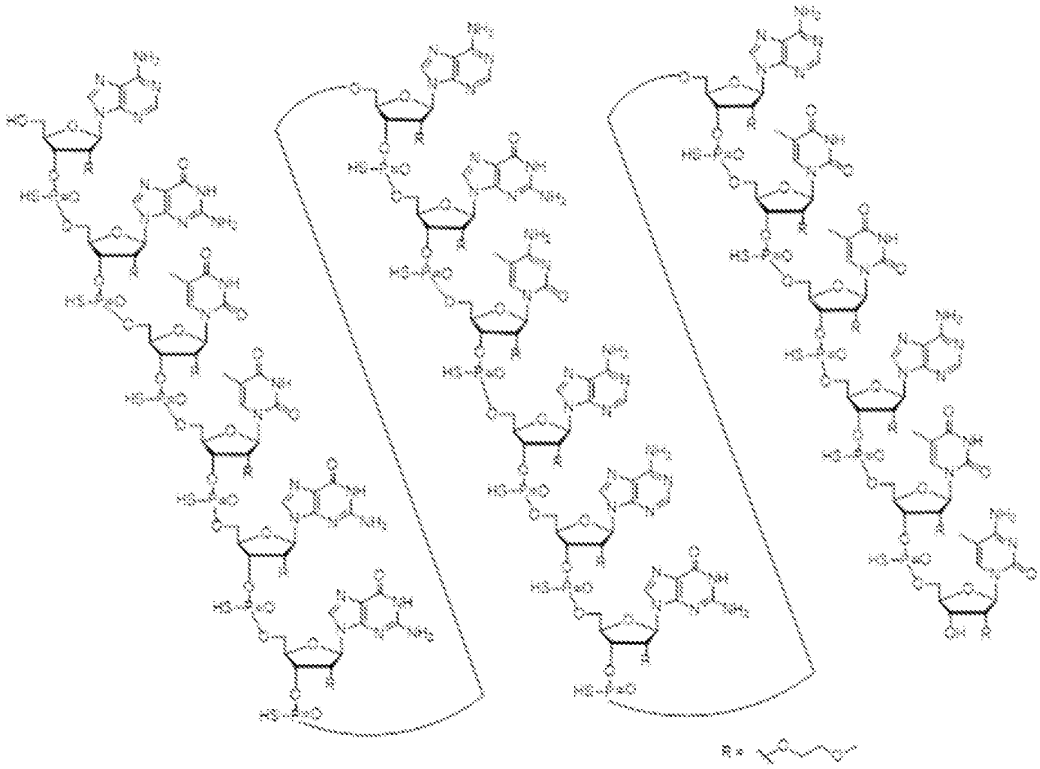
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0088] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 6 months after the third loading dose, and each maintenance after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0089] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 30 mg.

[0090] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 45 mg.

[0091] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 50 mg.

[0092] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 60 mg.

[0093] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 70 mg.

[0094] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 30 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 25 mg.

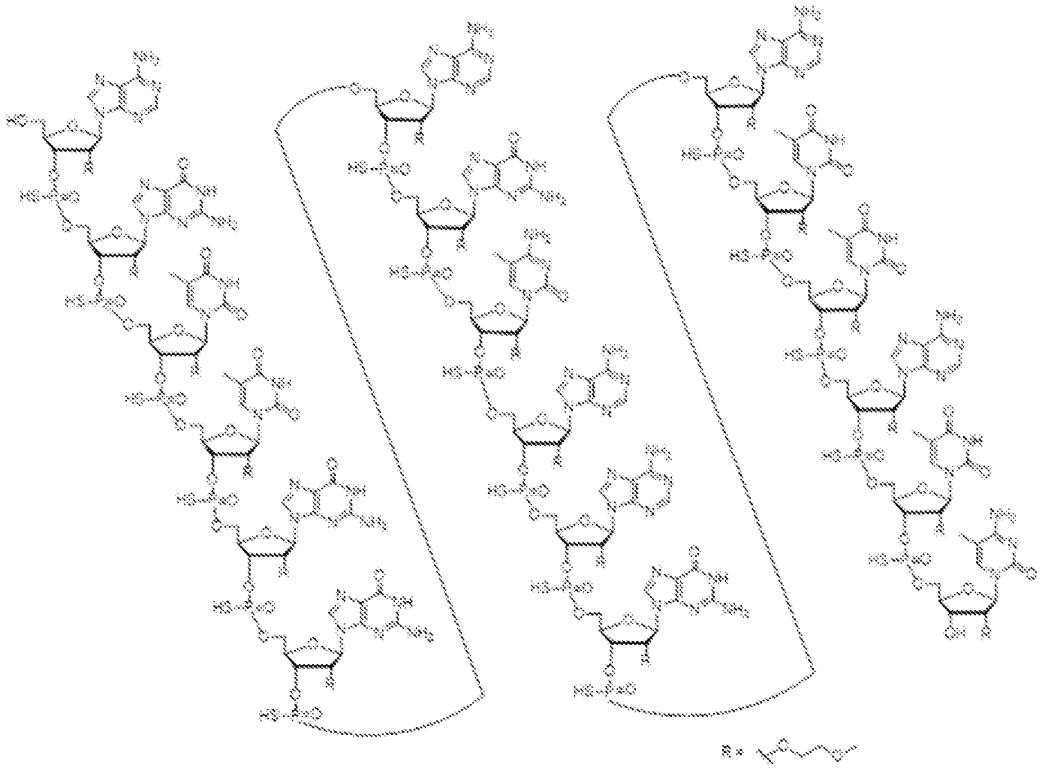
[0095] In some embodiments, the amount of the compound in each dose of the amount of the compound in each of the first loading dose, the second loading dose, and the third loading dose is about 45 mg, and the first maintenance dose and the one or more maintenance doses is about 40 mg.

[0096] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

[0097] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

[0098] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

[0099] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

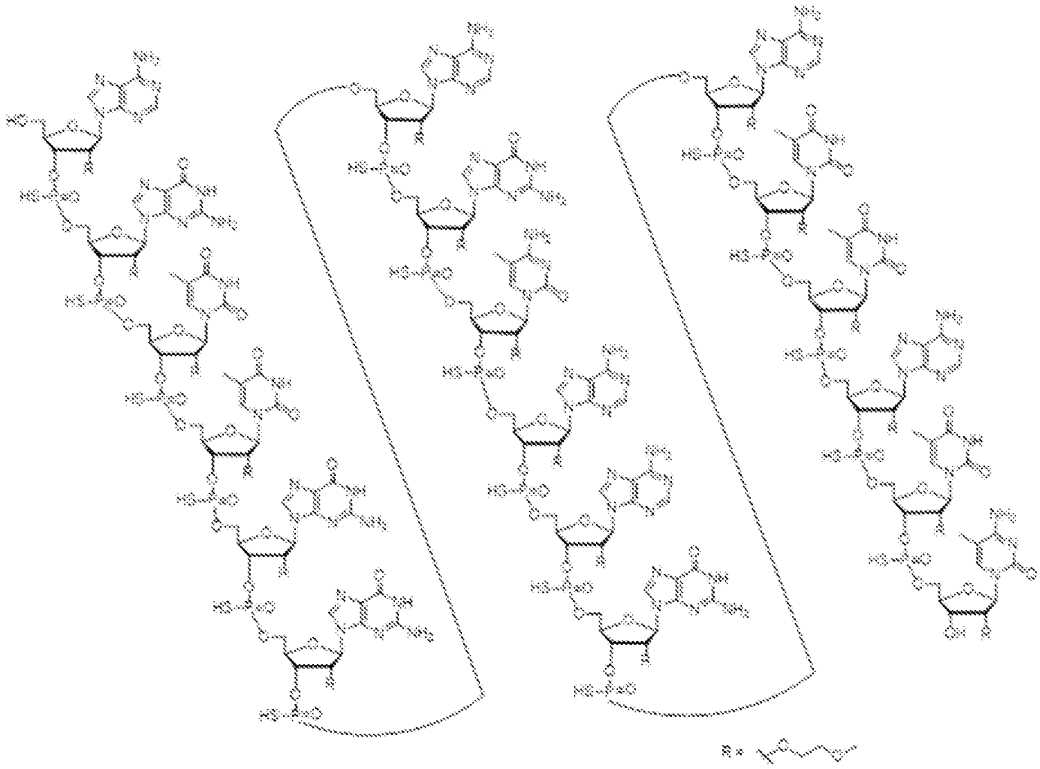


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0100] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

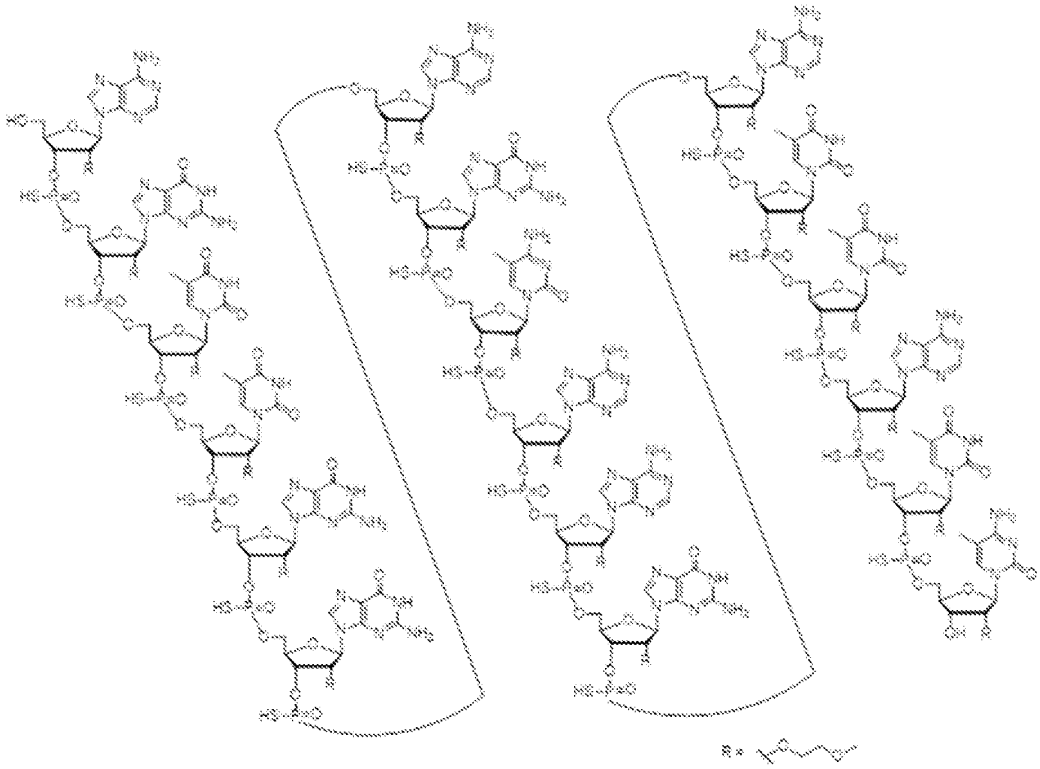


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0101] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

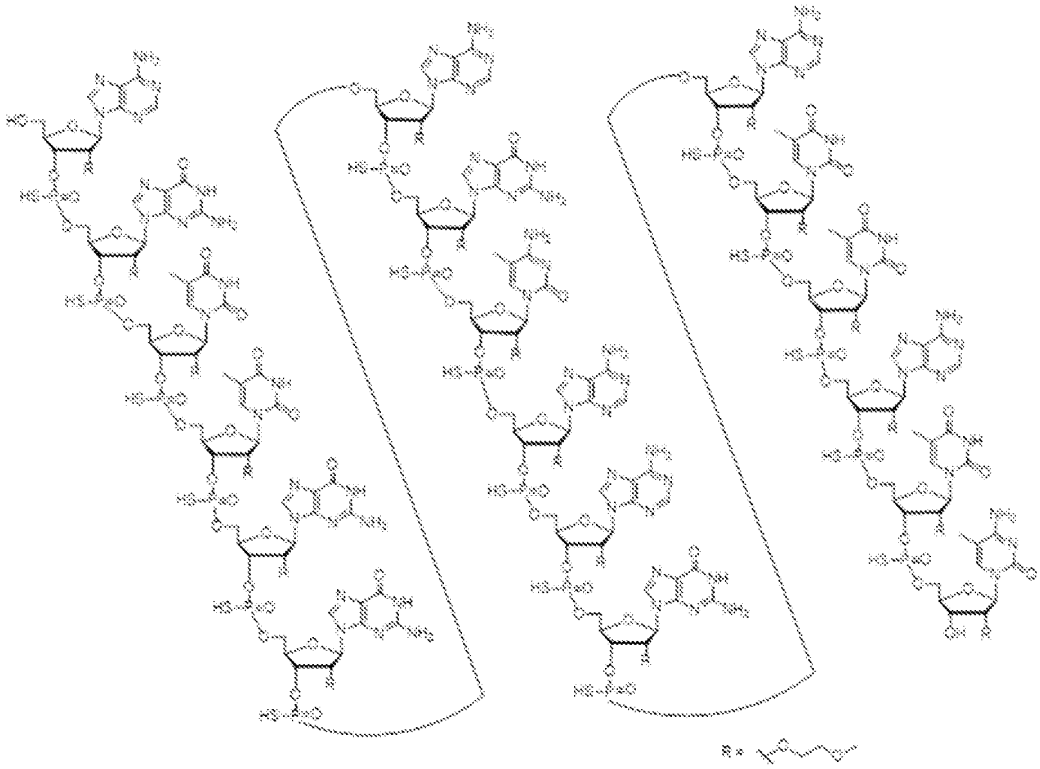


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0102] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

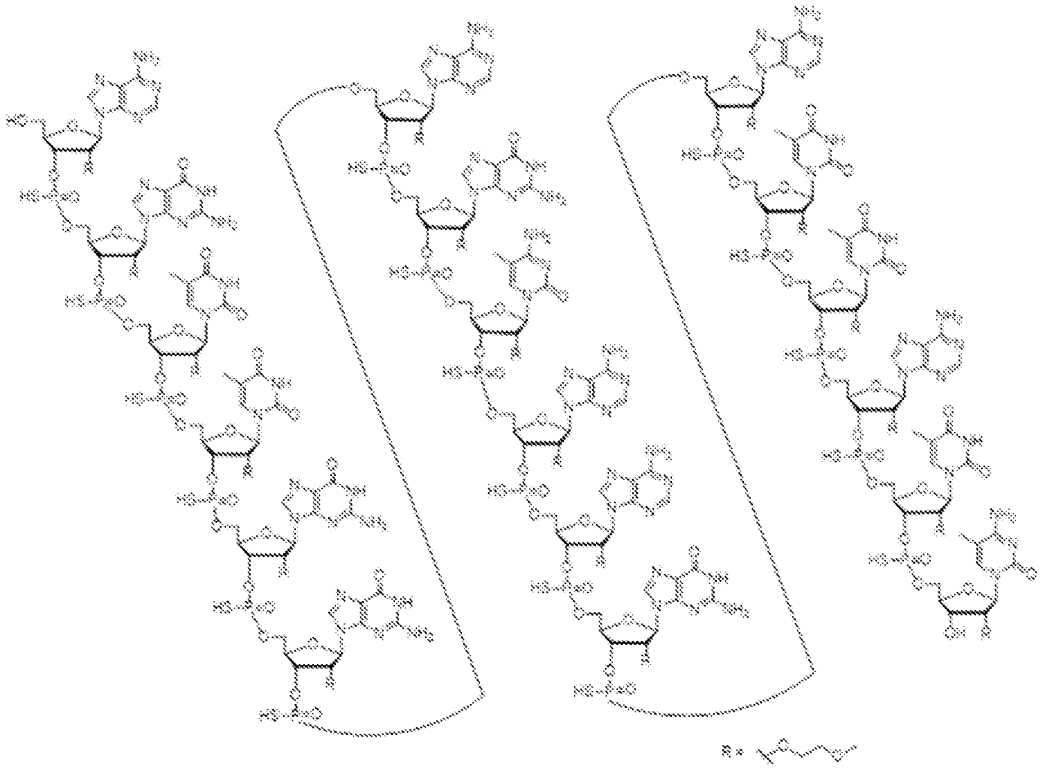


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 6 months after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0103] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

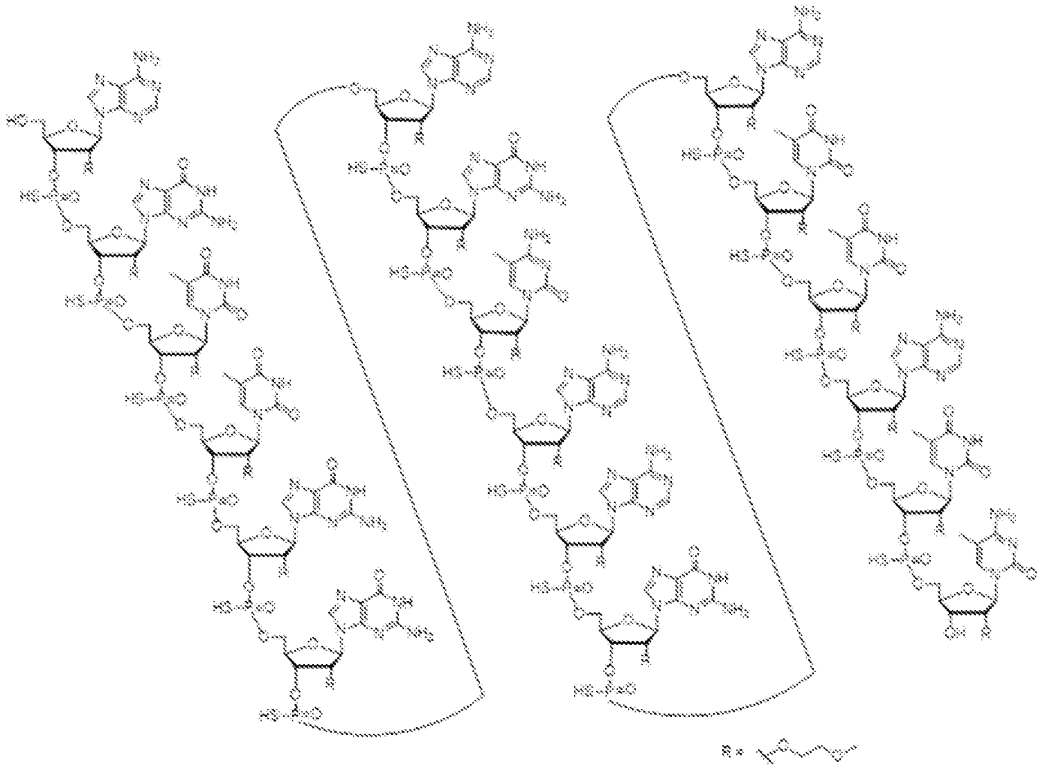


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0104] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

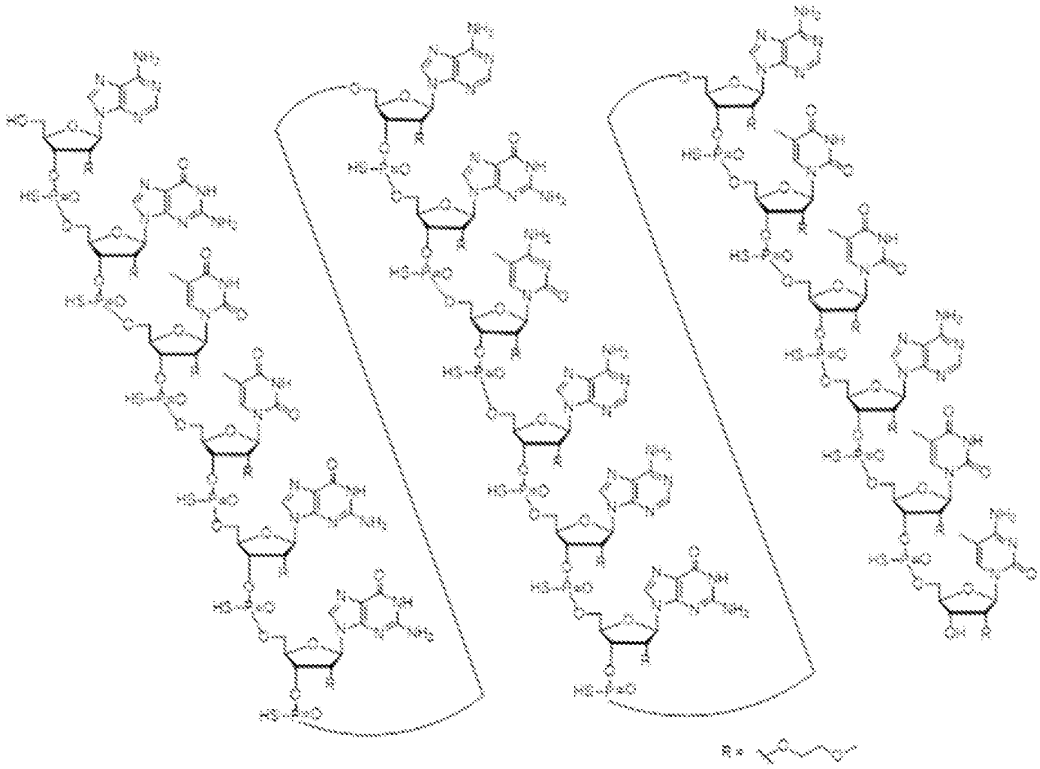


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0105] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

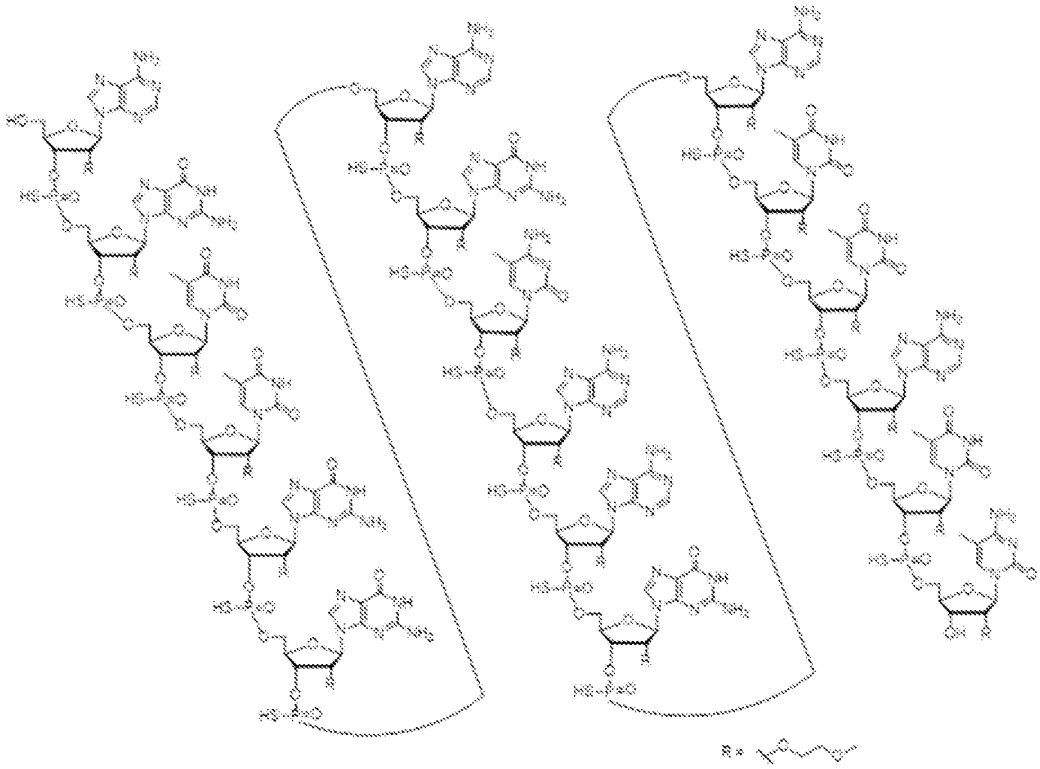


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0106] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

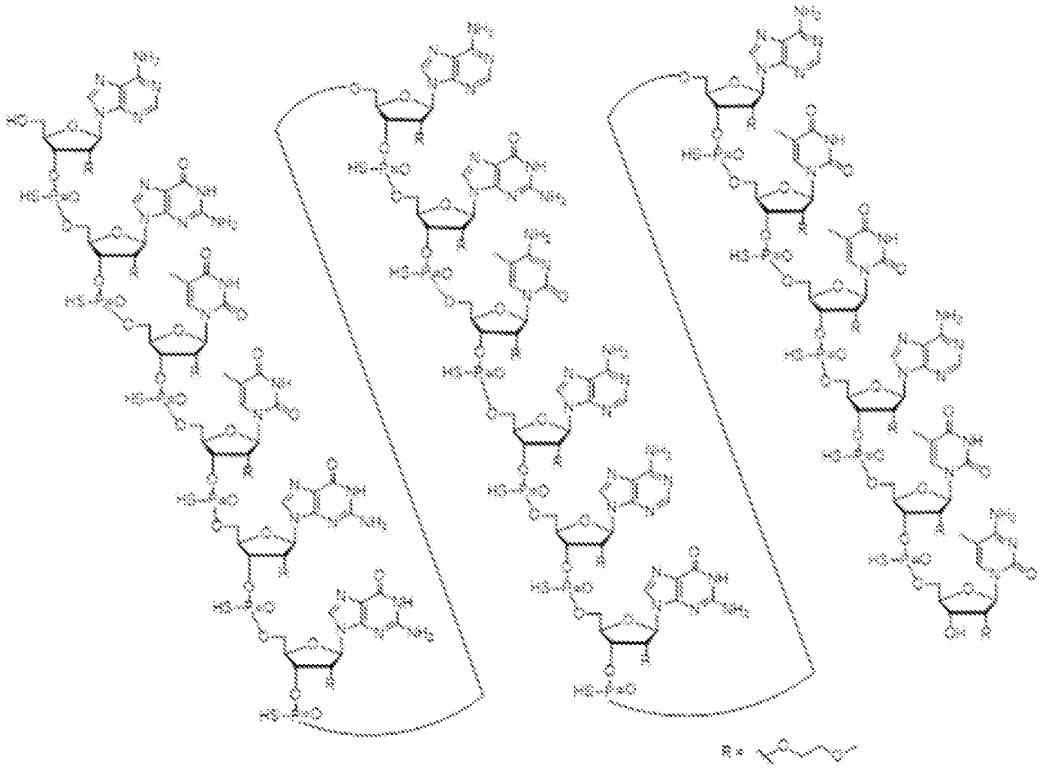


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0107] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

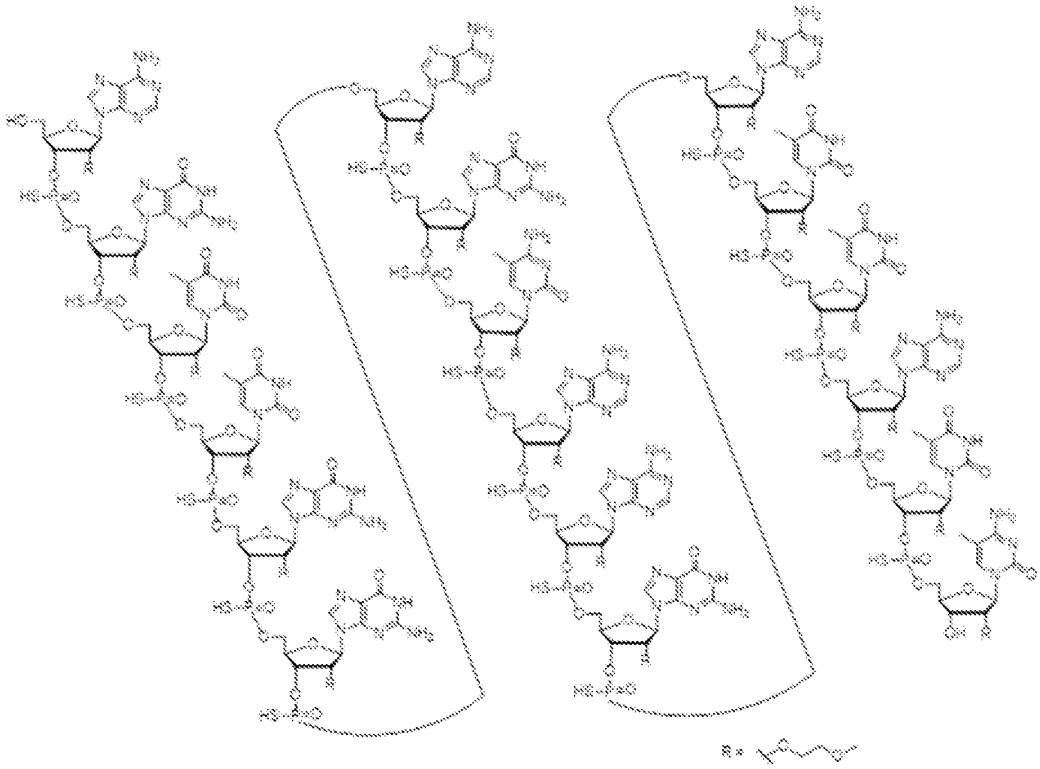


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0108] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

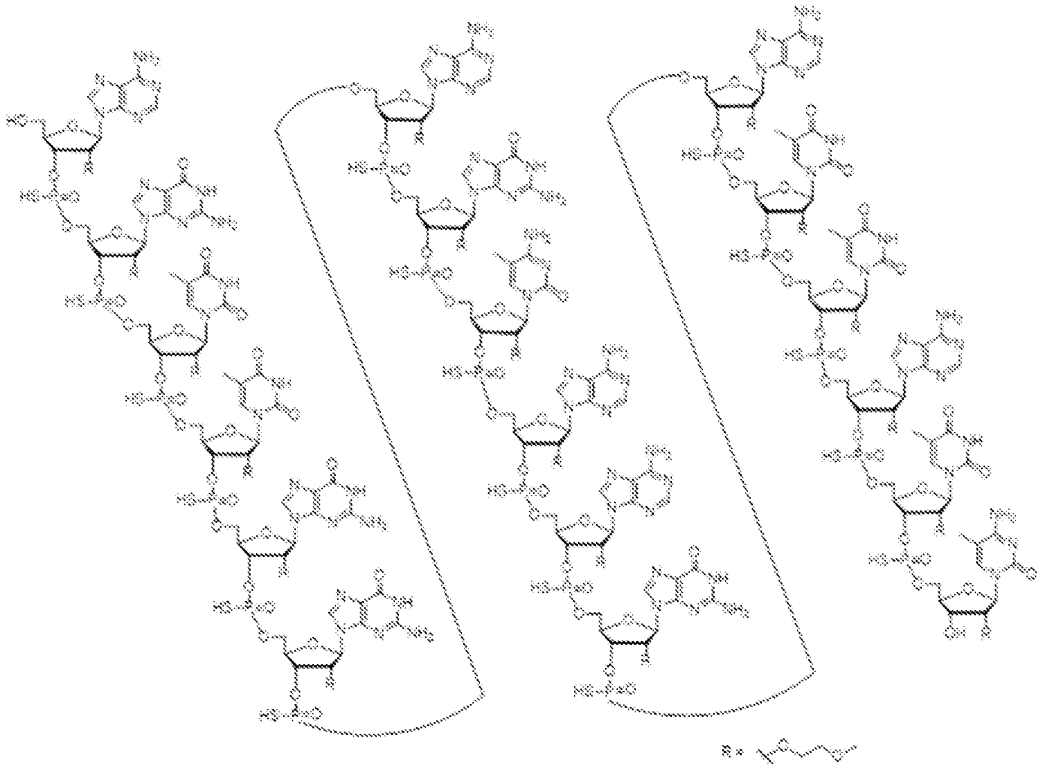


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0109] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

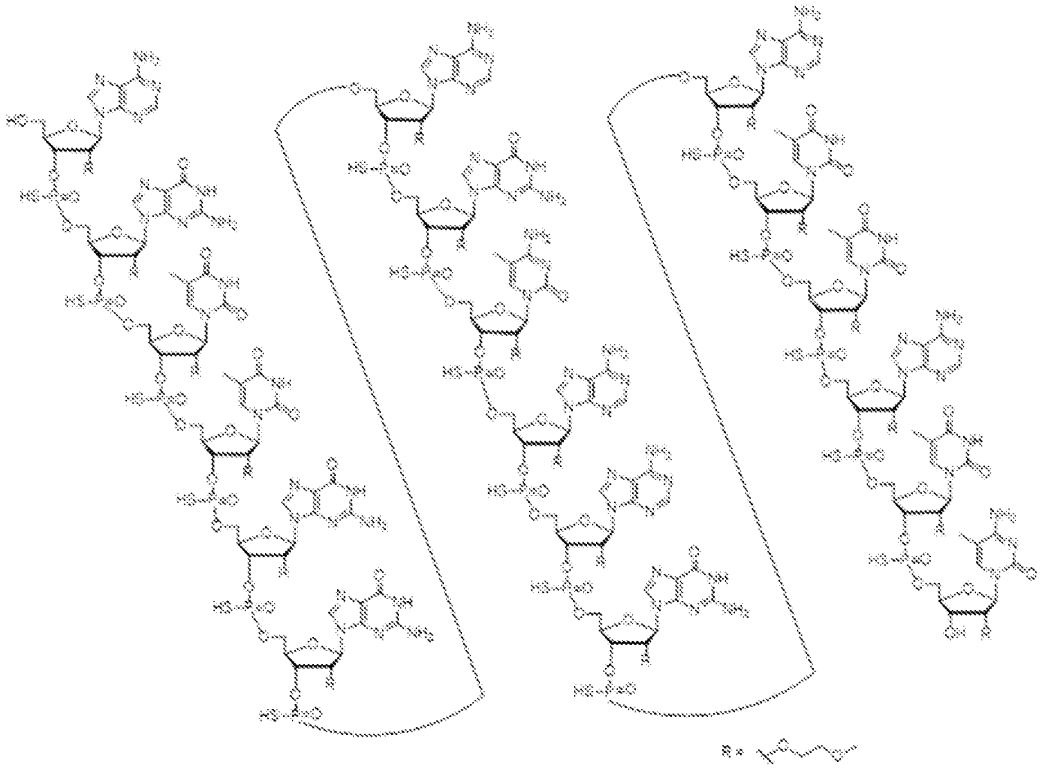


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0110] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

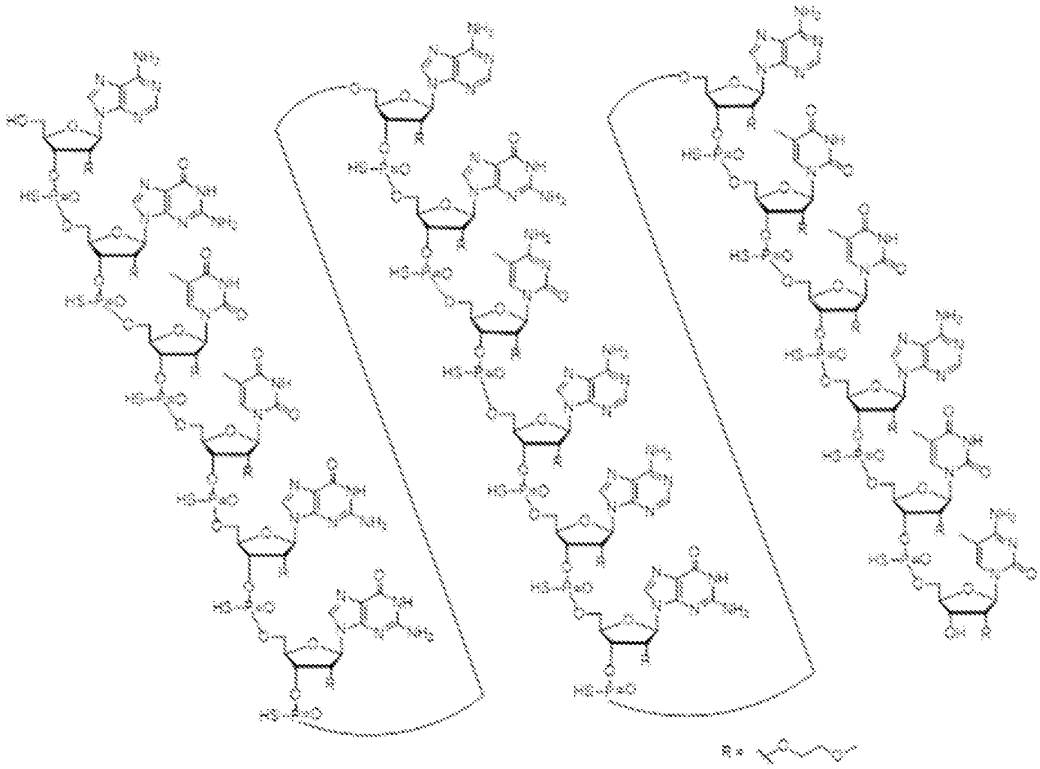


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0111] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

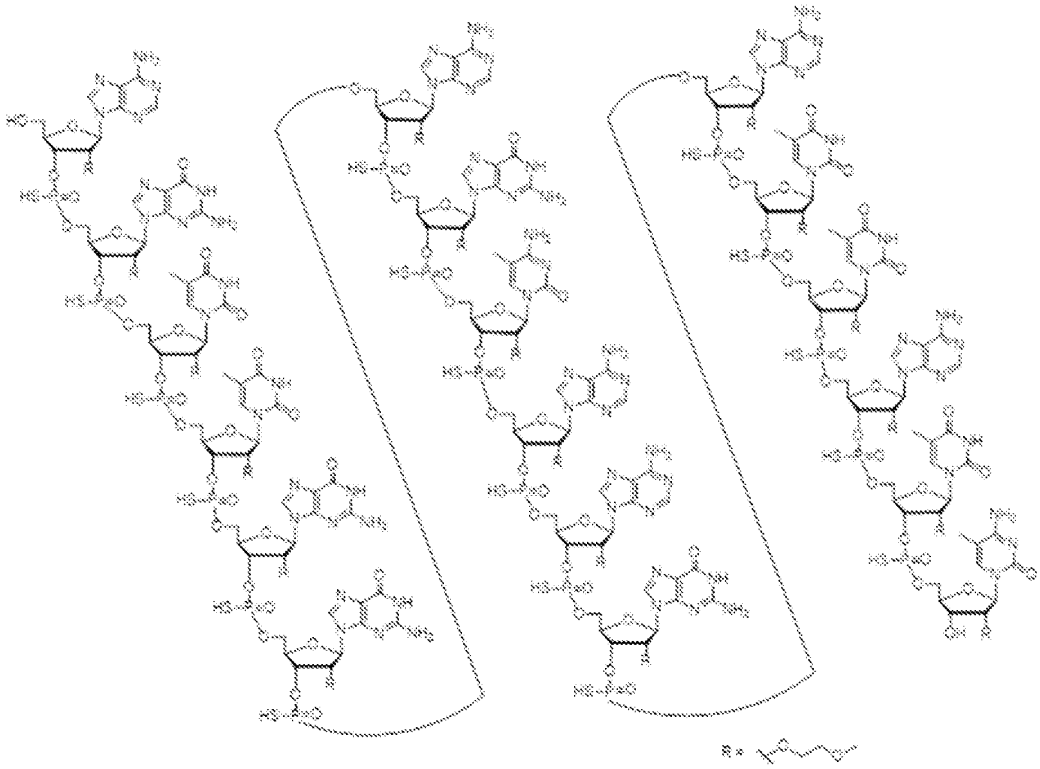


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0112] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

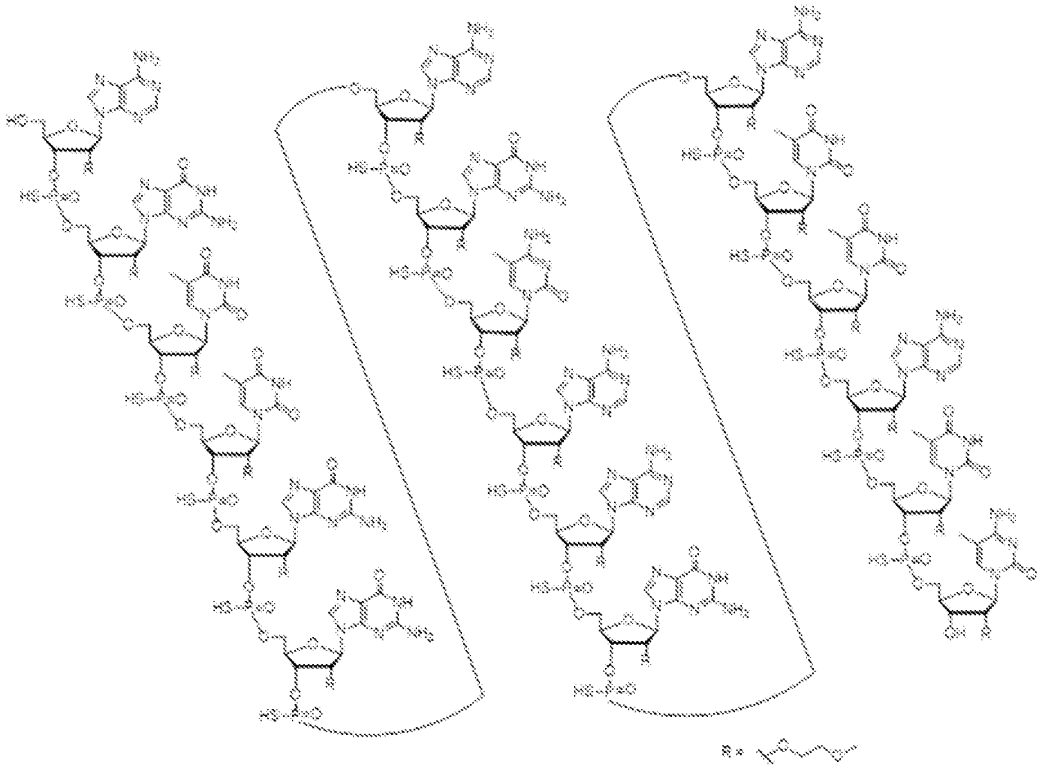


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0113] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

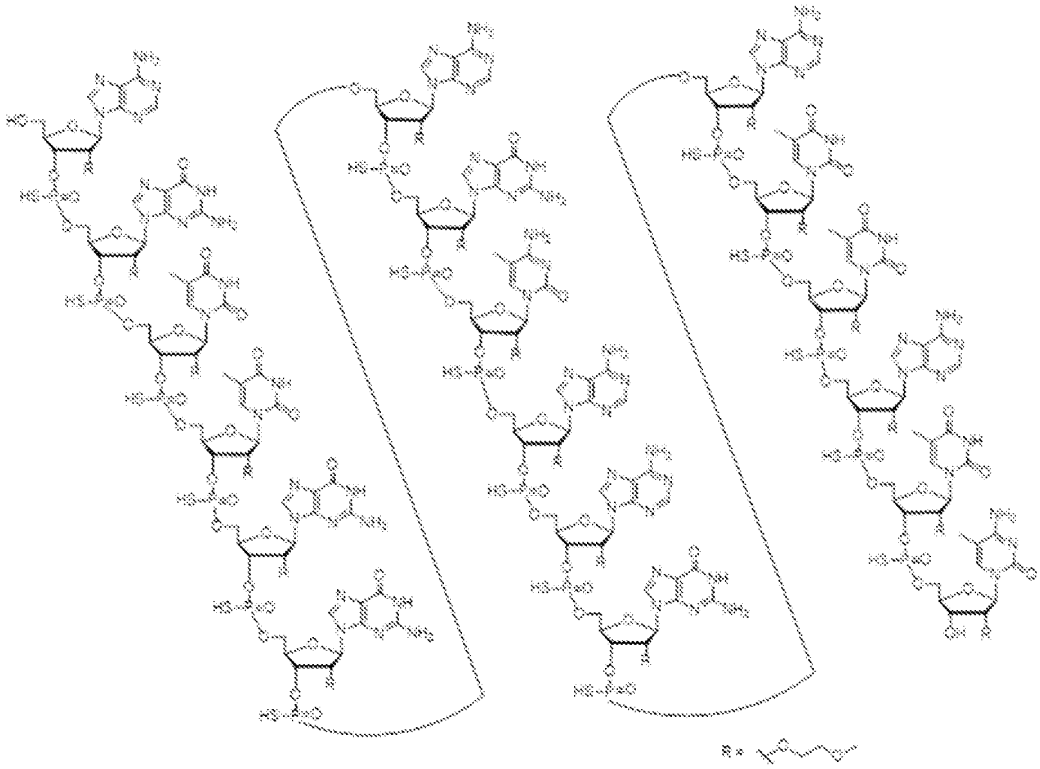


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0114] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

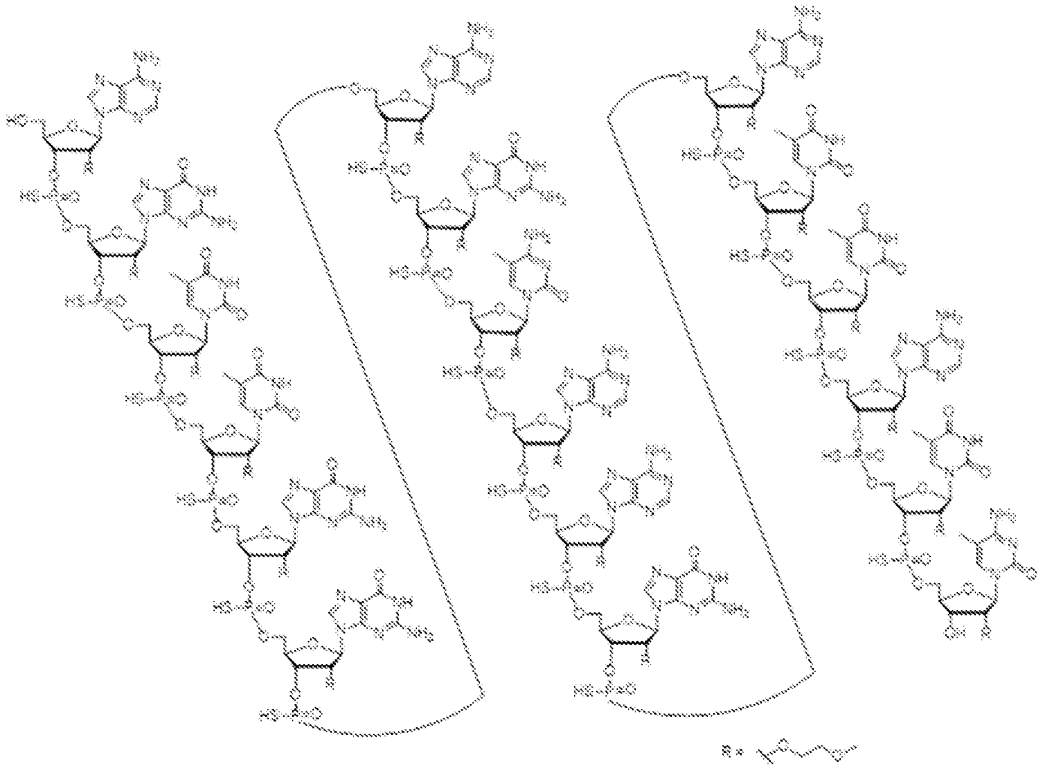


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 6 months after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0115] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

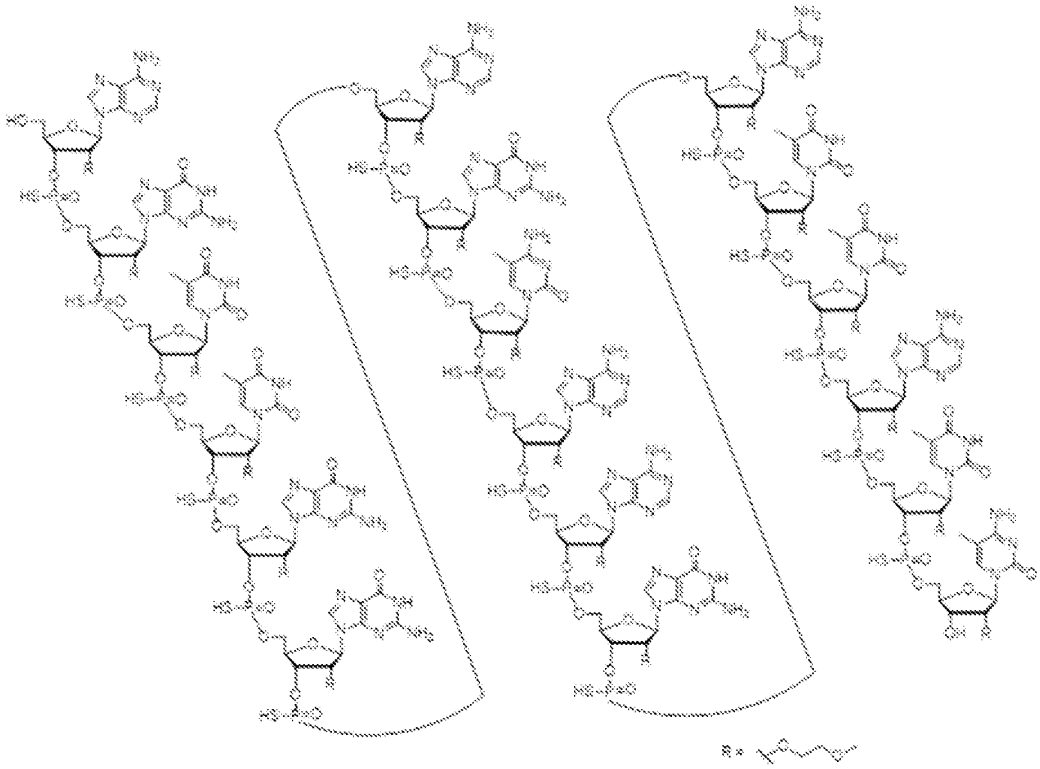


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0116] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

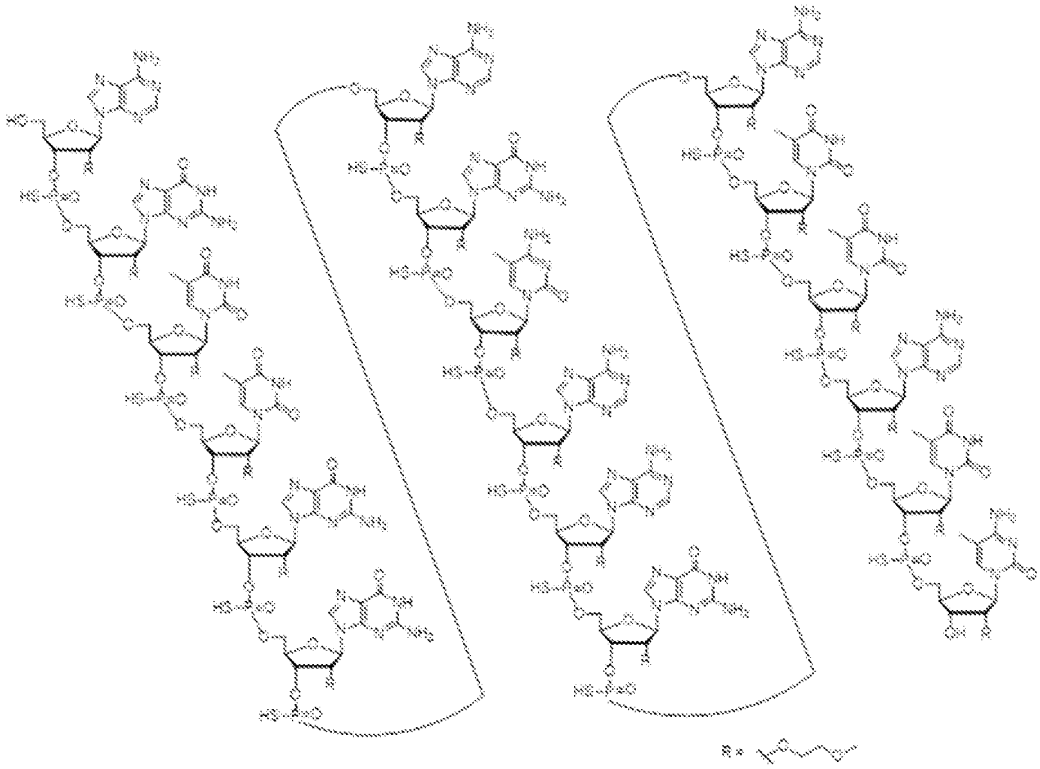


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0117] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

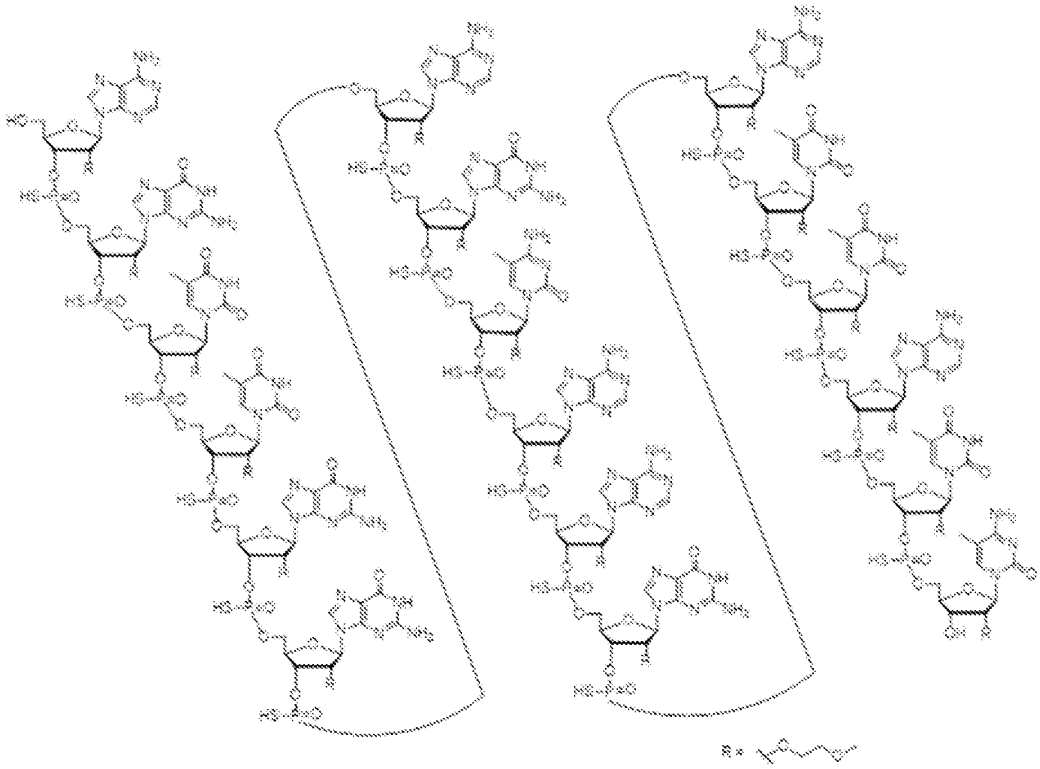


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0118] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

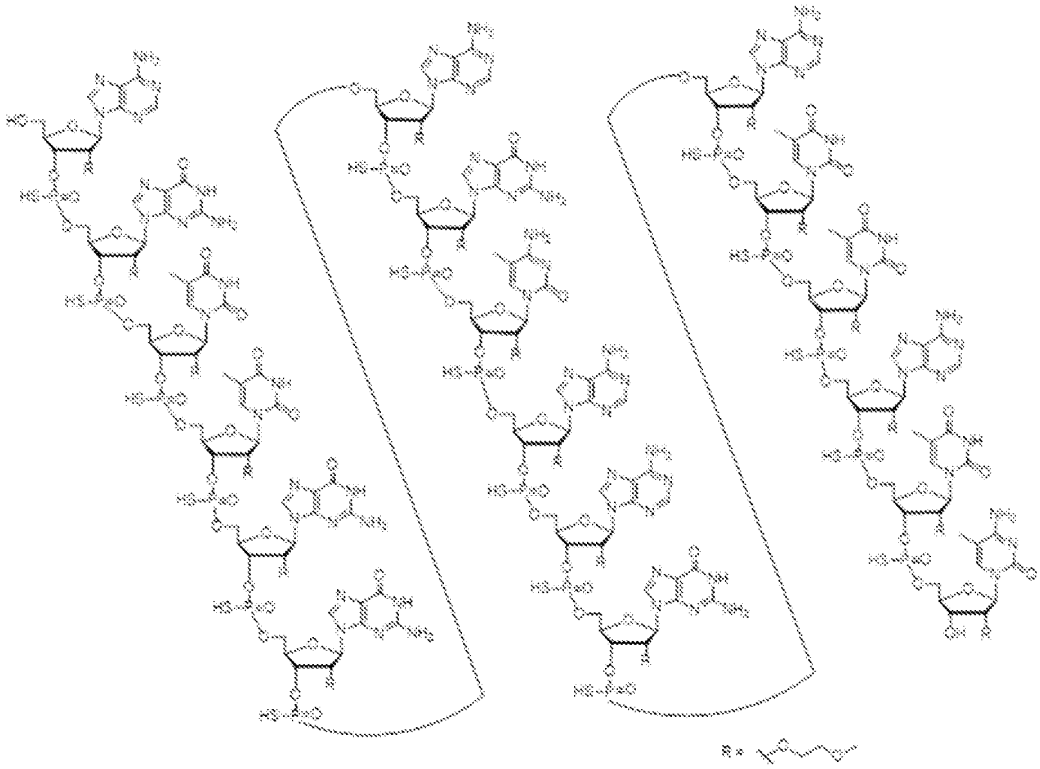


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0119] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

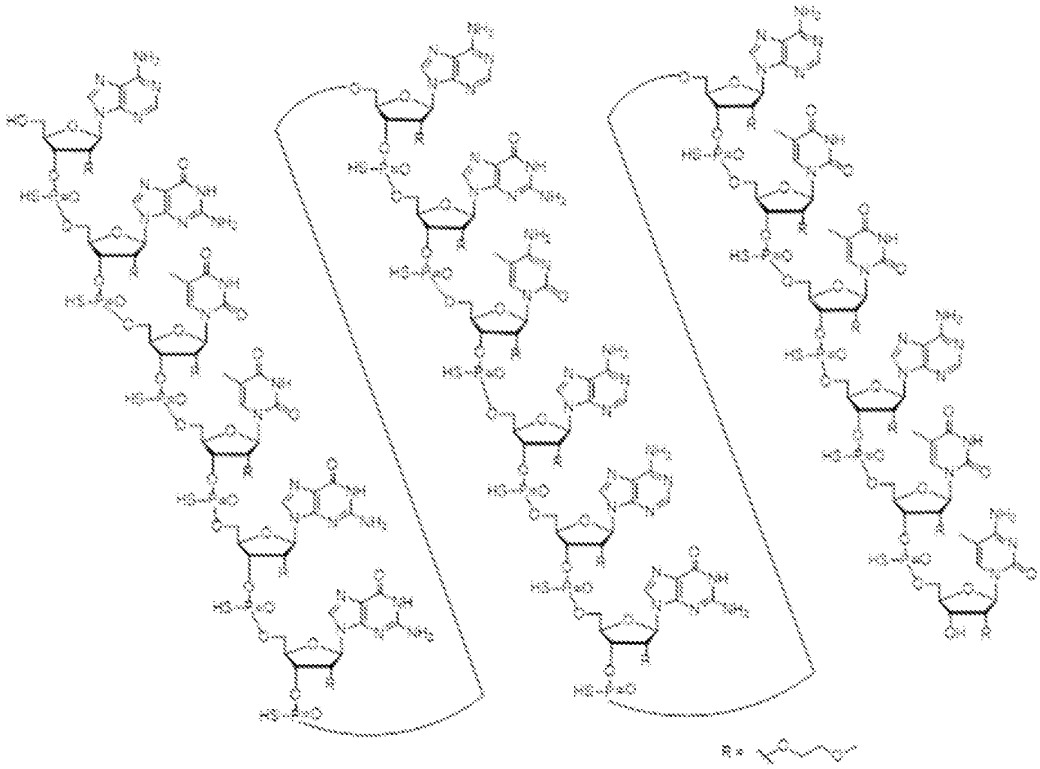


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

[0120] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

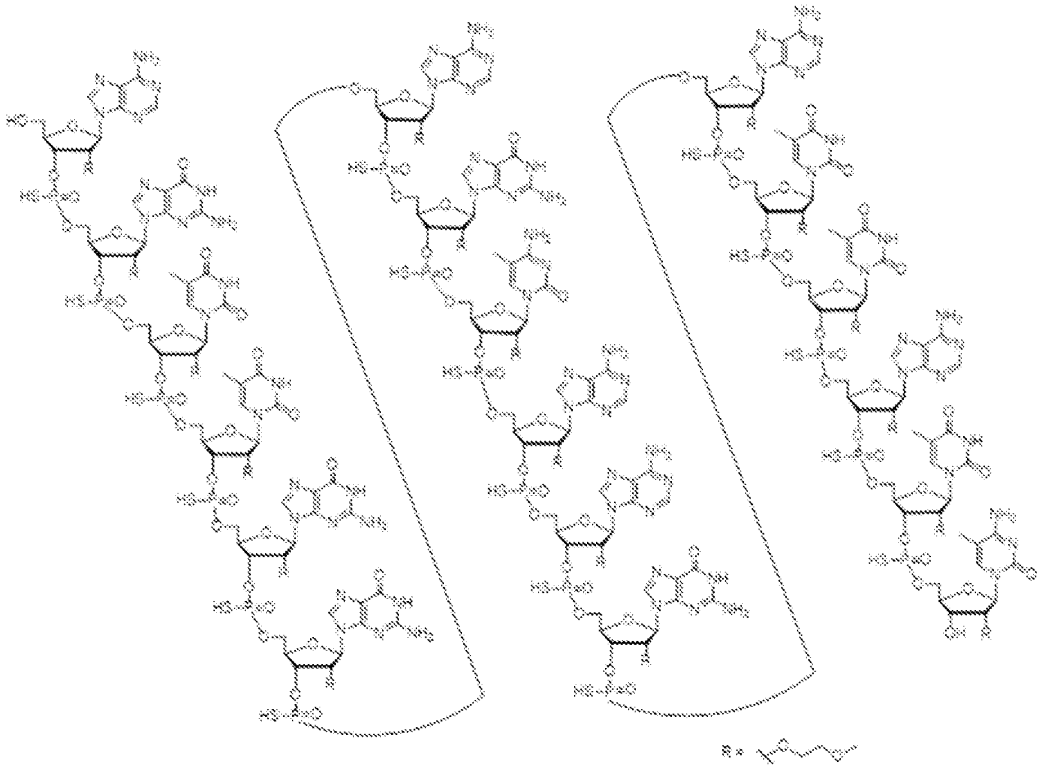


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0121] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

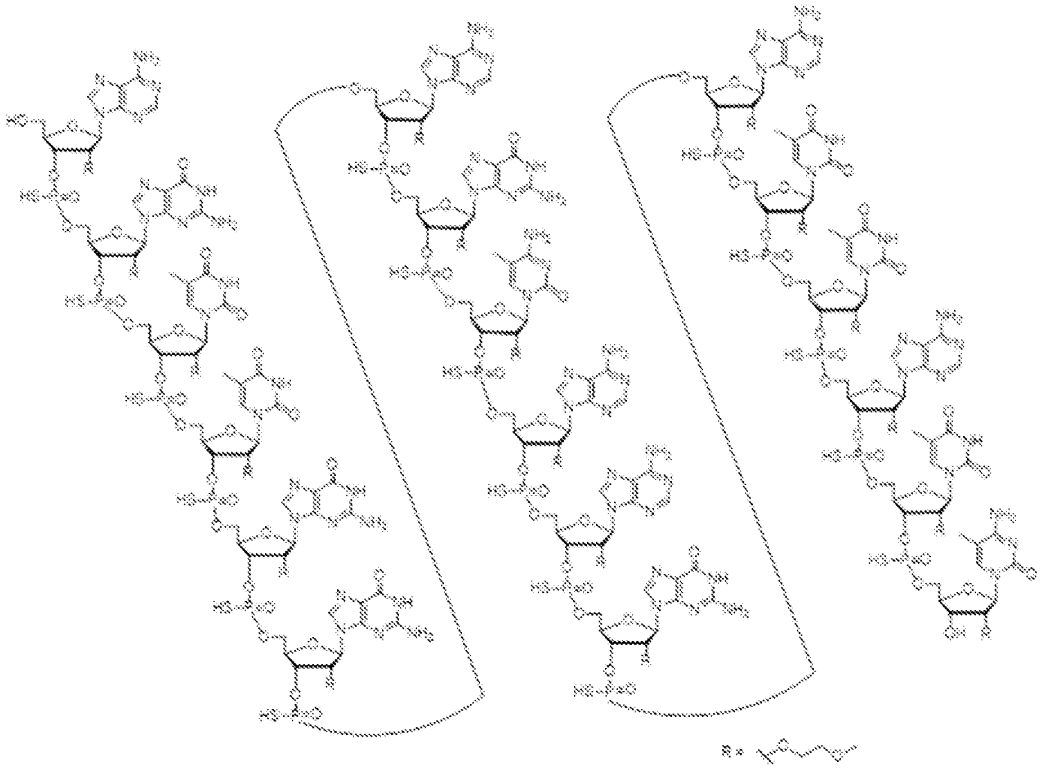


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

[0122] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

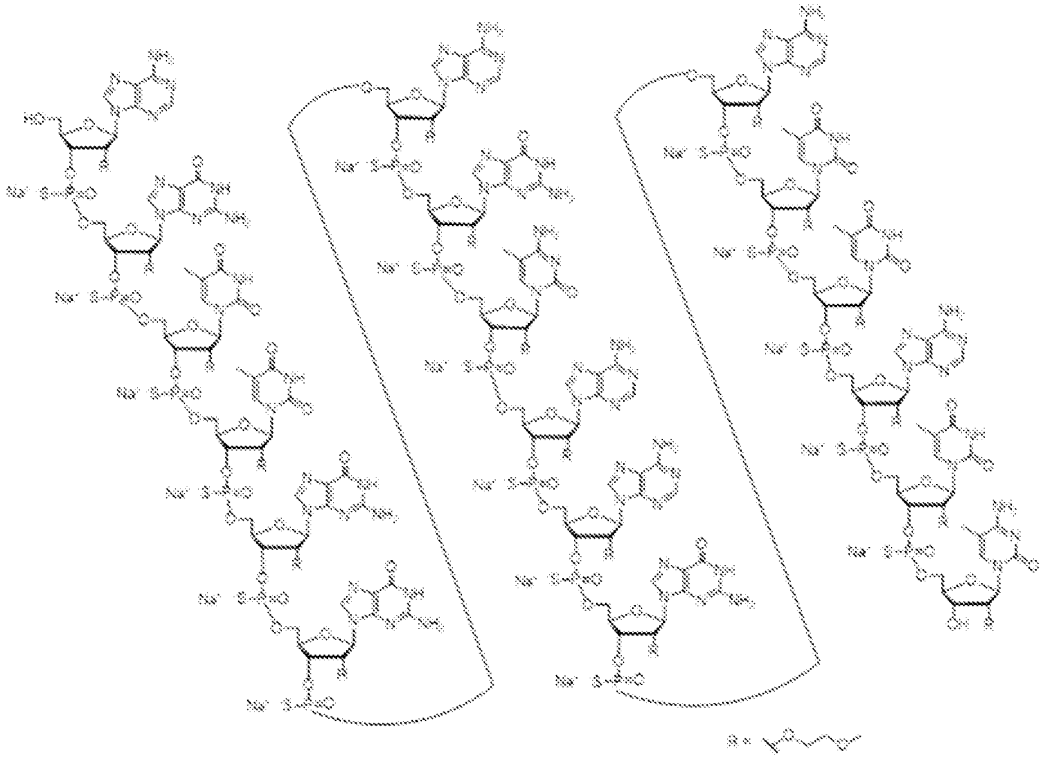


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

[0123] In some embodiments, the compound has the following structure:



(II).

[0124] In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient, carrier, or diluent.

[0125] In some embodiments, the pharmaceutical composition is a liquid composition.

[0126] In some embodiments, the pharmaceutical composition comprises from 0.1 mL to 50 mL of a diluent, and wherein the compound is solubilized or diluted in the diluent.

[0127] In some embodiments, the pharmaceutical composition comprises about 0.1 mL, 0.5 mL, 1 mL, 2 mL, 2.5 mL, 3 mL, 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, 10 mL, 11 mL, 12 mL, 13 mL, 14 mL, 15 mL, 16 mL, 17 mL, 18 mL, 19 mL, 20 mL, 25 mL, 30 mL, 35 mL, 40 mL, 45 mL, or 50 mL of the diluent.

[0128] In some embodiments, the pharmaceutical composition comprises 1 mL to 20 mL of the diluent, 2 mL to 10 mL of the diluent, or 1 mL to 5 mL of the diluent.

[0129] In some embodiments, the pharmaceutical composition comprises at least 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, or 10 mL of the diluent.

[0130] In some embodiments, the pharmaceutical composition comprises about 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, or 10 mL of the diluent.

[0131] In some embodiments, the pharmaceutical composition comprises about 4 mL of the diluent.

[0132] In some embodiments, the pharmaceutical composition comprises about 7 mL of the diluent.

[0133] In some embodiments, the pharmaceutical composition comprises about 9 mL of the diluent.

[0134] In some embodiments, the pharmaceutical composition comprises about 10 mL of the diluent.

[0135] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of 10 mL or higher.

[0136] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of 5 mL or higher.

[0137] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 10 mL.

[0138] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 15 mL.

[0139] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 20 mL.

[0140] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 25 mL.

[0141] In some embodiments, the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 30 mL.

[0142] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of 5 mL or higher.

[0143] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of 10 mL or higher.

[0144] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 5 mL.

[0145] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 10 mL.

[0146] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 15 mL.

[0147] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 20 mL.

[0148] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 25 mL.

[0149] In some embodiments, the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 30 mL.

[0150] In some embodiments, the diluent comprises a cerebral spinal fluid (CSF) sample from the subject or an artificial cerebral spinal fluid (aCSF) solution.

[0151] In some embodiments, the diluent is the aCSF solution that lacks sodium phosphate.

[0152] In some embodiments, each dose of the pharmaceutical composition comprises 10 mL of the diluent.

[0153] In some embodiments, the diluent is an isotonic solution.

[0154] In some embodiments, the diluent is a solution with at least pH 5.8.

[0155] In some embodiments, the diluent is a solution with pH 6.6 – 7.6.

[0156] In some embodiments, the diluent is a buffer comprising 25-250 mM NaCl.

[0157] In some embodiments, the diluent is a buffer comprising 0.1-20 mM KCl.

[0158] In some embodiments, the diluent is a buffer comprising 0.1-50 mM Na_2HPO_4.

[0159] In some embodiments, the diluent is a buffer comprising 0.1-50 mM NaH_2PO_4.

[0160] In some embodiments, the diluent is a buffer comprising 0.1-50 mM $CaCl_2$.

[0161] In some embodiments, the diluent is a buffer comprising 0.1-50 mM $MgCl_2$.

[0162] In some embodiments, the diluent is a buffer comprising 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$.

[0163] In some embodiments, the diluent is a buffer further comprising 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof.

[0164] In some embodiments, the diluent further comprises carbohydrates.

[0165] In some embodiments, the carbohydrates comprise D-glucose.

[0166] In some embodiments, the diluent comprises 1-100 mM D-glucose.

[0167] In some embodiments, the pharmaceutical composition comprises 0.1-50 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

[0168] In some embodiments, the pharmaceutical composition comprises 1-2 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

[0169] In some embodiments, the pharmaceutical composition comprises about 1.4 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

[0170] In some embodiments, the pharmaceutical composition further comprises 0.1-50 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

[0171] In some embodiments, the pharmaceutical composition comprises 0.5-1.5 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

[0172] In some embodiments, the pharmaceutical composition comprises about 0.79 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

[0173] In some embodiments, the pharmaceutical composition comprises 5-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$, and 0.1-50 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

[0174] In some embodiments, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM; (c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM; (d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and (e) water.

[0175] In some embodiments, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is 0.2 mM to 25 mM, 0.5 mM to 10 mM, 0.75 mM to 5 mM, or 1 mM to 2 mM.

[0176] In some embodiments, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is from about 1 mM to about 2 mM.

[0177] In some embodiments, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM.

[0178] In some embodiments, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is 0.2 mM to 25 mM, 0.3 mM to 15 mM, 0.4 mM to 5 mM, 0.5 mM to 1.5 mM, or 0.6 mM to 1 mM.

[0179] In some embodiments, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is from about 0.6 mM to about 1 mM.

[0180] In some embodiments, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM.

[0181] In some embodiments, the concentration of potassium chloride is 0.5 mM to 10 mM, 1 mM to 7.5 mM, or 2 mM to 5 mM.

[0182] In some embodiments, the concentration of potassium chloride is from about 2 mM to about 5 mM.

[0183] In some embodiments, the concentration of potassium chloride is about 3 mM.

[0184] In some embodiments, the concentration of sodium chloride is 25 mM to 250 mM, 100 mM to 160 mM, 110 mM to 140 mM, or 130 mM to 160 mM.

[0185] In some embodiments, the concentration of sodium chloride is from about 125 mM to 145 mM.

[0186] In some embodiments, the concentration of sodium chloride is about 130 mM.

[0187] In some embodiments, the concentration of sodium chloride is from about 140 mM to 160 mM.

[0188] In some embodiments, the concentration of sodium chloride is about 150 mM.

[0189] In some embodiments, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL,

(a) calcium ion (Ca^{2+}) at a concentration of about 0.1 mM to about 50 mM;

(b) magnesium ion (Mg^{2+}) at a concentration of about 0.1 mM to about 50 mM;

(c) potassium ion (K^+) at a concentration of about 0.1 mM to about 20 mM;

(d) sodium ion (Na^+) at a concentration of about 25 mM to about 250 mM;

(e) chloride ion (Cl^-) at a concentration of about 25 mM to about 250 mM; and

(f) water.

[0190] In some embodiments, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL,

(a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM;

(b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM;

(c) potassium ion (K^+) at a concentration of about 3 mM;

(d) sodium ion (Na^+) at a concentration of about 160 mM;

(e) chloride ion (Cl^-) at a concentration of about 160 mM; and

(f) water.

[0191] In some embodiments, the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4.

[0192] In some embodiments, the pharmaceutical composition lacks phosphate ion.

[0193] In some embodiments, each dose of the pharmaceutical composition comprises 10 mL of the diluent.

[0194] In some embodiments, the diluent further comprises an antioxidant.

[0195] In some embodiments, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof.

[0196] In some embodiments, the pharmaceutical composition is administered into the intrathecal space of the human subject.

[0197] In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid of the human subject.

[0198] In some embodiments, the pharmaceutical composition is administered into the brain of the human subject.

[0199] In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid in the brain of the human subject.

[0200] In some embodiments, the pharmaceutical composition is administered as a bolus injection.

[0201] In some embodiments, the method or the dosing regimen comprises administering the pharmaceutical composition as a bolus injection over 1 to 60 minutes, 1 to 50 minutes, 1 to 40 minutes, 1 to 30 minutes, 1 to 20 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes.

[0202] In some embodiments, the pharmaceutical composition is administered by infusion with a delivery pump.

[0203] In some embodiments, the pharmaceutical composition is administered by intracerebroventricular injection.

[0204] In some embodiments, the pharmaceutical composition is administered by intrathecal injection.

[0205] In some embodiments, each dose of the pharmaceutical composition comprises a diluent of a volume of 10 mL, and the diluent is an aCSF solution that lacks sodium phosphate.

[0206] In some embodiments, the pharmaceutical composition is administered by lumbar injection.

[0207] In some embodiments, the pharmaceutical composition does not comprise a preservative.

[0208] In some embodiments, the concentration of the compound in the pharmaceutical composition is about 0.1 mg/mL to about 250 mg/mL.

[0209] In some embodiments, the concentration of the compound in the pharmaceutical composition is from 6.7 mg/mL to 188 mg/mL, from 6.8 mg/mL to 187 mg/mL, from 3 mg/mL to 100 mg/mL, or from 3 mg/mL to 33 mg/mL.

[0210] In some embodiments, the concentration of the compound in the pharmaceutical composition is about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 4.5 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, 20 mg/mL, 22 mg/mL, 25 mg/mL, 28 mg/mL, or 33 mg/mL.

[0211] In some embodiments, the concentration of the compound in the pharmaceutical composition is 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL.

[0212] In some embodiments, the concentration of the compound in the pharmaceutical composition is about 3 mg/mL, 4 mg/mL, 4.5 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, 20 mg/mL, 22.5 mg/mL, 25 mg/mL, 27.5 mg/mL, 30 mg/mL, 32.5 mg/mL, 35 mg/mL, 37.5 mg/mL, 40 mg/mL, 42.5 mg/mL, 45 mg/mL, 47.5 mg/mL, 50 mg/mL, 52.5 mg/mL, 55 mg/mL, 57.5 mg/mL, 60 mg/mL, 62.5 mg/mL, 65 mg/mL, 67.5 mg/mL, 70 mg/mL, 72.5 mg/mL, 75 mg/mL, 77.5 mg/mL, 80 mg/mL, 82.5 mg/mL, 85 mg/mL, 87.5 mg/mL, 90 mg/mL, 92.5 mg/mL, 95 mg/mL, 97.5 mg/mL, 100 mg/mL, 102.5 mg/mL, 105 mg/mL, 107.5 mg/mL, 110 mg/mL, 112.5 mg/mL, 115 mg/mL, 117.5 mg/mL, 120 mg/mL, 122.5 mg/mL, 125 mg/mL, 127.5 mg/mL, 130 mg/mL, 132.5 mg/mL, 135 mg/mL, 137.5 mg/mL, 140 mg/mL, 142.5 mg/mL, 145 mg/mL, 147.5 mg/mL, 150 mg/mL, 152.5 mg/mL, 155 mg/mL, 157.5 mg/mL, 160 mg/mL, 162.5 mg/mL, 165 mg/mL, 167.5 mg/mL, 170 mg/mL, 172.5 mg/mL, 175 mg/mL, 177.5 mg/mL, 180 mg/mL, 182.5 mg/mL, 185 mg/mL, 187.5 mg/mL, 190 mg/mL, 192.5 mg/mL, 195 mg/mL, 197.5 mg/mL, 200 mg/mL, 202.5 mg/mL, 205 mg/mL, 207.5 mg/mL, 210 mg/mL, 212.5 mg/mL, 215 mg/mL, 217.5 mg/mL, 220 mg/mL, 222.5 mg/mL, 225 mg/mL, 227.5 mg/mL, 230 mg/mL, 232.5 mg/mL, 235 mg/mL, 237.5 mg/mL, 240 mg/mL, 242.5 mg/mL, 245 mg/mL, 247.5 mg/mL, or 250 mg/mL.

[0213] In some embodiments, the human subject is at most 18 years old at first loading dose.

[0214] In some embodiments, the human subject is at least 2 years old.

[0215] In some embodiments, the human subject is at least 6 months old.

[0216] In some embodiments, the human subject is from 6 months to 1 year old, or from 1 to 18, from 2 to 18, from 3 to 18, from 4 to 18, from 5 to 18, from 6 to 18, from 7 to 18, from 8 to 18, from 9 to 18, from 10 to 18, from 11 to 18, from 12 to 18, from 13 to 18, from 14 to 18, from 15 to 18, from 16 to 18, or from 17 to 18 years old.

[0217] In some embodiments, the human subject is a human from 6 months to 1 year old, or from 1 to 17, from 1 to 16, from 1 to 15, from 1 to 14, from 1 to 13, from 1 to 12, from 1 to 11, from 1 to 10, from 1 to 9, from 1 to 8, from 1 to 7, from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, or from 1 to 2 years old.

[0218] In some embodiments, the human subject is from 2 to 12 years old.

[0219] In some embodiments, the human subject is from 13 to 18 years old.

[0220] In some embodiments, the human subject is at least 13 years old.

[0221] In some embodiments, the race of the human subject is white.

[0222] In some embodiments, the race of the human subject is Asian.

[0223] In some embodiments, the race of the human subject is black or African American

[0224] In some embodiments, the human subject receives administration of at least one concomitant anti-seizure medication.

[0225] In some embodiments, the human subject receives administration of at least 3 or 4 concomitant anti-seizure medications.

[0226] In some embodiments, the human subject receives administration of fenfluramine.

[0227] In some embodiments, the disease or condition is treated.

[0228] In some embodiments, the disease or condition is Dravet Syndrome.

[0229] In some embodiments, the subject is characterized by having:

(i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or (ix) any combination of (i) – (viii).

[0230] In some embodiments, the subject is additionally characterized by not having one or more of the following:

(a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr;

(b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease;

(c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin;

(d) clinically, significantly unstable medical conditions other than epilepsy;

(e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy;

(f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation;

(g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt;

(h) clinically significant abnormal laboratory values prior to administering;

(i) aspartate aminotransferase or alanine aminotransferase >2.5-fold upper limit of normal, serum creatinine greater than an upper limit of normal or platelet count less than a lower limit of normal;

(j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering;

(k) a psychiatric or behavioral disorder;

(l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin; or

(m) any combination of (a) – (l).

[0231] In some embodiments, the human subject comprises a deletion, a truncation, a missense, or a nonsense mutation in *SCN1A* gene.

[0232] In some embodiments, at least one symptom of Dravet Syndrome in the human subject is reduced or ameliorated.

[0233] In some embodiments, the symptom of Dravet Syndrome is a seizure.

[0234] In some embodiments, the method or the dosing regimen reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration.

[0235] In some embodiments, the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

[0236] In some embodiments, the method or the dosing regimen results in an improvement in a non-seizure-related aspect.

[0237] In some embodiments, the improvement in the non-seizure-related aspect is sustained for at least 6 months, 8 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

[0238] In some embodiments, the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills.

[0239] In some embodiments, the cognitive or behavioral aspect is determined according to a standardized assessment.

[0240] In some embodiments, the standardized assessment comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C); or any combination thereof.

[0241] In some embodiments, (i) the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV); (ii) the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1; or (iii) the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1.

[0242] In some embodiments, the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, or 9.000.

[0243] In some embodiments, the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1.

[0244] In some embodiments, the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1.

[0245] In some embodiments, the administration (a) reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration; and (b) results in an improvement in a non-seizure-related aspect.

[0246] In some embodiments, the method or the dosing regimen results in no treatment-emergent serious adverse event (TESAE) in the human subject related to the administration of the compound of formula (I) or a salt thereof.

[0247] In some embodiments, the method or the dosing regimen further comprises assessing tolerability or effectiveness of the pharmaceutical composition.

[0248] In some embodiments, the method or the dosing regimen further comprises administrating at least one additional therapeutic agent or therapy.

[0249] In some embodiments, the at least one additional therapeutic agent or therapy is administered at the same time as the first loading dose, the second loading dose and/or the third loading dose.

[0250] In some embodiments, the at least one additional therapeutic agent or therapy is administered at the same time as the first maintenance dose and/or the one or more further maintenance doses.

[0251] In some embodiments, the at least one additional therapeutic agent or therapy is administered prior to administration of the first loading dose.

[0252] In some embodiments, the at least one additional therapeutic agent or therapy is administered after administration of the first loading dose.

[0253] In some embodiments, the at least one additional therapeutic agent or therapy comprises fenfluramine.

[0254] In some embodiments, a predicted brain concentration of the compound in the subject after administration of the pharmaceutical composition is at least 1, 2, 4, 6, 8, or 10 μg/mL.

[0255] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0256] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose comprising 70 mg of the compound of

formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0257] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

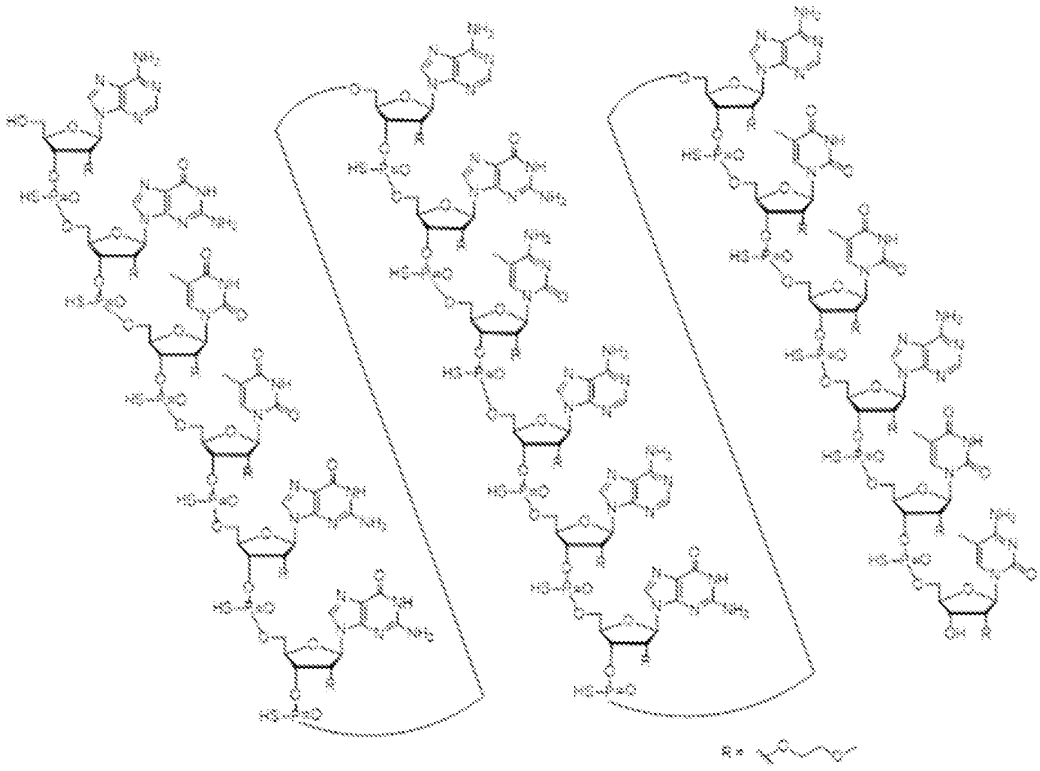
[0258] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0259] In some embodiments, after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0260] In some embodiments, after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0261] In some embodiments, after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, and intrathecal administration of the third loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

[0262] Provided herein, in some aspects, is a method of improving a non-seizure-related aspect in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

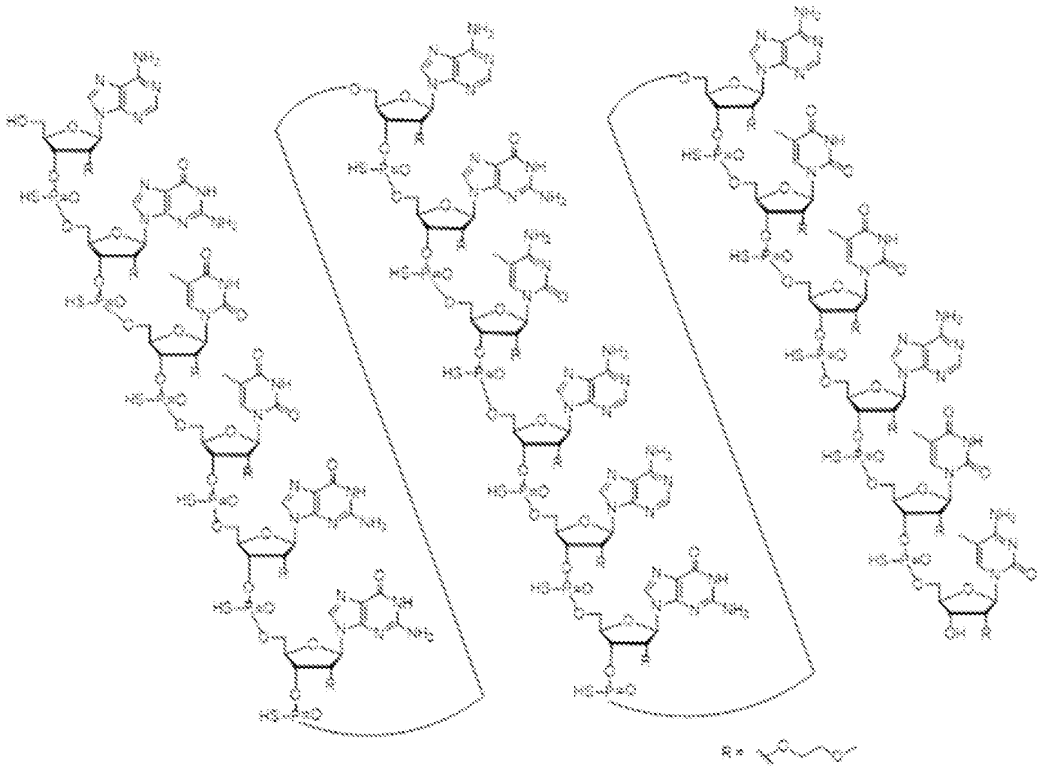
or a salt thereof, thereby improving a non-seizure-related aspect in the human subject, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills;

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose, and wherein each maintenance dose after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

[0263] Provided herein, in some aspects, is a method of improving a non-seizure-related aspect in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I), or a salt thereof, thereby improving a non-seizure-related aspect in the human subject, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills;

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose, and wherein each maintenance after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

[0264] In some embodiments, the cognitive or behavioral aspect is determined according to a standardized assessment.

[0265] In some embodiments, the standardized assessment comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C); or any combination thereof.

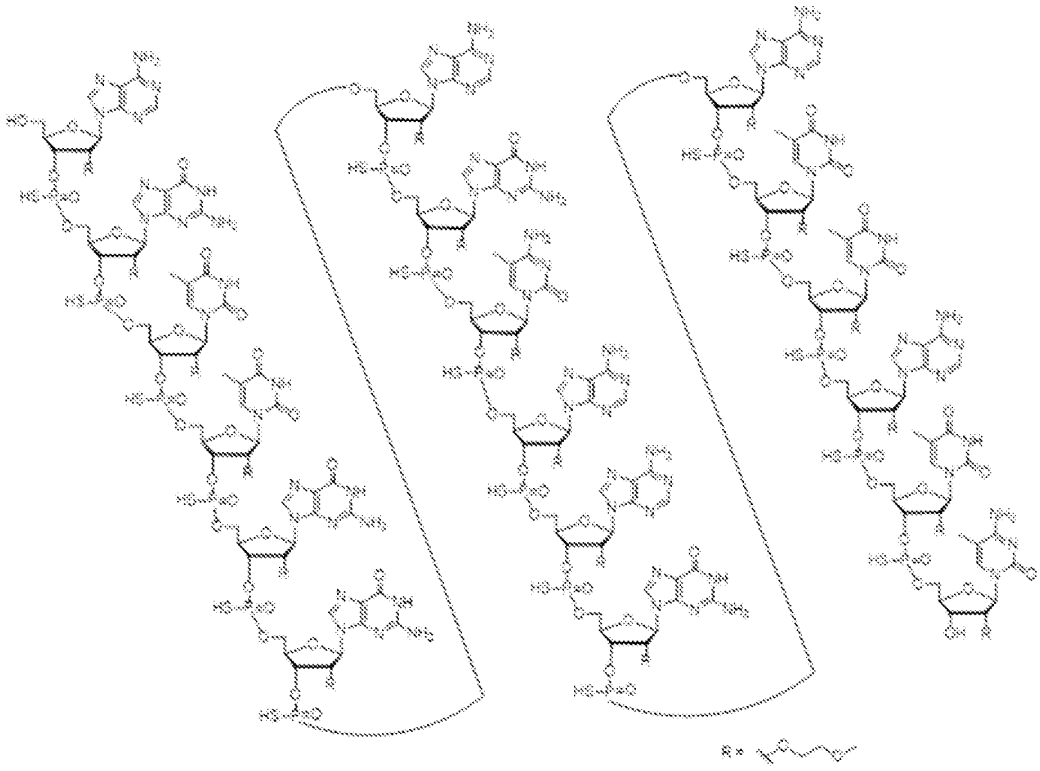
[0266] In some embodiments, (i) the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV); (ii) the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1; or (iii) standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1.

[0267] In some embodiments, the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, or 9.000.

[0268] In some embodiments, the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1.

[0269] In some embodiments, the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1.

[0270] Provided herein, in some aspects, is a method of reducing seizure frequency, seizure intensity, and/or seizure duration in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

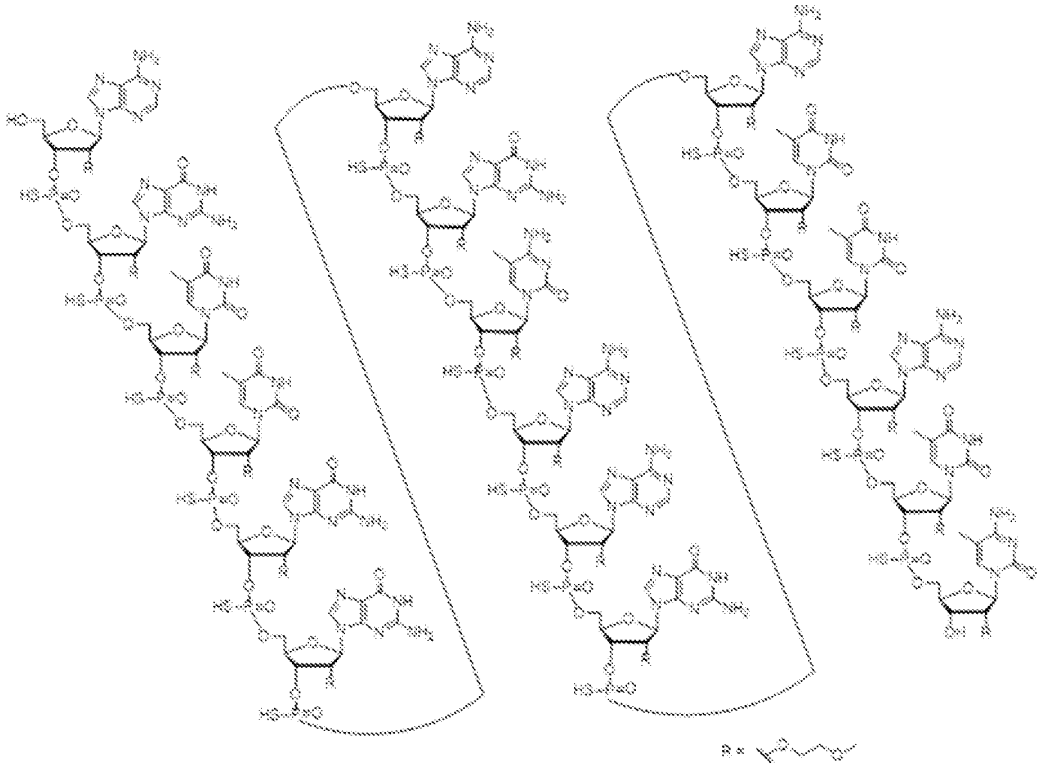
or a salt thereof, thereby reducing seizure frequency, seizure intensity, and/or seizure duration in the human subject,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose, and wherein each maintenance dose after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

[0271] Provided herein, in some aspects, is a method of reducing seizure frequency, seizure intensity, and/or seizure duration in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I), or a salt thereof, thereby reducing seizure frequency, seizure intensity, and/or seizure duration in the human subject,

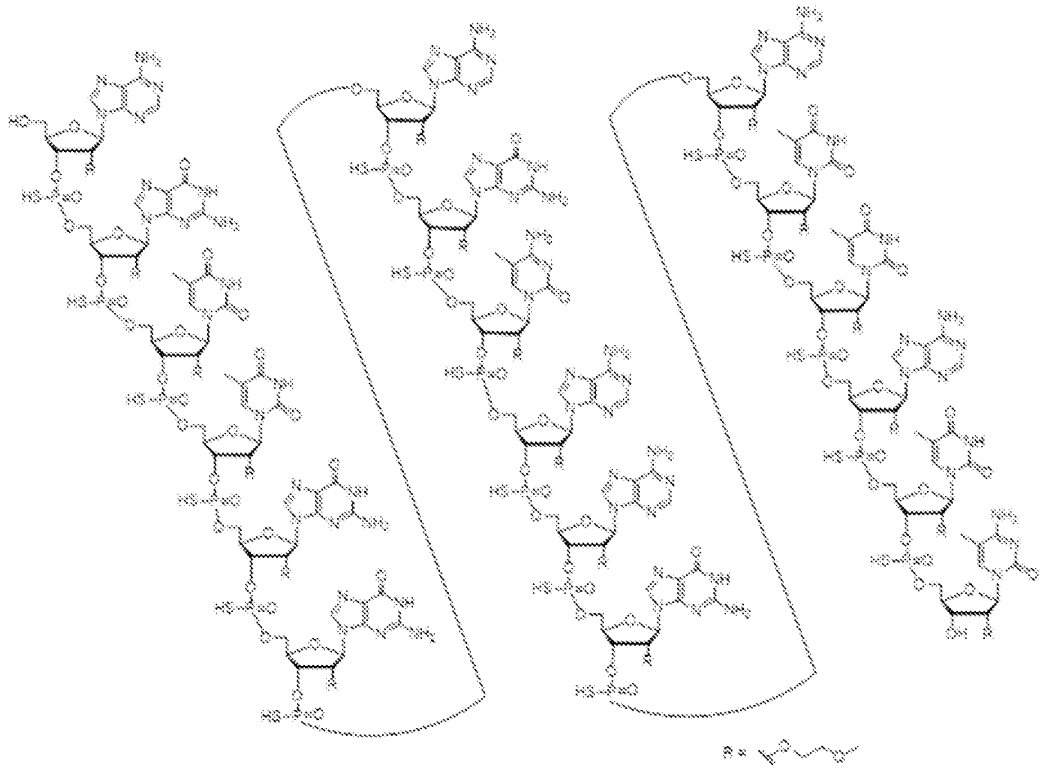
wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more

maintenance doses independently contains the compound at an amount of from about 25 to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose, and wherein each maintenance after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

[0272] Provided herein, in some aspects, is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising:

(1) obtaining a pharmaceutical composition that is a liquid composition comprising a compound in a diluent,

wherein the compound is according to the following chemical structure:



(I),

or a salt thereof, and

wherein the diluent comprises:

(a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM;

(b) magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM;

(c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM;

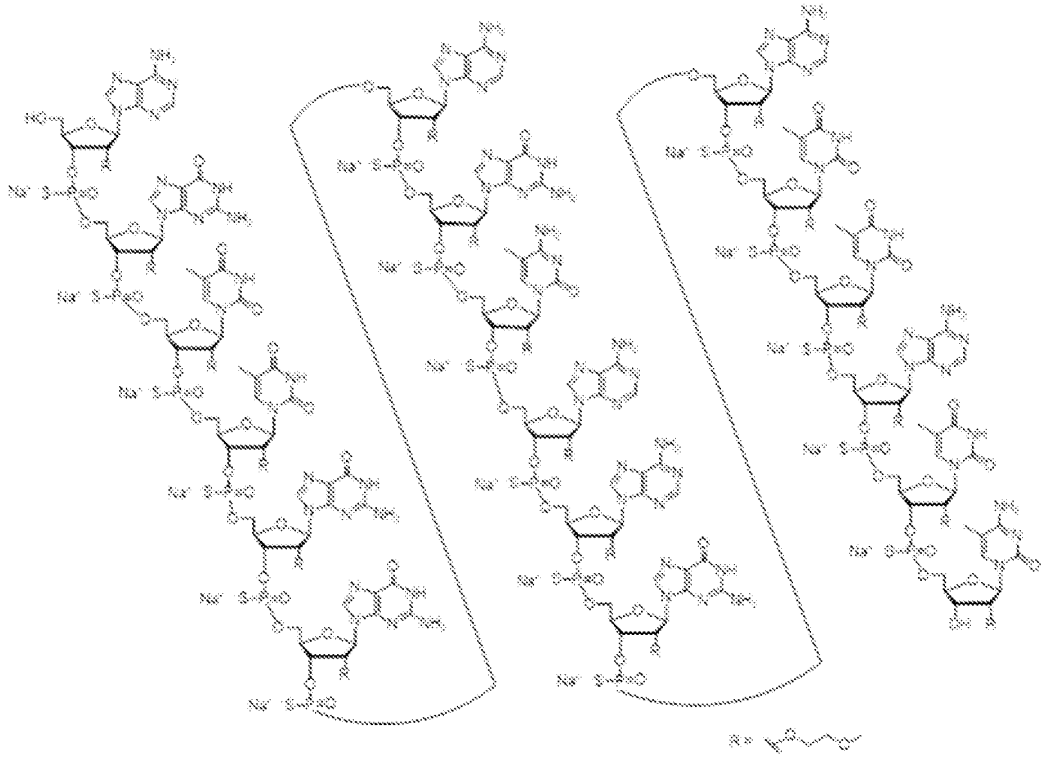
(d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and

(e) water; and

(2) administering to the human subject multiple doses of the pharmaceutical composition,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

[0273] In some embodiments, the obtaining comprises diluting a concentrate with the diluent up to one week prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the obtaining comprises diluting a concentrate with the diluent up to 3 days prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the obtaining comprises diluting a concentrate with the diluent up to 2 days prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the obtaining comprises diluting a concentrate with the diluent up to 24 hours prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the obtaining comprises diluting a concentrate with the diluent up to 5 hours prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the obtaining comprises diluting a concentrate with the diluent up to one hour prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent. In some of these embodiments, the compound has the following structure:



(II). In some of these embodiments, the pharmaceutical composition comprises the compound or a salt thereof at a concentration of about 3 mg/mL, about 4.5 mg/mL or about 7 mg/mL. In some of these embodiments, the concentrate comprises the compound or a salt thereof at a concentration of from about 20 mg/mL to about 200 mg/mL, from about 30 mg/mL to about 150 mg/mL, from about 40 mg/mL to about 120 mg/mL, from about 50 mg/mL to about 100 mg/mL, or from about 60 mg/mL to about 80 mg/mL. In some of these embodiments, the concentrate comprises the compound or a salt thereof at a concentration of about 33 mg/mL, about 45 mg/mL, or about 70 mg/mL. In some of these embodiments, the diluent lacks sodium phosphate. In some of these embodiments, the pharmaceutical composition comprises 1-2 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$. In some of these embodiments, the pharmaceutical composition comprises about 1.4 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$. In some of these embodiments, the pharmaceutical composition comprises 0.5-1.5 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$. In some of these embodiments, the pharmaceutical composition comprises about 0.79 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$. In some of these embodiments, the pharmaceutical composition comprises from about 1 mM to about 2 mM calcium chloride dihydrate. In some of these embodiments, the pharmaceutical composition comprises about 1.4 mM calcium chloride dihydrate. In some of these embodiments, the pharmaceutical composition comprises from about 0.6 mM to about 1 mM chloride hexahydrate. In some of these embodiments, the pharmaceutical composition comprises about 0.79 mM magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$). In some of these embodiments, the pharmaceutical composition comprises from about 2 mM to about 5 mM potassium chloride. In some of these embodiments, the pharmaceutical composition comprises about 3 mM potassium chloride. In some of these embodiments, the pharmaceutical composition comprises from about 125 mM to 145 mM sodium

chloride. In some of these embodiments, the pharmaceutical composition comprises about 130 mM sodium chloride. In some of these embodiments, the pharmaceutical composition comprises from about 140 mM to 160 mM sodium chloride. In some of these embodiments, the pharmaceutical composition comprises about 150 mM sodium chloride. In some of these embodiments, in the pharmaceutical composition: (i) the concentration of the compound is about 3 mg/mL, about 4.5 mg/mL or about 7 mg/mL; (ii) the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM; (iii) the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM; (iv) the concentration of potassium chloride is about 3 mM; and (v) the concentration of sodium chloride is about 150 mM. In some of these embodiments, the pharmaceutical composition comprises: (a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM; (c) potassium ion (K^+) at a concentration of about 3 mM; (d) sodium ion (Na^+) at a concentration of about 160 mM; (e) chloride ion (Cl^-) at a concentration of about 160 mM; and (f) water. In some of these embodiments, the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4. In some of these embodiments, the pharmaceutical composition lacks phosphate ion. In some of these embodiments, each dose of the pharmaceutical composition comprises 10 mL of the diluent. In some of these embodiments, the pharmaceutical composition is administered as a bolus injection. In some of these embodiments, the method or the dosing regimen comprises administering the pharmaceutical composition as a bolus injection over 1 to 60 minutes, 1 to 50 minutes, 1 to 40 minutes, 1 to 30 minutes, 1 to 20 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes. In some of these embodiments, the pharmaceutical composition is administered by infusion with a delivery pump. In some of these embodiments, the pharmaceutical composition is administered by intrathecal injection. In some of these embodiments, each dose of the pharmaceutical composition comprises a diluent of a volume of 10 mL, and the diluent is a solution that lacks sodium phosphate. In some of these embodiments, the pharmaceutical composition does not comprise a preservative. In certain embodiments, any method described herein treats or reduces the likelihood of developing the disease or condition in the human subject.

INCORPORATION BY REFERENCE

[0274] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application is specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0275] The features of the present disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0276] **FIGS. 1A-1B** depict a schematic representation of a target pre-mRNA that contains a nonsense-mediated RNA decay-inducing exon (NMD exon mRNA) and therapeutic agent-mediated exclusion of

the nonsense-mediated mRNA decay-inducing exon from the pre-mRNA to increase expression of the full-length target protein or functional RNA. **FIG. 1A** shows a cell divided into nuclear and cytoplasmic compartments. In the nucleus, a pre-mRNA transcript of a target gene undergoes splicing to generate processed mRNA, and this processed mRNA is exported to the cytoplasm and translated into target protein. For this target gene, some fraction of the processed mRNA contains a nonsense-mediated mRNA decay-inducing exon (NMD exon mRNA) that is degraded in the cytoplasm, thus leading to no target protein production. **FIG. 1B** shows an example of the same cell divided into nuclear and cytoplasmic compartments. Treatment with a therapeutic agent, such as an antisense oligomer (ASO), promotes the exclusion of the nonsense-mediated mRNA decay-inducing exon from the pre-mRNA and results in an increase in processed mRNA, which is in turn translated into higher levels of target protein.

[0277] **FIG. 1C** is a schematic representation of therapeutic ASO-mediated exclusion of a nonsense-mediated mRNA decay-inducing exon from a pre-mRNA, which decreases non-productive processed mRNA (*e.g.,* with an NMD exon) and increases productive mRNA (*e.g.,* without an NMD exon) and increases expression of the full-length target protein from the productive mRNA.

[0278] **FIG. 1D** shows identification of an exemplary sequence in the *SCN1A* gene that encodes a nonsense-mediated mRNA decay (NMD)-inducing exon. The identification of the sequence in the *SCN1A* gene that encodes the NMD-inducing exon using comparative genomics is shown, visualized in the UCSC genome browser. The upper panel shows a graphic representation of the *SCN1A* gene to scale. The conservation level across 100 vertebrate species is shown as peaks. The highest peaks correspond to exons (black boxes), while no peaks are observed for the majority of the introns (lines with arrow heads). Peaks of conservation were identified in intron 20 (NM_006920), shown in the middle panel. Inspection of the conserved sequences identified an exon-like sequence of 64 bp (bottom panel, sequence highlighted in grey) flanked by 3′ and 5′ splice sites (underlined sequence). Inclusion of this exon leads to a frameshift and the introduction of a premature termination codon in exon 21 rendering the transcript a target of NMD.

[0279] **FIG. 2** shows a study design timeline for monitoring wild type (WT) and Dravet Syndrome (DS) mice as well as a Kaplan-Meier curve showing DS and WT littermate mice monitored to 14 weeks for survival.

[0280] **FIG. 3** shows an experimental design for the EEG seizure monitoring study in DS mice and their WT littermates.

[0281] **FIGS. 4A-4E** show the results of monitoring seizures in mice administered with ASO-22 (sequence set forth in SEQ ID NO: 42) or phosphate buffered saline (PBS). **FIG. 4A** shows exemplary EEG recordings in DS mice. **FIG. 4B** shows the number of seizures occurring in various regions of the brain in the two mice groups. *Indicates $p<0.05$. **FIG. 4C** summarizes the total number of spontaneous seizures (generalized and focal) recorded between Postnatal Day 22 (P22) and Postnatal Day 46 (P46) in DS mice dosed with PBS (n=21) or ASO-22 (n=21). *Indicates $p<0.05$. **FIG. 4D** shows the number of mice that had a number of seizures in each group. **FIG. 4E** shows the effect of ASO-22 on the latency to the first recorded seizure between P22 and P46 in DS mice dosed with PBS (n=21) or ASO-22 (n=21).

[0282] **FIGS. 5A-5G** show that a single ICV injection of 20 μg ASO-22 at P2 results in reduced sudden unexpected death in epilepsy (SUDEP) incidence and increased $Na_V1.1$ protein expression in DS mice. **FIG. 5A** is a schematic for the experimental design. **FIGS. 5B, 5C, 5D, 5E, 5F,** and **5G** illustrate the ASO-22 exposure, fold change in *Scn1a* gene expression, and $Na_V1.1$ expression in brain tissues at 7 weeks **(FIGS. 5B-5D)** or 14 weeks **(FIGS. 5E-5G)** after a single ICV injection of ASO-22 (20 μg) or PBS at P2.

[0283] **FIGS. 6A-6B** show the percent survival of DS and WT mice after a single ICV injection of ASO-22 (60 μg) or PBS on P14. **FIG. 6A** is a schematic showing the study design. **FIG. 6B** is a line chart showing the percent survival (y-axis) of the mice in various conditions (wild-type mice treated with PBS; wild-type mice treated with ASO-22; *Scn1a*$^{+/-}$ mice treated with ASO-22; and *Scn1a*$^{+/-}$ mice treated with PBS) over the course of days (x-axis).

[0284] **FIGS. 7A-7F** show the ASO-22 exposure, *Scn1a* expression, and $Na_V1.1$ expression in brain tissues at P35 **(FIGS. 7A-7C)** and P90 **(FIGS. 7D-7F)** after a single ICV injection of ASO-22 (60 μg) or PBS on P14. **FIG. 7A** illustrates the concentration of ASO-22 in brain tissue (μg/g), **FIG. 7B** shows the fold change of *Scn1a* gene expression, and **FIG. 7C** shows the $Na_V1.1$ expression relative to adult brain tissue at P35 for wild-type and *Scn1a*$^{+/-}$ mice after ICV injection with either ASO-22 (60 μg) or PBS on P14. **FIG. 7D** illustrates the concentration of ASO-22 in brain tissue (μg/g), **FIG. 7E** shows the fold change of *Scn1a* gene expression, and **FIG. 7F** shows the $Na_V1.1$ expression relative to adult brain tissue at P90 for wild-type and *Scn1a*$^{+/-}$ mice after ICV injection with either ASO-22 (60 μg) or PBS on P14.

[0285] **FIG. 8** shows the experimental conditions and numbers of monkeys used per group.

[0286] **FIGS. 9A-9B** show the levels of ASO-22 in the cynomolgus monkey brain on study day 3 **(FIG. 9A)** and day 29 **(FIG. 9B)**.

[0287] **FIGS. 10A-10B** show the levels of $Na_V1.1$ protein in cynomolgus monkey brain regions on study day 3 **(FIG. 10A)** and day 29 **(FIG. 10B)**.

[0288] **FIGS. 11A-11B** show the percentages of productive *SCN1A* gene to total *SCN1A* gene as an evaluation of target engagement in cynomolgus monkeys on study day 3 **(FIG. 11A)** and day 29 **(FIG. 11B)**.

[0289] **FIG. 12A** shows the plasma pharmacokinetics in cynomolgus monkey after Intrathecal Administration of ASO-22. **FIG. 12B** shows the levels of ASO-22 in the cynomolgus monkey cerebrospinal fluid (CSF) on study day 3 and 29.

[0290] **FIGS. 13A-13D** depict identification of an alternative splicing event in *SCN1A* that results in NMD. **FIG. 13A** shows *SCN1A* splicing isoforms with or without inclusion of the alternative exon in ReNcells as demonstrated by RT-PCR. **FIG. 13B** shows results from an evaluation of the alternative splice event of the *SCN1A* gene in the cerebral cortex from 4 species. **FIG. 13C** shows an image of a TBE PAGE gel of RT-PCR products corresponding to *Scn1a* productive (lower bands, 498 bp) and non-productive transcript (upper bands, 562 bp) amplified from total RNA extracted from WT C57BL/6J mouse brains from P0 to P20 and at 10 months. Mouse *Gapdh* was used as a loading control. **FIG. 13D**

summarizes expression of *Scn1a* productive and non-productive transcript in postnatal mouse brains, calculated with optical densities of PCR products shown in **FIG. 13C**.

[0291] **FIGS. 14A-14E** depict that selected ASOs suppressed the NMD splicing event and increased the expression of productive *SCN1A* mRNA in ReNcells. **FIG. 14A** is an exemplary TBE PAGE gel image of RT-PCR products corresponding to *SCN1A* productive (lower bands, 549 bp) and non-productive mRNA containing exon 20X (upper bands, 613 bp) in ReNcells after gymnotic (free) uptake of ASO. **FIG. 14B** is a histogram showing the percentage of Exon 20X inclusion (y-axis) after treatment with various ASOs (x-axis). **FIG. 14C** is a histogram showing the fold change in *Scn1a* gene expression (y-axis) after treatment with various ASOs (x-axis). **FIG. 14D** is a graph illustrating the fold change in *Scn1a* gene expression (y-axis) after treatment with ASO-22 at various concentrations in nM (x-axis) by free uptake or nucleofection. **FIG. 14E** is a histogram showing the fold change in *Scn1a* gene expression (y-axis) after treatment with either a non-targeting ASO (NT) or ASO-22, each at various concentrations (20 μM, 8 μM, 3 μM) (x-axis).

[0292] **FIGS. 15A-15C** show dose-dependent effects of ASO-22 on splicing and expression of *SCN1A* mRNA in ReNcells. **FIG. 15A** shows an exemplary TBE PAGE gel image of RT-PCR products corresponding to *SCN1A* productive mRNA (lower bands, 549 bp) and non-productive mRNA containing exon 20X (upper bands, 613 bp) in ReNcells. *RPL32* was used as the loading control. **FIG. 15B** is a histogram showing the fold change in *SCN1A* productive mRNA after treatment with various controls (sham, sham with cycloheximide, non-targeting (NT) ASO, or NT ASO with cycloheximide), ASO-22 at various concentrations (20 μM, 8 μM, 3 μM), or ASO-22 with cycloheximide at various concentrations (20 μM, 8 μM, 3 μM) as indicated on the x-axis. **FIG. 15C** is a histogram showing the fold change in *SCN1A* non-productive mRNA after treatment with various controls (sham, sham with cycloheximide, non-targeting (NT) ASO, or NT ASO with cycloheximide), ASO-22 at various concentrations (20 μM, 8 μM, 3 μM), or ASO-22 with cycloheximide at various concentrations (20 μM, 8 μM, 3 μM) as indicated on the x-axis.

[0293] **FIGS. 16A-16H** show that ASO-22 ICV injection causes dose-dependent and durable increases in *Scn1a* mRNA and $Na_V1.1$ protein expression in mouse brain. **FIG. 16A** is a schematic illustrating the experimental study design for ASO-22. **FIG. 16B** is a graph showing the percentage of Exon 21X inclusion (amount of non-productive *Scn1a* transcript) after a single ICV injection of ASO-22 at 0.3, 1, 3, 5, 10, 20 or 30 μg (x-axis). **FIG. 16C** is a graph showing the fold change in mRNA (amount of productive *Scn1a* transcript) after a single ICV injection of ASO-22 at 0.3, 1, 3, 5, 10, 20 or 30 μg (x-axis). **FIG. 16D** is a graph showing the percentage of $Na_V1.1$ protein expression relative to adult brain tissue after a single ICV injection of ASO-22 at 0.3, 1, 3, 5, 10, 20 or 30 μg (x-axis). **FIG. 16E** is a histogram showing the effect of ASO-22 (fold change in mRNA) on expression of the 9 VGSC α subunit genes in mouse brain. Expression of *Scn1a* productive transcript and the remaining 8 VGSC α subunit genes plus Nax (*Scn7a*) in mouse brains following ICV injection of PBS, a non-target ASO control (NT, 20 μg) or different doses of ASO-22 was measured by probe-based qPCR. Expression of each transcript was first normalized to endogenous *Gapdh* then compared to PBS injection controls. **FIG. 16F** is a

schematic of the experimental study design used to determine the durability of the ASO-22 effect in brain. **FIG. 16G** shows the relative expression of productive *Scn1a* transcript (y-axis) after treatment with ASO-22 or PBS over the course of days (x-axis). **FIG. 16H** shows the percentage of $Na_V1.1$ protein expression relative to adult brain tissue (y-axis) after treatment with ASO-22 or PBS over the course of days (x-axis).

[0294] FIG. 17 shows dose-dependent effects of ASO-22 on the expression of *Scn1a* mRNA in ICV-injected neonatal mouse brains (§ = nonproductive; * = productive).

[0295] FIG. 18 shows dose-dependent effects of ASO-22 on the expression of $Na_V1.1$ in ICV-injected neonatal mouse brains.

[0296] FIG. 19 shows expression of *Scn1a* mRNA in mouse brains at different post-injection days (§ = nonproductive; * = productive).

[0297] FIG. 20 shows expression of $Na_V1.1$ in mouse brains at different post-injection days.

[0298] FIG. 21 shows validation of the two anti-$Na_V1.1$ antibodies used in the Examples. Specificity of the two anti-$Na_V1.1$ antibodies, Alomone ASC-001 and NeuroMab 75-023, was tested using total protein prepared from a *Scn1a*$^{-/-}$ mouse brain (middle lane) and brains of two WT littermates (left and right lanes).

[0299] FIG. 22 shows a schematic representation of clinical manifestations of Dravet Syndrome and their relative incidences according to age. AA: atypical absences; AE: acute encephalopathy; CG: crouching gait; CPS: complex partial seizures; DD: developmental delay; DS: Dravet syndrome; EEG: electroencephalogram; FSz: complex febrile seizures; GMS: generalized motor seizures; HS: hyperthermia sensitivity; m: month; MSz: myoclonic seizures; OS: obtundation status; SE: status epilepticus; SUDEP: sudden unexpected death in epilepsy; y: years; * Moderate fever for 60%, mostly clonic generalized and unilateral motor seizures; ** Difficult to distinguish between AA and CPS without ictal EEG recording, so their precise incidence is unknown. *See, e.g.,* Gataullina and Dulac, 2017, of which the entire content is incorporated herein by reference.

[0300] FIG. 23 shows TANGO (Targeted Augmentation of Nuclear Gene Output) that may be used to treat Dravet syndrome.

[0301] FIG. 24 shows the transformative potential of TANGO technology in Dravet syndrome.

[0302] FIG. 25 shows the study design. Phase 1/2a open-label, 2-part study conducted at approximately 20 sites in the United States.

[0303] FIG. 26 shows a schematic representation of the study design.

[0304] FIG. 27 shows patient inclusion and exclusion criteria.

[0305] FIG. 28 shows study assessments.

[0306] FIG. 29 shows the workflow of a Phase 1/2a study of Compound-A.

[0307] FIG. 30 shows two plots summarizing cerebrospinal fluid (CSF) exposure of Compound-A in single ascending dose (SAD) cohorts and multiple ascending dose (MAD) cohorts, respectively.

[0308] FIGS. 31A-31B show two plots summarizing median percent change in seizure frequency from baseline level to the period between Day 29 and 84 post administration of Compound-A (in reference to

1st dose, Day 29-84) in 2- to 12-year-old subjects (**FIG. 31A**) and 13- to 18-year-old (**FIG. 31B**), all combined by cohort.

[0309] **FIGS. 32A-32B** show two plots summarizing median percent change in seizure frequency from baseline in patients of all ages as combined by cohort in the period between Day 1 and Day 84 (Day 1-84) post administration (**FIG. 32A**), and in the period between Day 29-84 (Day 29-84) post administration (**FIG. 32B**).

[0310] **FIGS. 33A-33C** show the study design for the Phase 1/2a clinical trials for ASO-1. **FIG. 33A** shows the study design and dosing schedule using the Single Ascending Dose (SAD) regime (MONARCH) before patients can become eligible to enroll in the LONGWING OLE. **FIG. 33B** shows the study design and dosing schedule using the Multiple Ascending Dose regime (MONARCH) before patients can become eligible to enroll in the LONGWING OLE. **FIG. 33C** shows the study design and dosing schedule using the Multiple Ascending Dose regime (ADMIRAL) before patients can become eligible to enroll in the LONGWING OLE.

[0311] **FIG. 34** shows a plot summarizing median percent change in seizure frequency from baseline in patients of all ages receiving 30 mg, 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study and the mean percent change in seizure frequency from baseline in patients of all ages receiving 30 mg, 45 mg, or 70 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the ADMIRAL study.

[0312] **FIG. 35** shows a plot summarizing median percent change in seizure frequency from baseline in patients of all ages receiving 30 mg or 45 mg of ASO-1 as combined by cohort in the period between Day 29 and Day 85 post administration in the MONARCH study and the mean percent change in seizure frequency from baseline in patients of all ages receiving 30 mg, 45 mg, or 70 mg of ASO-1 as combined by cohort in the period between Day 29 and Day 87 post administration in the ADMIRAL study.

[0313] **FIGS. 36A-36B** show plots summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg or 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study. **FIG. 36A** shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study. **FIG. 36B** shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study.

[0314] **FIGS. 37A-37C** show plots summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg, 45 mg, or 70 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. **FIG. 37A** shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL

study. **FIG. 37B** shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. **FIG. 37C**shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 70 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study.

[0315] FIG. 38 shows a plot summarizing mean percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 2 or 3 doses of 70 mg of ASO-1, as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study.

[0316] FIGS. 39A-39B show plots summarizing mean percent change in seizure frequency from baseline in all patients receiving 30 mg, 45 mg, or 70 mg of ASO-1, as analyzed 3 or 6 months post last dose administration. **FIG. 39A** shows a plot summarizing mean percent change in seizure frequency from baseline in all patients receiving 30 mg, 45 mg, or 70 mg of ASO-1, as analyzed 3 months post last dose administration. **FIG. 39B** shows a plot summarizing mean percent change in seizure frequency from baseline in all patients receiving 30 mg, 45 mg, or 70 mg of ASO-1, as analyzed 6 months post last dose administration.

[0317] FIGS. 40A-40B show plots summarizing mean percent change in seizure frequency from baseline in all patients receiving 2 or 3 doses of 70 mg of ASO-1, as analyzed 3 or 6 months post last dose administration in the ADMIRAL study. **FIG. 40A** shows a plot summarizing mean percent change in seizure frequency from baseline in all patients receiving 2 or 3 doses of 70 mg of ASO-1, as analyzed 3 months post last dose administration in the ADMIRAL study. **FIG. 40B** shows a plot summarizing mean percent change in seizure frequency from baseline in all patients receiving 2 or 3 doses of 70 mg of ASO-1, as analyzed 6 months post last dose administration in the ADMIRAL study.

[0318] FIG. 41 shows a plot summarizing mean percent change in seizure frequency from baseline in all patients receiving 30 mg or 45 mg of ASO-1 maintenance dose every 4 months in the OLE study.

[0319] FIGS. 42A-42B show plots showing improvement in receptive communication and expressive communication in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale. **FIG. 42A** shows a plot showing improvement in receptive communication in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale. **FIG. 42B** shows a plot showing improvement in receptive communication in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale.

[0320] FIG. 43 shows a plot showing improvement in gross motor skills in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale.

[0321] **FIG. 44** shows a plot showing improvement in executive function in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured by Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) Global Executive Composite (GEC). A decrease in BRIEF-P score indicates an improvement in executive function.

[0322] **FIGS. 45A-45B** show plots showing improvement in clinical and caregiver impression of change in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale. **FIG. 45A** shows a plot showing improvement in clinical impression of change in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale. **FIG. 45B** shows a plot showing improvement in caregiver impression of change in patients receiving ASO-1 for over one year of dosing compared to observed natural history of the disease measured on the Vineland (VABS-III) scale. Measurements for Clinical Global Impression of Change (CGI-C) (**FIG. 45A**) and Caregiver Global Impression of Change (CaGI-C) (**FIG. 45B**) are recorded as scores on a 7-point scale, presented in Least Square (LS) means, shown with a 95% confidence interval (CI).

[0323] **FIG. 46** is a line chart illustrating the median percentage change of convulsive seizure frequency from baseline after two or three administrations of a dose of ASO (30 mg, 45 mg, or 70 mg) over time measured in days after the first administration. The dotted line is the baseline, and data on this line indicates no change from baseline. Reductions in convulsive seizure frequency are represented by data points below the dotted line. The number of days elapsed since the first dosage administration are indicated on the x-axis (*e.g.,* D1-28 represents day 1 to day 28 after the first loading dose the patient received).

[0324] **FIGS. 47A-47D** are data showing reductions in convulsive seizure frequency from baseline after administration of various doses of ASO-1. **FIGS. 47A-47C** are histograms illustrating the median percentage change in convulsive seizure frequency at three months (**FIG. 47A**), four months (**FIG. 47B**), and six months (**FIG. 47C**) after the administration of the last loading dose compared to baseline convulsive seizure frequency. Left columns in each histogram represent data from cohorts administered with one 70-mg loading dose (Single Ascending Dose, or SAD). Center columns represent data from the cohort that was administered with two loading doses, each at 70 mg (Multiple Administered Doses, or MAD – 2 doses). Right columns represent data from the cohort that was administered with three loading doses, each at 70 mg (Multiple Administered Doses, or MAD – 3 doses). Data were evaluated from eight participants in the SAD cohort (n=8), five participants in the MAD – 2 doses cohort (n=5), and five participants in the MAD – 3 doses cohort (n=5) at the three-month mark. Data were evaluated from eight participants in the SAD cohort (n=8), five participants in the MAD – 2 doses cohort (n=5), and four participants in the MAD – 3 doses cohort (n=4) at the four-month mark. Data were evaluated from seven participants in the SAD cohort (n=7), five participants in the MAD – 2 doses cohort (n=5), and four participants in the MAD – 3 doses cohort (n=4) at the six-month mark. A reduction in convulsive seizure frequency from baseline corresponds to a negative percentage. **FIG. 47D** is a line chart showing the reductions in convulsive seizure frequency from baseline after MONARCH and ADMIRAL participants

were administered either 1, 2, or 3 doses of 70 mg ASO-1. ASO-1 was administered on Days 1, 29 and 57 in MONARCH, and on Days 1, 57 and 85 in ADMIRAL. MONARCH ended at Day 225 and ADMIRAL ended at Day 253. D represents "day."

[0325] **FIGS. 48A-48B** are histograms illustrating the median percentage change in convulsive seizure frequency at three, four, and six months after the administration of the last loading dose of a single 70-mg dose (**FIG. 48A**), or the last loading dose of multiple 70-mg doses (**FIG. 48B**) compared to baseline convulsive seizure frequency. Left columns in each histogram represent data from three months after administration of the last loading dose for a single 70-mg dose (**FIG. 48A**, left column), or multiple 70-mg doses (**FIG. 48B**, left column). Center columns in each histogram represent data from four months after administration of the last loading dose for a single 70-mg dose (**FIG. 48A**, center column), or multiple 70-mg doses (**FIG. 48B**, center column). Right columns in each histogram represent data from six months after administration of the last loading dose for a single 70-mg dose (**FIG. 48A**, right column), or multiple 70-mg doses (**FIG. 48B**, right column). Data were evaluated in the single 70-mg loading dose condition from eight participants (n=8) at the third month after loading dose injection, eight participants (n=8) at the fourth month, and seven (n=7) participants at the sixth month. Data were evaluated in the multiple 70-mg loading dose condition from ten participants (n=10) at the third month after the last loading dose injection, ten participants (n=10) at the fourth month, and nine participants (n=9) at the sixth month. A reduction in convulsive seizure frequency from baseline corresponds to a negative percentage.

[0326] **FIGS. 49A-49B** are bar charts showing the percentage change in convulsive seizure frequency (CSF) compared to baseline seizure frequency. **FIG. 49A** shows CSF data at 3 months, and **FIG. 49B** shows CSF data at 6 months after the last 70-mg dose for participants who were administered one, two, or three 70-mg doses. A reduction in seizure frequency is denoted as a negative percentage value. Bars that extend past the dotted line indicate a greater than 50% reduction in convulsive seizures. Each bar represents the data of a single patient, with the age of the patient located immediately below the bar.

[0327] **FIG. 49C** is a bar chart of data for Clinical Global Impression of Change (CGI-C), and **FIG. 49D** is a bar chart of data for Caregiver Global Impression of Change (CaGI-C), and both scales indicate improvements in the overall clinical status of patients who received single or multiple doses of 70 mg ASO-1 6 months after their last dose. The x-axis shows the possible scores* of the CGI-C and CaGI-C from Very Much Improved to Very Much Worse. The y-axis shows the number of patients. Percentages at the top of each bar represent the fraction of patients in each CGI-C and CaGI-C score. LS = "least-squares." *CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), or 7 (Very much worse). Sample size, N=63 for both assessments. Phase 1/2a data-cut was December 12, 2023 (after End of Study). †Mixed-effects model for repeated measures constructed with data from Phase 1/2a studies. One patient who received an incorrect dose and three patients with <4 seizures during baseline were excluded. Patients' quality of life (QoL) was improved as demonstrated by model outcomes for the EQ-VAS component of the EQ-5D-Y assessment.

[0328] **FIGS. 50A-50C** illustrate the median percentage change in convulsive seizure frequency (CSF) in the SWALLOWTAIL/LONGWING OLE studies. **FIG. 50A** is a line chart of the median percentage change in convulsive seizure frequency from the Phase 1/2 study's baseline seizure frequency over time (in weeks, x-axis) when ASO is administered at regular intervals, represented by "ASO-1" rectangles. Square data points represent data combined from the SWALLOWTAIL/LONGWING open-label extension (OLE) studies in which patients were administered either 30- or 45-mg doses at regular intervals (at weeks 1-4, weeks 17-20, and weeks 33-36). Triangular data points represent data from patients who had received three 70-mg doses from the Phase 1/2 study, after which 24 weeks had elapsed since the last dose, and a 45-mg maintenance dose was administered in the OLE studies. **FIG. 50B** is a line chart of the median percentage change in convulsive seizure frequency from the Phase 1/2 study's baseline seizure frequency over time (in months, x-axis) when ASO is administered at regular intervals of approximately every four months as indicated by the arrows in the axis, where the first dose is administered at the start of month 1, the second dose is administered at approximately the end of month 4, the third dose is administered at approximately the end of month 8, the fourth dose is administered at approximately the end of month 12, *etc.* Triangular data points represent data for participants who received one, two, or three 70-mg doses of ASO-1 in the MONARCH/ADMIRAL Phase 1/2a studies, followed by 30-mg or 45-mg maintenance doses of ASO-1 during the SWALLOWTAIL/LONGWING OLE studies over the course of 24 months. **FIG. 50C** is a line chart of the median percentage change in convulsive seizure frequency from the Phase 1/2 study's baseline seizure frequency over the course of 8 months. Participants who received one 70-mg dose in the MONARCH Phase 1/2a study, followed by 30-mg maintenance doses in the SWALLOWTAIL OLE study, are represented by light gray diamond data points. Participants who received two 70-mg doses in the ADMIRAL Phase 1/2a study, followed by 45-mg maintenance doses in the LONGWING OLE study, are represented by square data points. Participants who received three 70-mg doses in the ADMIRAL Phase 1/2a study, followed by 45-mg maintenance doses in the LONGWING OLE study, are represented by dark gray diamond data points.

[0329] **FIG. 51** is a schematic illustrating the four main domains (communication, daily living skills, socialization, and motor skills) and eleven subdomains of cognition and behavior evaluated in a Vineland Adaptive Behavior Scale (VABS-III). Highlighted subdomains were selected for further analysis. Dravet Syndrome (DS) patients experience floor effects in other subdomains.

[0330] **FIG. 52** is a chart showing the change in Growth Scale Value (GSV) (x-axis) for various cognitive and behavioral skills in ADMIRAL participants as assessed by Vineland Adaptive Behavior Scales, Third Edition (Vineland-3). Bars to the right of the 0 mark (positive direction) indicate improvement in a specified behavior, while bars to the left of the 0 mark (negative direction) indicate worsening of a specified behavior. Eighteen ADMIRAL Phase 1/2 study patients were evaluated at the initial screen, and seventeen were evaluated at week 36.

[0331] **FIGS. 53A-53B** are bar charts showing Clinical Global Impression of Change (CGI-C) (**FIG. 53A**) and Caregiver Global Impression of Change (CaGI-C) (**FIG. 53B**) measurements recorded as scores on a 7-point scale, presented in Least Square (LS) means, shown with a 95% confidence interval

(CI). The BUTTERFLY natural history scores were used as the baseline reference scores (dotted line). MONARCH/ADMIRAL scores for both CGI-C and CaGI-C were lower than each of the reference BUTTERFLY scores, indicating improvement in patient condition after treatment with at least a 30-mg dose of ASO.

[0332] **FIGS. 54A-54B** are histograms illustrating the results of Vineland-3 for expressive communication (**FIG. 54A**) and receptive communication (**FIG. 54B**) for participants of the BUTTERFLY natural history study (**FIGS. 54A-54B**, left columns) and ADMIRAL Phase 1/2 study (**FIGS. 54A-54B**, right columns) at the end of 36 weeks. Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV. At week 36 (or month 9), participants of the BUTTERLY natural history study had a change in GSV of 0.118 in expressive communication and -3.148 in receptive communication; participants of the ADMIRAL Phase 1/2 study had a change in GSV of 3.222 in expressive communication and 6.250 in receptive communication.

[0333] **FIGS. 55A-55B** are histograms illustrating the results of Vineland-3 for personal skills (**FIG. 55A**) and interpersonal skills (**FIG. 55B**) for participants of the BUTTERFLY natural history study (**FIGS. 55A-55B**, left columns) and ADMIRAL Phase 1/2 study (**FIGS. 55A-55B**, right columns) at the end of 36 weeks. Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV. At week 36 (or month 9), participants of the BUTTERLY natural history study had a change in GSV of 0.484 in personal skills and -1.434 in interpersonal relationships skills; participants of the ADMIRAL Phase 1/2 study had a change in GSV of 1.855 in personal skills and 4.407 in interpersonal skills.

[0334] **FIGS. 56A-56C** are charts showing the change in Growth Scale Value (GSV) (x-axis) for various cognitive and behavioral skills in SWALLOWTAIL and LONGWING participants as assessed by Vineland Adaptive Behavior Scales, Third Edition (Vineland-3). Bars to the right of the 0 mark (positive direction) indicate improvement in a specified behavior, while bars to the left of the 0 mark (negative direction) indicate worsening of a specified behavior. SWALLOWTAIL and LONGWING participants were treated at regular time intervals with either 30- or 45-mg doses of ASO and evaluated at month 12 (**FIG. 56A**) and month 24 (**FIG. 56B**). **FIG. 56C** is a summative chart comparing the Vineland-3 data at month 12 (light gray bars) and month 24 (dark gray bars). Change in GSV is measured using the OLE study as the baseline.

[0335] **FIGS. 57A-57B** are histograms showing change in GSV over time for expressive communication (**FIG. 57A**) and receptive communication (**FIG. 57B**) in the BUTTERFLY natural history study and SWALLOWTAIL/LONGWING studies. Improvements in behavior correspond to a positive change in GSV (bars above line demarcated by 0), and worsened behavior correspond to a negative change in GSV (bars below line demarcated by 0). SWALLOWTAIL/LONGWING study participants were observed to have positive changes in GSV for both expressive and receptive communication over the course of 12 months. BUTTERFLY natural history participants had nearly negligible positive change in GSV in expressive communication and worsening of receptive

communication over the course of 12 months. At month 4, expressive communication in the natural history study had a change in GSV of 0.054 and receptive communication had a change in GSV of -2.166, while expressive communication in the SWALLOWTAIL/LONGWING studies had a change in GSV of 0.185 and receptive communication had a change in GSV of 1.623. At month 8, expressive communication in the natural history study had a change in GSV of 0.105 and receptive communication had a change in GSV of -2.951, while expressive communication in the SWALLOWTAIL/LONGWING studies had a change in GSV of 1.209 and receptive communication had a change in GSV of 2.337. At month 12, expressive communication in the natural history study had a change in GSV of 0.171 and receptive communication had a change in GSV of -3.934, while expressive communication in the SWALLOWTAIL/LONGWING studies had a change in GSV of 2.490 and receptive communication had a change in GSV of 3.231.

[0336] **FIGS. 58A-58B** are histograms showing change in GSV over time for personal skills (**FIG. 58A**) and interpersonal relationship skills (**FIG. 58B**) in the BUTTERFLY natural history study and SWALLOWTAIL/LONGWING studies. Improvements in behavior correspond to a positive change in GSV (bars above line demarcated by 0), and worsened behavior correspond to a negative change in GSV (bars below line demarcated by 0). SWALLOWTAIL/LONGWING study participants were observed to have positive changes in GSV for both expressive and interpersonal skills over the course of 12 months. BUTTERFLY natural history participants had nearly negligible positive change in GSV in personal skills and slight improvement of interpersonal relationship skills over the course of 12 months. At month 4, personal skills in the natural history study had a change in GSV of 0.408 and interpersonal skills had a change in GSV of -2.629, while interpersonal skills in the SWALLOWTAIL/LONGWING studies had a change in GSV of 1.276. At month 8, personal skills in the natural history study had a change in GSV of 0.469 and interpersonal skills had a change in GSV of -1.673, while personal skills in the SWALLOWTAIL/LONGWING studies had a change in GSV of 1.687 and interpersonal skills had a change in GSV of 2.389. At month 12, personal skills in the natural history study had a change in GSV of 0.530 and interpersonal skills had a change in GSV of -0.478, while personal skills in the SWALLOWTAIL/LONGWING studies had a change in GSV of 2.970 and interpersonal skills had a change in GSV of 3.780.

[0337] **FIGS. 59A-59D** are bar charts showing Clinical Global Impression of Change (CGI-C) and Caregiver Global Impression of Change (CaGI-C) for SWALLOWTAIL and LONGWING participants administered maintenance doses of 30 mg or 45 mg of ASO-1. **FIG. 59A** shows CGI-C data and **FIG. 59B** shows CaGI-C data at 4, 8, and 12 months (x-axis) with the least-squares means values (y-axis) for both BUTTERFLY and SWALLOWTAIL/LONGWING participants. CGI-C and CaGI-C measurements were recorded as scores on a 7-point scale. Data are presented in Least Square (LS) means, shown with a 95% confidence interval (CI). The BUTTERFLY natural history scores were used as the baseline reference scores (dotted line). SWALLOWTAIL/LONGWING scores for both CGI-C and CaGI-C were lower than each of the reference BUTTERFLY scores, indicating improvement in patient condition after treatment with either a 30- or 45-mg dose of ASO. **FIG. 59C** shows CGI-C data at 24 months and **FIG.**

59D shows CaGI-C data at 24 months for SWALLOWTAIL/LONGWING OLE participants, with both scales indicating substantial and ongoing improvements in overall clinical status through Month 24 of the OLEs. The x-axis shows the possible scores* of the CGI-C and CaGI-C from Very Much Improved to Very Much Worse. The y-axis shows the number of patients. Percentages at the top of each bar represent the fraction of patients in each CGI-C and CaGI-C parameter. LS = "Least-Squares." *CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), or 7 (Very much worse). †Mixed-effects model for repeated measures constructed using data through Month 24 (Week 96) from enrolled patients in OLE studies. One patient who received an incorrect dose in Phase 1/2a study was excluded. SWALLOWTAIL/LONGWING sample sizes: n=70 at Week 16, n=50 (CGI-C) and 51 (CaGI-C) at Week 48, n=22 at Week 96. OLE data-cut: June 28, 2024.

[0338] **FIGS. 60A-60B** are line charts of Exposure-Response (ER) seizure models produced when two loading doses of 70 mg ASO are followed by 70-mg maintenance doses administered at regular time intervals (**FIG. 60A**) and when three loading doses of 70 mg followed by 70-mg maintenance doses administered at regular intervals (**FIG. 60B**). Predicted median percentage change in convulsive seizure frequency (y-axis) is plotted against time in weeks (x-axis). Arrows with "70" at the top of the charts indicate the time points during which 70-mg doses of ASO would be administered. The model based on two 70-mg loading doses, followed by four 70-mg maintenance doses, estimates that there would be a -65% reduction in seizure frequency by four months after the 4th maintenance dose. The model based on three 70-mg loading doses, followed by four 70-mg maintenance doses, estimates that there would be a -67% reduction in seizure frequency by four months after the 4th maintenance dose.

[0339] **FIGS. 61A-61B** are graphs generated from a PK model used to predict when the brain would achieve a steady state of 26.0 μg ASO drug per gram of brain weight *sans* thalamus when a patient is administered either two 70-mg loading doses followed by four 70-mg maintenance doses (**FIG. 61A**), or three 70-mg loading doses followed by four 70-mg maintenance doses (**FIG. 61B**). Concentration as μg ASO drug per gram of mean brain weight *sans* thalamus (μg/g) (y-axis) is plotted against time in days (x-axis). The number 70 indicates the timepoints at which 70 mg of ASO would be administered. The arrows at the tops of the graphs indicate the predicted time at which the brain achieves the 26.0 μg/g steady state.

[0340] **FIGS. 62A-62B** are line charts of Exposure-Response (ER) seizure models produced when two 70-mg loading doses are followed by four 70-mg maintenance doses administered at regular time intervals (**FIG. 62A**) and when two 70-mg loading doses are followed by four 45-mg maintenance doses administered at regular time intervals (**FIG. 62B**). Predicted median percentage change in convulsive seizure frequency (y-axis) is plotted against time in weeks (x-axis). Arrows with "70" or "45" at the top of the charts indicate the time points during which either 70-mg or 45-mg doses of ASO would be administered. The model based on two 70-mg loading doses, followed by four 70-mg maintenance doses, estimates that there would be a -65% reduction in seizure frequency by four months after the fourth maintenance dose. The model based on two 70-mg loading doses, followed by four 45-mg maintenance

doses, estimates that there would be a -55% reduction in seizure frequency by four months after the fourth maintenance dose.

[0341] **FIGS. 63A-63B** are graphs generated from a PK model used to predict when the brain would achieve a steady state of a certain concentration comprising the eight of ASO drug in μg per gram of brain weight *sans* thalamus. A patient who is administered two 70-mg loading doses followed by four 70-mg maintenance doses was predicted to reach a 26.0 μg/g steady state by 2 months (**FIG. 63A**), and a patient who is administered two 70-mg loading doses followed by four 45-mg maintenance doses was predicted to reach a 16.7 μg/g steady state by 10 months (**FIG. 63B**). Concentration as μg ASO drug per gram of mean brain weight *sans* thalamus (μg/g) (y-axis) is plotted against time in days (x-axis). The numbers "70" and "45" indicate the timepoints at which either 70 mg or 45 mg of ASO would be administered. The arrows at the tops of the graphs indicate the predicted time at which the brain achieves a steady state.

[0342] **FIG. 64** is a schematic illustrating the sequence of events scheduled to occur during the study period of administering two 70-mg loading doses followed by 70-mg maintenance doses. The observation period is 6 weeks long; the initial treatment period is 24 weeks long; and the ongoing treatment period is 16 weeks long. Either a placebo or the ASO drug is administered at the time points marked by the corresponding icons (syringe icon = ASO drug; threaded needle icon = placebo).

[0343] **FIG. 65** is a chart showing the change in Growth Scale Value (GSV) (x-axis) for various cognitive and behavioral skills in BUTTERFLY natural history study participants as assessed by Vineland Adaptive Behavior Scales, Third Edition (Vineland-3). Bars to the right of the 0 mark (positive direction) indicate improvement in a specified behavior, while bars to the left of the 0 mark (negative direction) indicate worsening of a specified behavior. BUTTERFLY participants received no doses and were evaluated at month 12. The change in GSV is measured using the OLE study as the baseline.

[0344] **FIGS. 66A-66B** are graphs illustrating growth scale values (GSV) in receptive communication (**FIG. 66A**) and coping skills (**FIG. 66B**) of BUTTERFLY study participants over the course of 24 months as measured with Vineland-3. Growth scale values obtained from Vineland-3 were used for modeling disease progression. Modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit. Progression for neurotypical peers (dotted lines) was plotted using normative tables from the Vineland-3 manual that show correlations between age equivalents and growth scale values. Progression for BUTTERFLY study participants can be seen from the solid lines. P-values are provided for statistically significant changes.

[0345] **FIGS. 67A-67B** are plots showing assessment of disease progression as measured by Caregiver Global Impression of Change (CaGI-C) (**FIG. 67A**) and Clinical Global Impression of Change (CGI-C) (**FIG. 67B**) in BUTTERFLY study participants over the course of 24 months. For both assessments, change was scored on a 7-point scale with improvement ranging from "very much improved" (scored as 1) to "very much worse" (scored as 7). P-values are provided for statistically significant changes. Y-axes in both figures represent the estimated rating of change. X-axes in both figures represent the timepoints in the study in months. Worsening is denoted by estimated rating of change values above 4, improvement

is denoted by estimated rating of change values below 4, and no change is denoted by estimated rating of change values of 4.

[0346] **FIGS. 68A-68B** are graphs showing the change in convulsive seizure frequency (**FIG. 68A**) and Gillette FAQ data (**FIG. 68B**) of BUTTERFLY study participants over the course of 24 months. Disease progression modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit. The y-axis of **FIG. 68A** represent the estimated percentage of change from baseline in convulsive seizure frequency. The y-axis of **FIG. 68B** represent the estimated total score. X-axes in both graphs represent timepoints of the study in months.

[0347] **FIG. 69** is a graphic representation of the dosing frequency of participants in the SWALLOWTAIL/LONGWING open-label extension studies. Dose 1 is administered on Day 1, Dose 2 at Week 16, and Dose 3 at Week 32. Patients who tolerated these treatment doses were dosed every 16 weeks thereafter. Follow-up assessments were done 24 weeks after the last dose.

[0348] **FIGS. 70A-70C** show comparisons of Vineland-3 data from SWALLOWTAIL/LONGWING with the BUTTERFLY DS natural history study. Negative values for the estimated change in GSV indicate worsening in the Vineland-3 subdomain, and positive values for the estimated change in GSV indicate improvements in the Vineland-3 subdomain. **FIG. 70A** shows a comparison of the change in Vineland-3 subdomain GSVs for SWALLOWTAIL/LONGWING (bars with hatch fill) from the OLE baseline. Analysis was based on a mixed-effects model for repeated measures with an unstructured covariance structure. Data from the BUTTERFLY DS natural history study (solid fill bars) through Month 24 was analyzed with machine learning. Baseline covariates in BUTTERFLY including baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency matched to SWALLOWTAIL/LONGWING patient population means. SWALLOWTAIL/LONGWING sample size: n=48 at screen, n=28 at Week 48 and n=15 at Week 64, except in Fine Motor where n=45 at screen, n=28 at Week 48, and n=14 at Week 64. BUTTERFLY sample size: n=36 at screen and n=25 at Month 12, except n=24 at Month 12 for Interpersonal Relationships and n=31 at screen and n=18 at Month 12 for Fine Motor. CI, confidence interval; GSV, growth scale value; OLE, open-label extension. **FIG. 70B** shows the comparison for receptive communication, and **FIG. 70C** shows the comparison for interpersonal relationships. In **FIGS. 70B-70C**, triangles represent data from SWALLOWTAIL/LONGWING OLE studies while squares represent data from the BUTTERFLY study.

[0349] **FIGS. 71A-71B** are data showing improvements in overall clinical status that were observed within the first 9 months of treatment in Phase 1/2a and continued with ongoing treatment in the OLEs. **FIG. 71A** shows a bar chart of data for Clinical Global Impression of Change (CGI-C)* and **FIG. 71B** shows a bar chart of data for Caregiver Global Impression of Change (CaGI-C)* through 24 months of the SWALLOWTAIL and LONGWING OLE studies. Phase 1/2a data-cut: December 12, 2023 (after end of study); OLE data-cut: June 28, 2024. *CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse) or 7 (Very much worse). Data cutoff was December

12, 2023, for MONARCH/ADMIRAL. †Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies.

[0350] **FIG. 72** is a bar chart showing EuroQol visual analogue scale (EQ-VAS) data representing the Quality of Life (QoL) improvements observed in participants at month 4, month 12, and month 24. The Least-Squares (LS) mean change from OLE baseline is shown on the y-axis, and the timepoints in months are shown on the x-axis. An increase in LS mean change indicates improvement.

DETAILED DESCRIPTION

[0351] Certain specific details of this description are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the present disclosure may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments.

[0352] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods, and materials are described below.

Definitions

[0353] As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise.

[0354] It should be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise. The terms "and/or" and "any combination thereof" and their grammatical equivalents as used herein, can be used interchangeably. These terms can convey that any combination is specifically contemplated. Solely for illustrative purposes, the following phrases "A, B, and/or C" or "A, B, C, or any combination thereof" can mean "A individually; B individually; C individually; A and B; B and C; A and C; and A, B, and C." The term "or" can be used conjunctively or disjunctively, unless the context specifically refers to a disjunctive use.

[0355] The term "about" or "approximately" can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.,* the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated, the term "about" meaning within an acceptable error range for the particular value should be assumed.

[0356] As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude

additional, unrecited elements or method steps. It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method or composition of the present disclosure, and vice versa. Furthermore, compositions of the present disclosure can be used to achieve methods of the present disclosure.

[0357] Reference in the specification to "embodiments," "some embodiments," "an embodiment," "one embodiment," "certain embodiments," or "other embodiments" means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the present disclosures. To facilitate an understanding of the present disclosure, a number of terms and phrases are defined below.

[0358] The terms "oligonucleotide sequence," "nucleic acid sequence," "polynucleic acid sequence," "nucleotide sequence," and "nucleotide acid sequence" are used herein interchangeably in its broadest sense and have the identical meaning herein and refer to preferably DNA or RNA. A nucleic acid sequence is a polymer comprising or consisting of nucleotide monomers, which are covalently linked to each other by phosphodiester-bonds of a sugar/phosphate-backbone. The term "nucleic acid sequence" also encompasses modified nucleic acid sequences, such as base-modified, sugar-modified, or backbone-modified, *etc.*, DNA or RNA.

[0359] The term "fragment" or "fragment of a sequence," which have the identical meaning herein, is a shorter portion of a full-length sequence of *e.g.,* a nucleic acid molecule like DNA or RNA or a protein. Accordingly, a fragment, typically, consists of a sequence that is identical to the corresponding stretch within the full-length sequence. A preferred fragment of a sequence in the context of the present invention consists of a continuous stretch of entities, such as nucleotides or amino acids corresponding to a continuous stretch of entities in the molecule the fragment is derived from, which represents at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, at least 99.5%, or even 100% of the total (*i.e.,* full-length) molecule from which the fragment is derived. For example, a "fragment" or "functional fragment" of a polynucleotide or a polypeptide is a fragment of the polynucleotide or the polypeptide that is shorter than the full-length, immature, or mature nucleotide or polypeptide and has at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, at least 99.5%, or even 100% or more of the activity of the full-length mature reference polynucleotide or polypeptide. Fragments of interest can be made by recombinant, synthetic, or digestive methods.

[0360] The term "recombinant" when used with reference, for example, to a cell, a nucleic acid, a protein, or a vector, indicates that the cell, nucleic acid, protein, or vector has been modified by or is the result of laboratory methods. Thus, for example, the term "recombinant polynucleotide" can refer to a

polynucleotide that is not naturally occurring and are synthesized or manipulated *in vitro*, such as polynucleotides produced by laboratory methods. A recombinant polynucleotide can be synthesized in a laboratory and/or can be prepared by using recombinant DNA technology by using enzymatic modification of DNA, such as enzymatic restriction digestion, ligation, and cloning. A recombinant polypeptide can be prepared by *in vitro* transcription of a recombinant DNA followed by *in vitro* translation of the produced messenger RNA (mRNA). Alternatively, under suitable conditions, a recombinant polynucleic acid or RNA can be incorporated into a cell and a recombinant polypeptide can be expressed within the cell. Recombinant proteins can include amino acid residues not found within the native (non-recombinant) form of the protein or can include amino acid residues that have been modified, *e.g.*, labeled.

[0361] The term "isolated" means separated from constituents, cellular and otherwise, in which the polynucleotide, polypeptide, protein, or fragments thereof, are normally associated with in nature. For example, with respect to a polynucleotide, an isolated polynucleotide is one that is separated from the 5' and 3' ends with which it is normally associated in the naturally occurring sequence. As is apparent to those of skill in the art, a non-naturally occurring polynucleotide, polypeptide, protein, or fragments thereof, does not require "isolation" to distinguish it from its naturally occurring counterpart. In addition, a "concentrated," "separated," or "diluted" polynucleotide, polypeptide, protein, or fragments thereof, is distinguishable from its naturally occurring counterpart in that the concentration or number of molecules per volume is greater than "concentrated," or less than "separated" or "diluted," than that of its naturally occurring counterpart.

[0362] As used herein, "nucleotide" means a nucleoside further comprising a phosphate linking group. As used herein, "linked nucleosides" may or may not be linked by phosphate linkages and thus includes, but is not limited to, "linked nucleotides." As used herein, "linked nucleosides" are nucleosides that are connected in a continuous sequence (*i.e.*, no additional nucleosides are present between those that are linked).

[0363] As used herein, "nucleobase" means a group of atoms that can be linked to a sugar moiety to create a nucleoside that is capable of incorporation into an oligonucleotide, and wherein the group of atoms is capable of bonding with a complementary naturally occurring nucleobase of another oligonucleotide or nucleic acid. Nucleobases may be naturally occurring or may be modified.

[0364] As used herein, "nucleoside" means a compound comprising a nucleobase moiety and a sugar moiety. Nucleosides include, but are not limited to, naturally occurring nucleosides (as found in DNA and RNA) and modified nucleosides. Nucleosides may be linked to a phosphate moiety.

[0365] As used herein, "naturally occurring sugar moiety" means a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA.

[0366] As used herein, "sugar moiety" means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside.

[0367] As used herein, "modified sugar moiety" means a substituted sugar moiety, a bicyclic or tricyclic sugar moiety, or a sugar surrogate.

[0368] The term "antisense oligonucleotide," as used herein, refers to synthetic antinucleotide oligonucleotide (ASO) or antisense oligonucleotide analogs usually between 12 and 30 nucleotides in length that are designed to hybridize to RNA by Watson-Crick base pairing. ASOs can be designed to bind to protein coding RNAs (mRNAs) as well as noncoding RNAs such as microRNAs or large noncoding RNAs. After binding to the targeted RNA, the ASO can modulate the function of the targeted RNA by several different mechanisms, including degradation of the pre-mRNA in the nucleus or mature RNA in the cytoplasm by RNase H1, and degradation of RNA in the cytoplasm by the RISC complex (Ago2) or ribozymes or DNAzymes. ASOs can also modulate RNA function by nondegradative mechanisms such as splicing or polyadenylation modulation in the nucleus and modulate protein translation in the cytoplasm.

[0369] The term "to hybridize" means to form hydrogen bond, which may be via Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases. "Complementary," as used herein, refers to the capacity for precise pairing between two nucleotides. The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other.

[0370] The terms "identical" or percent "identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same (*i.e.,* 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% identity over a specified region, *e.g.,* of the entire polypeptide sequences of the invention or individual domains of the polypeptides of the invention), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using a sequence comparison algorithm or by manual alignment and visual inspection. Such sequences that are at least about 80% identical are said to be "substantially identical." In some embodiments, two sequences are 100% identical. In some embodiments, two sequences are 100% identical over the entire length of one of the sequences (*e.g.,* the shorter of the two sequences where the sequences have different lengths). In various embodiments, identity may refer to the complement of a test sequence.

[0371] In some embodiments, the identity exists over a region that is at least about 2 to about 400 amino acids or nucleotides in length. In some embodiments, the identity exists over a region that is at least about 2 to about 390, at least about 2 to about 380, at least about 2 to about 370, at least about 2 to about 360, at least about 2 to about 350, at least about 2 to about 340, at least about 2 to about 330, at least about 2 to about 320, at least about 2 to about 310, at least about 2 to about 300, at least about 2 to about 290, at least about 2 to about 280, at least about 2 to about 270, at least about 2 to about 260, at least about 2 to about 250, at least about 2 to about 200, at least about 2 to about 150, at least about 2 to about 100 amino acids or nucleotides in length. In some embodiments, the identity exists over a region that is at least about 2 to about 90, at least about 2 to about 85, at least about 2 to about 80, at least about 2 to about 75, at least about 2 to about 70, at least about 2 to about 65, at least about 2 to about 60, at least about 2 to

about 55, at least about 2 to about 50, at least about 2 to about 45, at least about 2 to about 40, at least about 2 to about 35, at least about 2 to about 30, at least about 2 to about 25, at least about 2 to about 20, at least about 2 to about 10, or at least about 2 to about 5 amino acids or nucleotides in length.

[0372] In some embodiments, the identity exists over a region that is at least about 3 to about 400, about 4 to about 400, about 5 to about 400, about 6 to about 400, about 7 to about 400, about 8 to about 400, about 9 to about 400, about 10 to about 400, about 11 to about 400, about 12 to about 400, about 13 to about 400, about 14 to about 400, about 15 to about 400, about 16 to about 400, about 17 to about 400, about 18 to about 400, about 19 to about 400, about 20 to about 400, about 21 to about 400, about 22 to about 400, about 23 to about 400, about 24 to about 400, about 25 to about 400, about 26 to about 400, about 27 to about 400, about 28 to about 400, about 29 to about 400, about 30 to about 400, about 31 to about 400, about 32 to about 400, about 33 to about 400, about 34 to about 400, about 35 to about 400 amino acids or nucleotides in length. In some embodiments, the identity exists over a region that is at least about 40 to about 400, about 45 to about 400, about 50 to about 400, about 55 to about 400, about 60 to about 400, about 61 to about 400, about 62 to about 400, about 63 to about 400, about 64 to about 400, about 65 to about 400, about 66 to about 400, about 67 to about 400, about 68 to about 400, about 69 to about 400, about 70, to about 400, about 71 to about 400, about 72 to about 400, about 73 to about 400, about 74 to about 400, about 75 to about 400, about 80 to about 400, about 85 to about 400, about 90 to about 400, about 100 to about 400, about 150 to about 400, about 200 to about 400, about 250 to about 400, about 300 to about 400, or about 350 to about 400 amino acids or nucleotides in length.

[0373] In some embodiments, the identity exists over a region that is at least about 2 to about 343, about 3 to about 343, about 4 to about 343, about 7 to about 343, about 9 to about 343, about 11 to about 343, about 15 to about 343, about 16 to about 343, about 20 to about 343, about 25 to about 343, about 62 to about 343, about 2 to about 317, about 3 to about 317, about 4 to about 317, about 7 to about 317, about 9 to about 317, about 11 to about 317, about 15 to about 317, about 16 to about 317, about 20 to about 317, about 25 to about 317, about 62 to about 317, about 2 to about 300, about 3 to about 300, about 4 to about 300, about 7 to about 300, about 9 to about 300, about 11 to about 300, about 15 to about 300, about 16 to about 300, about 20 to about 300, about 25 to about 300, about 62 to about 300, about 2 to about 62, about 3 to about 62, about 4 to about 62, about 7 to about 62, about 9 to about 62, about 11 to about 62, about 15 to about 62, about 16 to about 62, about 20 to about 62, or about 25 to about 62 amino acids or nucleotides in length.

[0374] The term "genetically modified" means containing and/or expressing a foreign gene or nucleic acid sequence which in turn, modifies the genotype or phenotype of the cell or its progeny. In other words, it refers to any addition, deletion, or disruption to a cell's endogenous nucleotides.

[0375] The term "operably linked" can refer to a functional relationship between two or more nucleic acid sequences, *e.g.*, a functional relationship of a transcriptional regulatory or signal sequence to a transcribed sequence. For example, a target motif or a nucleic acid encoding a target motif is operably linked to a coding sequence if it is expressed as a preprotein that participates in targeting the polypeptide encoded by the coding sequence to a cell membrane, intracellular, or an extracellular compartment. For

example, a signal peptide or a nucleic acid encoding a signal peptide is operably linked to a coding sequence if it is expressed as a preprotein that participates in the secretion of the polypeptide encoded by the coding sequence. For example, a promoter is operably linked if it stimulates or modulates the transcription of the coding sequence.

[0376] The term "subject" or "patient" encompasses vertebrates or mammals. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs, and the like. In one aspect, the mammal is a human. The term "animal" as used herein comprises human beings and non-human animals. In one embodiment, a "non-human animal" is a mammal, for example, a rodent such as rat or a mouse. In one embodiment, a non-human animal is a mouse.

[0377] A "control" is an alternative subject or sample used in an experiment for comparison purpose. A control can be "positive" or "negative."

Methods of Treatment

[0378] In some aspects, provided herein is a method of treating or preventing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof comprising administering to the human subject a pharmaceutical composition comprising a compound at a first dose of about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg, wherein the compound is an antisense oligomer (ASO) that comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099, thereby treating or preventing the disease or condition in the human subject. In some embodiments, the ASO comprises a sequence with at least 80% sequence identity to any one of the sequences listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, thereby treating or preventing the disease or condition in the human subject.

[0379] In some aspects, provided herein is a method of treating or preventing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof comprising administering to the human subject a pharmaceutical composition comprising a first dose of a compound, wherein the compound is an ASO that comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099, thereby treating or preventing the disease or condition in the human subject; wherein the human subject is at most 18 years old. In some embodiments, the ASO comprises a sequence with at least 80% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, thereby treating or preventing the disease or condition in the human subject; wherein the human subject is at most 18 years old.

[0380] In some aspects, provided herein is a method of treating or preventing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof comprising administering to the human subject a pharmaceutical composition comprising a single dose of

an antisense oligomer (ASO), wherein the ASO comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099, thereby treating or preventing the disease or condition in the human subject. In some embodiments, the ASO comprises a sequence with at least 80% sequence identity to any one of any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, thereby treating or preventing the disease or condition in the human subject.

[0381] In some embodiments, the pharmaceutical composition is administered into the intrathecal space of the human subject. In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid of the human subject. In some embodiments, the pharmaceutical composition is administered into the brain of the human subject. In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid in the brain of the human subject.

[0382] In some embodiments, the pharmaceutical composition is administered as a bolus injection. In some embodiments, the pharmaceutical composition is administered by infusion with a delivery pump. In some embodiments, the pharmaceutical composition is administered by intracerebroventricular injection. In some embodiments, the pharmaceutical composition is administered by intrathecal injection.

Therapeutic Dose

[0383] In some embodiments, the first dose is a single dose. In some embodiments, the method further comprises assessing tolerability or effectiveness of the pharmaceutical composition.

[0384] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising a compound as described herein at a first dose of about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg.

[0385] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from about 0.1 to about 1000 mg, from about 0.2 to about 1000 mg, from about 0.3 to about 1000 mg, from about 0.4 to about 1000 mg, from about 0.5 to about 1000 mg, from about 0.6 to about 1000 mg, from about 0.7 to about 1000 mg, from about 0.8 to about 1000 mg, from about 0.9 to about 1000 mg, 1 to about 1000 mg, from about 2 to about 1000 mg, from about 3 to about 1000 mg, from about 4 to about 1000 mg, from about 5 to about 1000 mg, from about 6 to about 1000 mg, from about 7 to about 1000 mg, from about 8 to about 1000 mg, from about 9 to about 1000 mg, from about 10 to about 1000 mg, from about 15 to about 1000 mg, from about 20 to about 1000 mg, from about 25 to about 1000 mg, from about 30 to about 1000 mg, from about 35 to about 1000 mg, from about 40 to about 1000 mg, from about 45 to about 1000 mg, from about 50 to about 1000 mg, from about 55 to about 1000 mg, from about 60 to about 1000 mg, from about 65 to about 1000 mg, from about 70 to about 1000 mg, from about 75 to about 1000 mg, from about 80 to about 1000 mg, from about 85 to about 1000 mg, from about 90 to about 1000 mg, from about 95 to about 1000 mg, from about 100 to about 1000 mg, from about 150 to about 1000 mg, from about 200 to about 1000 mg, from about 250 to about 1000 mg, from about 300 to about 1000 mg, from about 350 to about 1000 mg, from about 400 to about 1000 mg, from

about 450 to about 1000 mg, from about 500 to about 1000 mg, from about 550 to about 1000 mg, from about 600 to about 1000 mg, from about 650 to about 1000 mg, from about 700 to about 1000 mg, from about 750 to about 1000 mg, from about 800 to about 1000 mg, from about 850 to about 1000 mg, from about 900 to about 1000 mg, or from about 950 to about 1000 mg.

[0386] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from 0.1 to 1000 mg, from 0.2 to 1000 mg, from 0.3 to 1000 mg, from 0.4 to 1000 mg, from 0.5 to 1000 mg, from 0.6 to 1000 mg, from 0.7 to 1000 mg, from 0.8 to 1000 mg, from 0.9 to 1000 mg, 1 to 1000 mg, from 2 to 1000 mg, from 3 to 1000 mg, from 4 to 1000 mg, from 5 to 1000 mg, from 6 to 1000 mg, from 7 to 1000 mg, from 8 to 1000 mg, from 9 to 1000 mg, from 10 to 1000 mg, from 15 to 1000 mg, from 20 to 1000 mg, from 25 to 1000 mg, from 30 to 1000 mg, from 35 to 1000 mg, from 40 to 1000 mg, from 45 to 1000 mg, from 50 to 1000 mg, from 55 to 1000 mg, from 60 to 1000 mg, from 65 to 1000 mg, from 70 to 1000 mg, from 75 to 1000 mg, from 80 to 1000 mg, from 85 to 1000 mg, from 90 to 1000 mg, from 95 to 1000 mg, from 100 to 1000 mg, from 150 to 1000 mg, from 200 to 1000 mg, from 250 to 1000 mg, from 300 to 1000 mg, from 350 to 1000 mg, from 400 to 1000 mg, from 450 to 1000 mg, from 500 to 1000 mg, from 550 to 1000 mg, from 600 to 1000 mg, from 650 to 1000 mg, from 700 to 1000 mg, from 750 to 1000 mg, from 800 to 1000 mg, from 850 to 1000 mg, from 900 to 1000 mg, or from 950 to 1000 mg.

[0387] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from about 0.1 to about 950 mg, from about 0.1 to about 900 mg, from about 0.1 to about 850 mg, from about 0.1 to about 800 mg, from about 0.1 to about 750 mg, from about 0.1 to about 700 mg, from about 0.1 to about 650 mg, from about 0.1 to about 600 mg, from about 0.1 to about 550 mg, from about 0.1 to about 500 mg, from about 0.1 to about 450 mg, from about 0.1 to about 400 mg, from about 0.1 to about 350 mg, from about 0.1 to about 300 mg, from about 0.1 to about 250 mg, from about 0.1 to about 200 mg, from about 0.1 to about 150 mg, from about 0.1 to about 100 mg, from about 0.1 to about 95 mg, from about 0.1 to about 90 mg, from about 0.1 to about 85 mg, from about 0.1 to about 80 mg, from about 0.1 to about 75 mg, from about 0.1 to about 70 mg, from about 0.1 to about 65 mg, from about 0.1 to about 60 mg, from about 0.1 to about 55 mg, from about 0.1 to about 50 mg, from about 0.1 to about 45 mg, from about 0.1 to about 40 mg, from about 0.1 to about 35 mg, from about 0.1 to about 30 mg, from about 0.1 to about mg, from about 0.1 to about 25 mg, from about 0.1 to about 20 mg, from about 0.1 to about 10 mg, from about 0.1 to about 9 mg, from about 0.1 to about 8 mg, from about 0.1 to about 7 mg, from about 0.1 to about 6 mg, from about 0.1 to about 5 mg, from about 0.1 to about 4 mg, from about 0.1 to about 3, from about 0.1 to about 2 mg, from about 0.1 to about 1 mg, from about 0.1 to about 0.9 mg, from about 0.1 to about 0.8 mg, from about 0.1 to about 0.7 mg, from about 0.1 to about 0.6 mg, from about 0.1 to about 0.5 mg, from about 0.1 to about 0.4 mg, from about 0.1 to about 0.3, or from about 0.1 to about 0.2 mg.

[0388] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from 0.1 to 950 mg, from 0.1 to 900 mg, from 0.1 to 850 mg, from 0.1 to 800 mg, from 0.1 to 750 mg, from 0.1 to 700 mg, from 0.1 to 650 mg, from 0.1 to 600 mg, from 0.1 to 550 mg, from 0.1 to 500 mg, from 0.1 to 450 mg, from 0.1 to 400 mg, from 0.1 to 350 mg, from 0.1 to 300 mg, from 0.1 to 250 mg, from 0.1 to 200 mg, from 0.1 to 150 mg, from 0.1 to 100 mg, from 0.1 to 95 mg, from 0.1 to 90 mg, from 0.1 to 85 mg, from 0.1 to 80 mg, from 0.1 to 75 mg, from 0.1 to 70 mg, from 0.1 to 65 mg, from 0.1 to 60 mg, from 0.1 to 55 mg, from 0.1 to 50 mg, from 0.1 to 45 mg, from 0.1 to 40 mg, from 0.1 to 35 mg, from 0.1 to 30 mg, from 0.1 to mg, from 0.1 to 25 mg, from 0.1 to 20 mg, from 0.1 to 10 mg, from 0.1 to 9 mg, from 0.1 to 8 mg, from 0.1 to 7 mg, from 0.1 to 6 mg, from 0.1 to 5 mg, from 0.1 to 4 mg, from 0.1 to 3, from 0.1 to 2 mg, from 0.1 to 1 mg, from 0.1 to 0.9 mg, from 0.1 to 0.8 mg, from 0.1 to 0.7 mg, from 0.1 to 0.6 mg, from 0.1 to 0.5 mg, from 0.1 to 0.4 mg, from 0.1 to 0.3, or from 0.1 to 0.2 mg.

[0389] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from about 1 to about 400 mg, from about 2 to about 400 mg, from about 3 to about 400 mg, from about 4 to about 400 mg, from about 5 to about 400 mg, from about 6 to about 400 mg, from about 7 to about 400 mg, from about 8 to about 400 mg, from about 9 to about 400 mg, from about 10 to about 400 mg, from about 20 to about 400 mg, from about 30 to about 400 mg, from about 40 to about 400 mg, from about 50 to about 400 mg, from about 60 to about 400 mg, from about 70 to about 400 mg, from about 80 to about 400 mg, from about 90 to about 400 mg, from about 100 to about 400 mg, from about 110 to about 400 mg, from about 120 to about 400 mg, from about 130 to about 400 mg, from about140 to about 400 mg, from about 150 to about 400 mg, from about160 to about 400 mg, from about 170 to about 400 mg, from about 180 to about 400 mg, from about 190 to about 400 mg, from about 200 to about 400 mg, from about 210 to about 400 mg, from about 220 to about 400 mg, from about 230 to about 400 mg, from about 240 to about 400 mg, from about 250 to about 400 mg, from about 260 to about 400 mg, from about 270 to about 400 mg, from about 280 to about 400 mg, from about 290 to about 400 mg, from about 300 to about 400 mg, from about 310 to about 400 mg, from about 320 to about 400 mg, from about 330 to about 400 mg, from about 340 to about 400 mg, from about 350 to about 400 mg, from about 360 to about 400 mg, from about 370 to about 400 mg, from about 380 to about 400 mg, or from about 390 to about 400 mg.

[0390] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from 1 to 400 mg, from 2 to 400 mg, from 3 to 400 mg, from 4 to 400 mg, from 5 to 400 mg, from 6 to 400 mg, from 7 to 400 mg, from 8 to 400 mg, from 9 to 400 mg, from 10 to 400 mg, from 20 to 400 mg, from 30 to 400 mg, from 40 to 400 mg, from 50 to 400 mg, from 60 to 400 mg, from 70 to 400 mg, from 80 to 400 mg, from 90 to 400 mg, from 100 to 400 mg, from 110 to 400 mg, from 120 to 400 mg, from 130 to 400 mg, from about 140 to 400 mg, from 150 to 400 mg, from about160 to 400 mg, from 170 to 400 mg, from 180 to 400 mg, from 190 to 400 mg, from 200 to 400 mg, from 210 to 400 mg, from 220 to

400 mg, from 230 to 400 mg, from 240 to 400 mg, from 250 to 400 mg, from 260 to 400 mg, from 270 to 400 mg, from 280 to 400 mg, from 290 to 400 mg, from 300 to 400 mg, from 310 to 400 mg, from 320 to 400 mg, from 330 to 400 mg, from 340 to 400 mg, from 350 to 400 mg, from 360 to 400 mg, from 370 to 400 mg, from 380 to 400 mg, or from 390 to 400 mg.

[0391] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from about 10 to about 390 mg, from about 10 to about 380 mg, from about 10 to about 370 mg, from about 10 to about 360 mg, from about 10 to about 350 mg, from about 10 to about 340 mg, from about 10 to about 330 mg, from about 10 to about 320 mg, from about 10 to about 310 mg, from about 10 to about 300 mg, from about 10 to about 290 mg, from about 10 to about 280 mg, from about 10 to about 270 mg, from about 10 to about 260 mg, from about 10 to about 250 mg, from about 10 to about 240 mg, from about 10 to about 230 mg, from about 10 to about 220 mg, from about 10 to about 210 mg, from about 10 to about 200 mg, from about 10 to about 190 mg, from about 10 to about 180 mg, from about 10 to about 170 mg, from about 10 to about 160 mg, from about 10 to about 150 mg, from about 10 to about 140 mg, from about 10 to about 130 mg, from about 10 to about 120 mg, from about 10 to about 110 mg, from about 10 to about 90 mg, from about 10 to about 80 mg, from about 10 to about 70 mg, from about 10 to about 60 mg, from about 10 to about 50 mg, from about 10 to about 40 mg, from about 10 to about 30 mg, or from about 10 to about 20 mg.

[0392] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of from 10 to 390 mg, from 10 to 380 mg, from 10 to 370 mg, from 10 to 360 mg, from 10 to 350 mg, from 10 to 340 mg, from 10 to 330 mg, from 10 to 320 mg, from 10 to 310 mg, from 10 to 300 mg, from 10 to 290 mg, from 10 to 280 mg, from 10 to 270 mg, from 10 to 260 mg, from 10 to 250 mg, from 10 to 240 mg, from 10 to 230 mg, from 10 to 220 mg, from 10 to 210 mg, from 10 to 200 mg, from 10 to 190 mg, from 10 to 180 mg, from 10 to 170 mg, from 10 to 160 mg, from 10 to 150 mg, from 10 to 140 mg, from 10 to 130 mg, from 10 to 120 mg, from 10 to 110 mg, from 10 to 90 mg, from 10 to 80 mg, from 10 to 70 mg, from 10 to 60 mg, from 10 to 50 mg, from 10 to 40 mg, from 10 to 30 mg, or from 10 to 20 mg.

[0393] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69

mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg, about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg, about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, about 140 mg, about 141 mg, about 142 mg, about 143 mg, about 144 mg, about 145 mg, about 146 mg, about 147 mg, about 148 mg, about 149 mg, about 150 mg, about 151 mg, about 152 mg, about 153 mg, about 154 mg, about 155 mg, about 156 mg, about 157 mg, about 158 mg, about 159 mg, about 160 mg, about 161 mg, about 162 mg, about 163 mg, about 164 mg, about 165 mg, about 166 mg, about 167 mg, about 168 mg, about 169 mg, about 170 mg, about 171 mg, about 172 mg, about 173 mg, about 174 mg, about 175 mg, about 176 mg, about 177 mg, about 178 mg, about 179 mg, about 180 mg, about 181 mg, about 182 mg, about 183 mg, about 184 mg, about 185 mg, about 186 mg, about 187 mg, about 188 mg, about 189 mg, about 190 mg, about 191 mg, about 192 mg, about 193 mg, about 194 mg, about 195 mg, about 196 mg, about 197 mg, about 198 mg, about 199 mg, about 200 mg, about 201 mg, about 202 mg, about 203 mg, about 204 mg, about 205 mg, about 206 mg, about 207 mg, about 208 mg, about 209 mg, about 210 mg, about 211 mg, about 212 mg, about 213 mg, about 214 mg, about 215 mg, about 216 mg, about 217 mg, about 218 mg, about 219 mg, about 220 mg, about 221 mg, about 222 mg, about 223 mg, about 224 mg, about 225 mg, about 226 mg, about 227 mg, about 228 mg, about 229 mg, about 230 mg, about 231 mg, about 232 mg, about 233 mg, about 234 mg, about 235 mg, about 236 mg, about 237 mg, about 238 mg, about 239 mg, about 240 mg, about 241 mg, about 242 mg, about 243 mg, about 244 mg, about 245 mg, about 246 mg, about 247 mg, about 248 mg, about 249 mg, about 250 mg, about 251 mg, about 252 mg, about 253 mg, about 254 mg, about 255 mg, about 256 mg, about 257 mg, about 258 mg, about 259 mg, about 260 mg, about 261 mg, about 262 mg, about 263 mg, about 264 mg, about 265 mg, about 266 mg, about 267 mg, about 268 mg, about 269 mg, about 270 mg, about 271 mg, about 272 mg, about 273 mg, about 274 mg, about 275 mg, about 276 mg, about 277 mg, about 278 mg, about 279 mg, about 280 mg, about 281 mg, about 282 mg, about 283 mg, about 284 mg, about 285 mg, about 286 mg, about 287 mg, about 288 mg, about 289 mg, about 290 mg, about 291 mg, about 292 mg, about 293 mg, about 294 mg, about 295 mg, about 296 mg, about 297 mg, about 298 mg, about 299 mg, about 300 mg, about 301 mg, about 302 mg, about 303 mg, about 304 mg, about 305 mg, about 306 mg, about 307 mg, about 308 mg, about 309 mg, about 310 mg, about 311 mg, about 312 mg, about 313 mg, about 314 mg, about 315 mg, about 316 mg, about 317 mg, about 318 mg, about 319 mg, about 320 mg, about 321 mg, about 322 mg, about 323 mg, about 324 mg, about 325 mg, about 326 mg, about 327 mg, about 328 mg, about 329 mg, about 330 mg, about 331 mg, about 332 mg, about 333 mg, about 334 mg, about 335 mg, about 336 mg, about 337

mg, about 338 mg, about 339 mg, about 340 mg, about 341 mg, about 342 mg, about 343 mg, about 344 mg, about 345 mg, about 346 mg, about 347 mg, about 348 mg, about 349 mg, about 350 mg, about 351 mg, about 352 mg, about 353 mg, about 354 mg, about 355 mg, about 356 mg, about 357 mg, about 358 mg, about 359 mg, about 360 mg, about 361 mg, about 362 mg, about 363 mg, about 364 mg, about 365 mg, about 366 mg, about 367 mg, about 368 mg, about 369 mg, about 370 mg, about 371 mg, about 372 mg, about 373 mg, about 374 mg, about 375 mg, about 376 mg, about 377 mg, about 378 mg, about 379 mg, about 380 mg, about 381 mg, about 382 mg, about 383 mg, about 384 mg, about 385 mg, about 386 mg, about 387 mg, about 388 mg, about 389 mg, about 390 mg, about 391 mg, about 392 mg, about 393 mg, about 394 mg, about 395 mg, about 396 mg, about 397 mg, about 398 mg, about 399 mg, or about 400 mg.

[0394] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a first dose of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg, 141 mg, 142 mg, 143 mg, 144 mg, 145 mg, 146 mg, 147 mg, 148 mg, 149 mg, 150 mg, 151 mg, 152 mg, 153 mg, 154 mg, 155 mg, 156 mg, 157 mg, 158 mg, 159 mg, 160 mg, 161 mg, 162 mg, 163 mg, 164 mg, 165 mg, 166 mg, 167 mg, 168 mg, 169 mg, 170 mg, 171 mg, 172 mg, 173 mg, 174 mg, 175 mg, 176 mg, 177 mg, 178 mg, 179 mg, 180 mg, 181 mg, 182 mg, 183 mg, 184 mg, 185 mg, 186 mg, 187 mg, 188 mg, 189 mg, 190 mg, 191 mg, 192 mg, 193 mg, 194 mg, 195 mg, 196 mg, 197 mg, 198 mg, 199 mg, 200 mg, 201 mg, 202 mg, 203 mg, 204 mg, 205 mg, 206 mg, 207 mg, 208 mg, 209 mg, 210 mg, 211 mg, 212 mg, 213 mg, 214 mg, 215 mg, 216 mg, 217 mg, 218 mg, 219 mg, 220 mg, 221 mg, 222 mg, 223 mg, 224 mg, 225 mg, 226 mg, 227 mg, 228 mg, 229 mg, 230 mg, 231 mg, 232 mg, 233 mg, 234 mg, 235 mg, 236 mg, 237 mg, 238 mg, 239 mg, 240 mg, 241 mg, 242 mg, 243 mg, 244 mg, 245 mg, 246 mg, 247 mg, 248 mg, 249 mg, 250 mg, 251 mg, 252 mg, 253 mg, 254 mg, 255 mg, 256 mg, 257 mg, 258 mg, 259 mg, 260 mg, 261 mg, 262 mg, 263 mg, 264 mg, 265 mg, 266 mg, 267 mg, 268 mg, 269 mg, 270 mg, 271 mg, 272 mg, 273 mg, 274 mg, 275 mg, 276 mg, 277 mg, 278 mg, 279 mg, 280 mg, 281 mg, 282 mg, 283 mg, 284 mg, 285 mg, 286 mg, 287 mg, 288 mg, 289 mg, 290 mg, 291 mg, 292 mg, 293 mg, 294 mg, 295 mg, 296 mg, 297 mg, 298 mg, 299 mg, 300 mg, 301 mg, 302 mg, 303 mg, 304 mg, 305 mg, 306 mg, 307 mg, 308 mg, 309 mg, 310 mg, 311 mg, 312 mg, 313 mg, 314 mg, 315 mg, 316 mg, 317 mg, 318 mg, 319 mg, 320 mg, 321 mg, 322 mg, 323 mg, 324 mg, 325 mg, 326 mg, 327 mg,

328 mg, 329 mg, 330 mg, 331 mg, 332 mg, 333 mg, 334 mg, 335 mg, 336 mg, 337 mg, 338 mg, 339 mg, 340 mg, 341 mg, 342 mg, 343 mg, 344 mg, 345 mg, 346 mg, 347 mg, 348 mg, 349 mg, 350 mg, 351 mg, 352 mg, 353 mg, 354 mg, 355 mg, 356 mg, 357 mg, 358 mg, 359 mg, 360 mg, 361 mg, 362 mg, 363 mg, 364 mg, 365 mg, 366 mg, 367 mg, 368 mg, 369 mg, 370 mg, 371 mg, 372 mg, 373 mg, 374 mg, 375 mg, 376 mg, 377 mg, 378 mg, 379 mg, 380 mg, 381 mg, 382 mg, 383 mg, 384 mg, 385 mg, 386 mg, 387 mg, 388 mg, 389 mg, 390 mg, 391 mg, 392 mg, 393 mg, 394 mg, 395 mg, 396 mg, 397 mg, 398 mg, 399 mg, or 400 mg.

Dosing Regimen

[0395] The terms "schedule," "schedules," "time interval," and "time intervals" are used herein interchangeably in their broadest sense. In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising an amount of a compound as described herein. In some embodiments, the multiple doses comprise loading doses and maintenance doses that are administered at defined schedules or time intervals. In some embodiments, the multiple doses comprise at least one loading dose and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise at least two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise at least three loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise three loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses comprise two loading doses and at least two maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise three loading doses and at least two maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise two loading doses and at least three maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise three loading doses and at least three maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise two loading doses and at least four maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise three loading doses and at least four maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, and two or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, and three or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some

embodiments, the multiple doses comprise a first loading dose, a second loading dose, and four or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and two or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and three or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and four or more maintenance doses following the second loading dose that are each administered at defined time intervals.

[0396] In some embodiments, the multiple doses consist of loading doses and maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of at least one loading dose and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of at least two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of at least three loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of two loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of three loading doses and at least one maintenance dose that are administered at defined time intervals. In some embodiments, the multiple doses consist of two loading doses and at least two maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of three loading doses and at least two maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of two loading doses and at least three maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of three loading doses and at least three maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of two loading doses and at least four maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of three loading doses and at least four maintenance doses that are administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, and two or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, and three or more maintenance doses following the second loading dose that are each administered at

defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, and four or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, a third loading dose, and two or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, a third loading dose, and three or more maintenance doses following the second loading dose that are each administered at defined time intervals. In some embodiments, the multiple doses consist of a first loading dose, a second loading dose, a third loading dose, and four or more maintenance doses following the second loading dose that are each administered at defined time intervals.

[0397] In some embodiments, the one or more maintenance doses comprises at least one maintenance dose. In some embodiments, the one or more maintenance doses comprises at least two maintenance doses. In some embodiments, the one or more maintenance doses comprises at least three maintenance doses. In some embodiments, the one or more maintenance doses comprises at least four maintenance doses. In some embodiments, the one or more maintenance doses comprises at least five maintenance doses. In some embodiments, the one or more maintenance doses comprises at least six maintenance doses. In some embodiments, the one or more maintenance doses comprises at least seven maintenance doses. In some embodiments, the one or more maintenance doses comprises at least eight maintenance doses. In some embodiments, the one or more maintenance doses comprises at least nine maintenance doses. In some embodiments, the one or more maintenance doses comprises at least ten maintenance doses. In some embodiments, the one or more maintenance doses comprises at least eleven maintenance doses. In some embodiments, the one or more maintenance doses comprises at least twelve maintenance doses. In some embodiments, the one or more maintenance doses comprise more than two maintenance doses. In some embodiments, the one or more maintenance doses comprise more than three maintenance doses. In some embodiments, the one or more maintenance doses comprise more than four maintenance doses. In some embodiments, the one or more maintenance doses consists of at least one maintenance dose. In some embodiments, the one or more maintenance doses consists of at least two maintenance doses. In some embodiments, the one or more maintenance doses consists of at least three maintenance doses. In some embodiments, the one or more maintenance doses consists of at least four maintenance doses. In some embodiments, the one or more maintenance doses consists of at least five maintenance doses. In some embodiments, the one or more maintenance doses consists of at least six maintenance doses. In some embodiments, the one or more maintenance doses consists of at least seven maintenance doses. In some embodiments, the one or more maintenance doses consists of at least eight maintenance doses. In some embodiments, the one or more maintenance doses consists of at least nine maintenance doses. In some embodiments, the one or more maintenance doses consists of at least ten maintenance doses. In some embodiments, the one or more maintenance doses consists of at least eleven maintenance

doses. In some embodiments, the one or more maintenance doses consists of at least twelve maintenance doses.

[0398] In some embodiments, the subject continues receiving standard of care, prior to, during, and/or after administration of a pharmaceutical composition comprising an amount of a compound as described herein, for instance, receiving administration of an antiepileptic drug (AED), *e.g.,* clobazam, fenfluramine, stiripentol, valproic acid, cannabidiol, or levetiracetam. In some cases, the AED administered to the subject is not an AED primarily acting as a sodium channel blocker (*e.g.,* phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide).

[0399] Dosing Regimen: Amounts of Compound in Loading and Maintenance Doses

[0400] In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising an amount of a compound as described herein. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 20 mg, 25 mg, 30 mg, 35 mg 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 85 mg. In

some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 90 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 95 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 100 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 90 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 95 mg. In some

embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses is about 100 mg.

[0401] In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 20 mg, and the amount of the compound in each of the one or more maintenance doses is about 15 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 25 mg, and the amount of the compound in each of the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 35 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 35 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 40 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 40 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 55 mg, and the amount of the compound in each of the one or more maintenance doses is

about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 55 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more

maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in

each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 85 mg, and the

amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading

dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 90 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first

loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose and the second loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 90 mg.

[0402] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 20 mg, and the amount of the compound in each of the one or more maintenance doses is about 15 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 25 mg, and the amount of the compound in each of the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 20 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 35 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 35 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 40 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 40 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 45 mg, and the amount of the compound in each of the one or

more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 55 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 55 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some

embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 65 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each

dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 75 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 80 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading

dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 85 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg.

[0403] In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading

dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 90 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the

amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 95 mg, and the amount of the compound in each of the one or more maintenance doses is about 90 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 35 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 40 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 50 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 55 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 60 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 65 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 70 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or

more maintenance doses is about 75 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 80 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 85 mg. In some embodiments, the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 100 mg, and the amount of the compound in each of the one or more maintenance doses is about 90 mg.

[0404] In some embodiments, the method or dosing regimen as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg.

[0405] In some embodiments, the method or dosing regimen as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from about 0.1 to about 1000 mg, from about 0.2 to about 1000 mg, from about 0.3 to about 1000 mg, from about 0.4 to about 1000 mg, from about 0.5 to about 1000 mg, from about 0.6 to about 1000 mg, from about 0.7 to about 1000 mg, from about 0.8 to about 1000 mg, from about 0.9 to about 1000 mg, 1 to about 1000 mg, from about 2 to about 1000 mg, from about 3 to about 1000 mg, from about 4 to about 1000 mg, from about 5 to about 1000 mg, from about 6 to about 1000 mg, from about 7 to about 1000 mg, from about 8 to about 1000 mg, from about 9 to about 1000 mg, from about 10 to about 1000 mg, from about 15 to about 1000 mg, from about 20 to about 1000 mg, from about 25 to about 1000 mg, from about 30 to about 1000 mg, from about 35 to about 1000 mg, from about 40 to about 1000 mg, from about 45 to about 1000 mg, from about 50 to about 1000 mg, from about 55 to about 1000 mg, from about 60 to about 1000 mg, from about 65 to about 1000 mg, from about 70 to about 1000 mg, from about 75 to about 1000 mg, from about 80 to about 1000 mg, from about 85 to about 1000 mg, from about 90 to about 1000 mg, from about 95 to about 1000 mg, from about 100 to about 1000 mg, from about 150 to about 1000 mg, from about 200 to about 1000 mg, from about 250 to about 1000 mg, from about 300 to about 1000 mg, from about 350 to about 1000 mg, from about 400 to about 1000 mg, from about 450 to about 1000 mg, from about 500 to about 1000 mg, from about 550 to about 1000 mg, from about 600 to about 1000 mg, from about 650 to about 1000 mg, from about 700 to about 1000 mg, from about 750 to about 1000 mg, from about 800 to about 1000 mg, from about 850 to about 1000 mg, from about 900 to about 1000 mg, or from about 950 to about 1000 mg.

[0406] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from 0.1 to 1000 mg, from 0.2 to 1000 mg, from 0.3 to 1000 mg, from 0.4 to 1000 mg, from 0.5 to 1000 mg, from 0.6 to 1000 mg, from 0.7 to 1000 mg, from 0.8 to 1000 mg, from 0.9 to 1000 mg, 1 to 1000 mg, from 2 to 1000 mg, from 3 to 1000 mg, from 4 to 1000 mg, from 5 to 1000 mg, from 6 to 1000

mg, from 7 to 1000 mg, from 8 to 1000 mg, from 9 to 1000 mg, from 10 to 1000 mg, from 15 to 1000 mg, from 20 to 1000 mg, from 25 to 1000 mg, from 30 to 1000 mg, from 35 to 1000 mg, from 40 to 1000 mg, from 45 to 1000 mg, from 50 to 1000 mg, from 55 to 1000 mg, from 60 to 1000 mg, from 65 to 1000 mg, from 70 to 1000 mg, from 75 to 1000 mg, from 80 to 1000 mg, from 85 to 1000 mg, from 90 to 1000 mg, from 95 to 1000 mg, from 100 to 1000 mg, from 150 to 1000 mg, from 200 to 1000 mg, from 250 to 1000 mg, from 300 to 1000 mg, from 350 to 1000 mg, from 400 to 1000 mg, from 450 to 1000 mg, from 500 to 1000 mg, from 550 to 1000 mg, from 600 to 1000 mg, from 650 to 1000 mg, from 700 to 1000 mg, from 750 to 1000 mg, from 800 to 1000 mg, from 850 to 1000 mg, from 900 to 1000 mg, or from 950 to 1000 mg.

[0407] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from about 0.1 to about 950 mg, from about 0.1 to about 900 mg, from about 0.1 to about 850 mg, from about 0.1 to about 800 mg, from about 0.1 to about 750 mg, from about 0.1 to about 700 mg, from about 0.1 to about 650 mg, from about 0.1 to about 600 mg, from about 0.1 to about 550 mg, from about 0.1 to about 500 mg, from about 0.1 to about 450 mg, from about 0.1 to about 400 mg, from about 0.1 to about 350 mg, from about 0.1 to about 300 mg, from about 0.1 to about 250 mg, from about 0.1 to about 200 mg, from about 0.1 to about 150 mg, from about 0.1 to about 100 mg, from about 0.1 to about 95 mg, from about 0.1 to about 90 mg, from about 0.1 to about 85 mg, from about 0.1 to about 80 mg, from about 0.1 to about 75 mg, from about 0.1 to about 70 mg, from about 0.1 to about 65 mg, from about 0.1 to about 60 mg, from about 0.1 to about 55 mg, from about 0.1 to about 50 mg, from about 0.1 to about 45 mg, from about 0.1 to about 40 mg, from about 0.1 to about 35 mg, from about 0.1 to about 30 mg, from about 0.1 to about mg, from about 0.1 to about 25 mg, from about 0.1 to about 20 mg, from about 0.1 to about 10 mg, from about 0.1 to about 9 mg, from about 0.1 to about 8 mg, from about 0.1 to about 7 mg, from about 0.1 to about 6 mg, from about 0.1 to about 5 mg, from about 0.1 to about 4 mg, from about 0.1 to about 3, from about 0.1 to about 2 mg, from about 0.1 to about 1 mg, from about 0.1 to about 0.9 mg, from about 0.1 to about 0.8 mg, from about 0.1 to about 0.7 mg, from about 0.1 to about 0.6 mg, from about 0.1 to about 0.5 mg, from about 0.1 to about 0.4 mg, from about 0.1 to about 0.3, or from about 0.1 to about 0.2 mg.

[0408] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from 0.1 to 950 mg, from 0.1 to 900 mg, from 0.1 to 850 mg, from 0.1 to 800 mg, from 0.1 to 750 mg, from 0.1 to 700 mg, from 0.1 to 650 mg, from 0.1 to 600 mg, from 0.1 to 550 mg, from 0.1 to 500 mg, from 0.1 to 450 mg, from 0.1 to 400 mg, from 0.1 to 350 mg, from 0.1 to 300 mg, from 0.1 to 250 mg, from 0.1 to 200 mg, from 0.1 to 150 mg, from 0.1 to 100 mg, from 0.1 to 95 mg, from 0.1 to 90 mg, from 0.1 to 85 mg, from 0.1 to 80 mg, from 0.1 to 75 mg, from 0.1 to 70 mg, from 0.1 to 65 mg, from 0.1 to 60 mg, from 0.1 to 55 mg, from 0.1 to 50 mg, from 0.1 to 45 mg, from 0.1 to 40 mg, from 0.1 to 35 mg, from 0.1 to 30 mg, from 0.1 to mg, from 0.1 to 25 mg, from 0.1 to 20 mg, from 0.1 to 10 mg, from 0.1 to 9 mg, from 0.1 to 8 mg, from 0.1 to 7 mg, from 0.1 to 6 mg, from 0.1 to 5 mg, from 0.1 to 4

mg, from 0.1 to 3, from 0.1 to 2 mg, from 0.1 to 1 mg, from 0.1 to 0.9 mg, from 0.1 to 0.8 mg, from 0.1 to 0.7 mg, from 0.1 to 0.6 mg, from 0.1 to 0.5 mg, from 0.1 to 0.4 mg, from 0.1 to 0.3, or from 0.1 to 0.2 mg.

[0409] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from about 1 to about 400 mg, from about 2 to about 400 mg, from about 3 to about 400 mg, from about 4 to about 400 mg, from about 5 to about 400 mg, from about 6 to about 400 mg, from about 7 to about 400 mg, from about 8 to about 400 mg, from about 9 to about 400 mg, from about 10 to about 400 mg, from about 20 to about 400 mg, from about 30 to about 400 mg, from about 40 to about 400 mg, from about 50 to about 400 mg, from about 60 to about 400 mg, from about 70 to about 400 mg, from about 80 to about 400 mg, from about 90 to about 400 mg, from about 100 to about 400 mg, from about 110 to about 400 mg, from about 120 to about 400 mg, from about 130 to about 400 mg, from about140 to about 400 mg, from about 150 to about 400 mg, from about160 to about 400 mg, from about 170 to about 400 mg, from about 180 to about 400 mg, from about 190 to about 400 mg, from about 200 to about 400 mg, from about 210 to about 400 mg, from about 220 to about 400 mg, from about 230 to about 400 mg, from about 240 to about 400 mg, from about 250 to about 400 mg, from about 260 to about 400 mg, from about 270 to about 400 mg, from about 280 to about 400 mg, from about 290 to about 400 mg, from about 300 to about 400 mg, from about 310 to about 400 mg, from about 320 to about 400 mg, from about 330 to about 400 mg, from about 340 to about 400 mg, from about 350 to about 400 mg, from about 360 to about 400 mg, from about 370 to about 400 mg, from about 380 to about 400 mg, or from about 390 to about 400 mg.

[0410] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from 1 to 400 mg, from 2 to 400 mg, from 3 to 400 mg, from 4 to 400 mg, from 5 to 400 mg, from 6 to 400 mg, from 7 to 400 mg, from 8 to 400 mg, from 9 to 400 mg, from 10 to 400 mg, from 20 to 400 mg, from 30 to 400 mg, from 40 to 400 mg, from 50 to 400 mg, from 60 to 400 mg, from 70 to 400 mg, from 80 to 400 mg, from 90 to 400 mg, from 100 to 400 mg, from 110 to 400 mg, from 120 to 400 mg, from 130 to 400 mg, from about140 to 400 mg, from 150 to 400 mg, from about160 to 400 mg, from 170 to 400 mg, from 180 to 400 mg, from 190 to 400 mg, from 200 to 400 mg, from 210 to 400 mg, from 220 to 400 mg, from 230 to 400 mg, from 240 to 400 mg, from 250 to 400 mg, from 260 to 400 mg, from 270 to 400 mg, from 280 to 400 mg, from 290 to 400 mg, from 300 to 400 mg, from 310 to 400 mg, from 320 to 400 mg, from 330 to 400 mg, from 340 to 400 mg, from 350 to 400 mg, from 360 to 400 mg, from 370 to 400 mg, from 380 to 400 mg, or from 390 to 400 mg.

[0411] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from about 10 to about 390 mg, from about 10 to about 380 mg, from about 10 to about 370 mg, from about 10 to about 360 mg, from about 10 to about 350 mg, from about 10 to about 340 mg, from about 10 to about 330 mg, from about 10 to about 320 mg, from about 10 to about 310 mg, from about 10

to about 300 mg, from about 10 to about 290 mg, from about 10 to about 280 mg, from about 10 to about 270 mg, from about 10 to about 260 mg, from about 10 to about 250 mg, from about 10 to about 240 mg, from about 10 to about 230 mg, from about 10 to about 220 mg, from about 10 to about 210 mg, from about 10 to about 200 mg, from about 10 to about 190 mg, from about 10 to about 180 mg, from about 10 to about 170 mg, from about 10 to about 160 mg, from about 10 to about 150 mg, from about 10 to about 140 mg, from about 10 to about 130 mg, from about 10 to about 120 mg, from about 10 to about 110 mg, from about 10 to about 90 mg, from about 10 to about 80 mg, from about 10 to about 70 mg, from about 10 to about 60 mg, from about 10 to about 50 mg, from about 10 to about 40 mg, from about 10 to about 30 mg, or from about 10 to about 20 mg.

[0412] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of from 10 to 390 mg, from 10 to 380 mg, from 10 to 370 mg, from 10 to 360 mg, from 10 to 350 mg, from 10 to 340 mg, from 10 to 330 mg, from 10 to 320 mg, from 10 to 310 mg, from 10 to 300 mg, from 10 to 290 mg, from 10 to 280 mg, from 10 to 270 mg, from 10 to 260 mg, from 10 to 250 mg, from 10 to 240 mg, from 10 to 230 mg, from 10 to 220 mg, from 10 to 210 mg, from 10 to 200 mg, from 10 to 190 mg, from 10 to 180 mg, from 10 to 170 mg, from 10 to 160 mg, from 10 to 150 mg, from 10 to 140 mg, from 10 to 130 mg, from 10 to 120 mg, from 10 to 110 mg, from 10 to 90 mg, from 10 to 80 mg, from 10 to 70 mg, from 10 to 60 mg, from 10 to 50 mg, from 10 to 40 mg, from 10 to 30 mg, or from 10 to 20 mg.

[0413] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg, about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg,

about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, about 140 mg, about 141 mg, about 142 mg, about 143 mg, about 144 mg, about 145 mg, about 146 mg, about 147 mg, about 148 mg, about 149 mg, about 150 mg, about 151 mg, about 152 mg, about 153 mg, about 154 mg, about 155 mg, about 156 mg, about 157 mg, about 158 mg, about 159 mg, about 160 mg, about 161 mg, about 162 mg, about 163 mg, about 164 mg, about 165 mg, about 166 mg, about 167 mg, about 168 mg, about 169 mg, about 170 mg, about 171 mg, about 172 mg, about 173 mg, about 174 mg, about 175 mg, about 176 mg, about 177 mg, about 178 mg, about 179 mg, about 180 mg, about 181 mg, about 182 mg, about 183 mg, about 184 mg, about 185 mg, about 186 mg, about 187 mg, about 188 mg, about 189 mg, about 190 mg, about 191 mg, about 192 mg, about 193 mg, about 194 mg, about 195 mg, about 196 mg, about 197 mg, about 198 mg, about 199 mg, about 200 mg, about 201 mg, about 202 mg, about 203 mg, about 204 mg, about 205 mg, about 206 mg, about 207 mg, about 208 mg, about 209 mg, about 210 mg, about 211 mg, about 212 mg, about 213 mg, about 214 mg, about 215 mg, about 216 mg, about 217 mg, about 218 mg, about 219 mg, about 220 mg, about 221 mg, about 222 mg, about 223 mg, about 224 mg, about 225 mg, about 226 mg, about 227 mg, about 228 mg, about 229 mg, about 230 mg, about 231 mg, about 232 mg, about 233 mg, about 234 mg, about 235 mg, about 236 mg, about 237 mg, about 238 mg, about 239 mg, about 240 mg, about 241 mg, about 242 mg, about 243 mg, about 244 mg, about 245 mg, about 246 mg, about 247 mg, about 248 mg, about 249 mg, about 250 mg, about 251 mg, about 252 mg, about 253 mg, about 254 mg, about 255 mg, about 256 mg, about 257 mg, about 258 mg, about 259 mg, about 260 mg, about 261 mg, about 262 mg, about 263 mg, about 264 mg, about 265 mg, about 266 mg, about 267 mg, about 268 mg, about 269 mg, about 270 mg, about 271 mg, about 272 mg, about 273 mg, about 274 mg, about 275 mg, about 276 mg, about 277 mg, about 278 mg, about 279 mg, about 280 mg, about 281 mg, about 282 mg, about 283 mg, about 284 mg, about 285 mg, about 286 mg, about 287 mg, about 288 mg, about 289 mg, about 290 mg, about 291 mg, about 292 mg, about 293 mg, about 294 mg, about 295 mg, about 296 mg, about 297 mg, about 298 mg, about 299 mg, about 300 mg, about 301 mg, about 302 mg, about 303 mg, about 304 mg, about 305 mg, about 306 mg, about 307 mg, about 308 mg, about 309 mg, about 310 mg, about 311 mg, about 312 mg, about 313 mg, about 314 mg, about 315 mg, about 316 mg, about 317 mg, about 318 mg, about 319 mg, about 320 mg, about 321 mg, about 322 mg, about 323 mg, about 324 mg, about 325 mg, about 326 mg, about 327 mg, about 328 mg, about 329 mg, about 330 mg, about 331 mg, about 332 mg, about 333 mg, about 334 mg, about 335 mg, about 336 mg, about 337 mg, about 338 mg, about 339 mg, about 340 mg, about 341 mg, about 342 mg, about 343 mg, about 344 mg, about 345 mg, about 346 mg, about 347 mg, about 348 mg, about 349 mg, about 350 mg, about 351 mg, about 352 mg, about 353 mg, about 354 mg, about 355 mg, about 356 mg, about 357 mg, about 358 mg, about 359 mg, about 360 mg, about 361 mg, about 362 mg, about 363 mg, about 364 mg, about 365 mg, about 366 mg, about 367 mg, about 368 mg, about 369 mg, about 370 mg, about 371 mg, about 372 mg, about 373 mg, about 374 mg, about 375 mg, about 376 mg, about 377 mg, about 378 mg, about 379 mg, about 380 mg, about 381 mg, about 382 mg, about 383 mg, about 384 mg, about 385 mg, about 386 mg, about 387 mg, about 388 mg, about 389 mg, about 390 mg, about 391 mg, about 392 mg,

about 393 mg, about 394 mg, about 395 mg, about 396 mg, about 397 mg, about 398 mg, about 399 mg, or about 400 mg.

[0414] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a loading dose of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg, 141 mg, 142 mg, 143 mg, 144 mg, 145 mg, 146 mg, 147 mg, 148 mg, 149 mg, 150 mg, 151 mg, 152 mg, 153 mg, 154 mg, 155 mg, 156 mg, 157 mg, 158 mg, 159 mg, 160 mg, 161 mg, 162 mg, 163 mg, 164 mg, 165 mg, 166 mg, 167 mg, 168 mg, 169 mg, 170 mg, 171 mg, 172 mg, 173 mg, 174 mg, 175 mg, 176 mg, 177 mg, 178 mg, 179 mg, 180 mg, 181 mg, 182 mg, 183 mg, 184 mg, 185 mg, 186 mg, 187 mg, 188 mg, 189 mg, 190 mg, 191 mg, 192 mg, 193 mg, 194 mg, 195 mg, 196 mg, 197 mg, 198 mg, 199 mg, 200 mg, 201 mg, 202 mg, 203 mg, 204 mg, 205 mg, 206 mg, 207 mg, 208 mg, 209 mg, 210 mg, 211 mg, 212 mg, 213 mg, 214 mg, 215 mg, 216 mg, 217 mg, 218 mg, 219 mg, 220 mg, 221 mg, 222 mg, 223 mg, 224 mg, 225 mg, 226 mg, 227 mg, 228 mg, 229 mg, 230 mg, 231 mg, 232 mg, 233 mg, 234 mg, 235 mg, 236 mg, 237 mg, 238 mg, 239 mg, 240 mg, 241 mg, 242 mg, 243 mg, 244 mg, 245 mg, 246 mg, 247 mg, 248 mg, 249 mg, 250 mg, 251 mg, 252 mg, 253 mg, 254 mg, 255 mg, 256 mg, 257 mg, 258 mg, 259 mg, 260 mg, 261 mg, 262 mg, 263 mg, 264 mg, 265 mg, 266 mg, 267 mg, 268 mg, 269 mg, 270 mg, 271 mg, 272 mg, 273 mg, 274 mg, 275 mg, 276 mg, 277 mg, 278 mg, 279 mg, 280 mg, 281 mg, 282 mg, 283 mg, 284 mg, 285 mg, 286 mg, 287 mg, 288 mg, 289 mg, 290 mg, 291 mg, 292 mg, 293 mg, 294 mg, 295 mg, 296 mg, 297 mg, 298 mg, 299 mg, 300 mg, 301 mg, 302 mg, 303 mg, 304 mg, 305 mg, 306 mg, 307 mg, 308 mg, 309 mg, 310 mg, 311 mg, 312 mg, 313 mg, 314 mg, 315 mg, 316 mg, 317 mg, 318 mg, 319 mg, 320 mg, 321 mg, 322 mg, 323 mg, 324 mg, 325 mg, 326 mg, 327 mg, 328 mg, 329 mg, 330 mg, 331 mg, 332 mg, 333 mg, 334 mg, 335 mg, 336 mg, 337 mg, 338 mg, 339 mg, 340 mg, 341 mg, 342 mg, 343 mg, 344 mg, 345 mg, 346 mg, 347 mg, 348 mg, 349 mg, 350 mg, 351 mg, 352 mg, 353 mg, 354 mg, 355 mg, 356 mg, 357 mg, 358 mg, 359 mg, 360 mg, 361 mg, 362 mg, 363 mg, 364 mg, 365 mg, 366 mg, 367 mg, 368 mg, 369 mg, 370 mg, 371 mg, 372 mg, 373 mg, 374 mg, 375 mg, 376 mg, 377 mg, 378 mg, 379 mg, 380 mg, 381 mg, 382 mg, 383 mg, 384 mg, 385 mg, 386 mg, 387 mg, 388 mg, 389 mg, 390 mg, 391 mg, 392 mg, 393 mg, 394 mg, 395 mg, 396 mg, 397 mg, 398 mg, 399 mg, or 400 mg.

[0415] In some embodiments, the method or dosing regimen as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg.

[0416] In some embodiments, the method or dosing regimen as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from about 0.1 to about 1000 mg, from about 0.2 to about 1000 mg, from about 0.3 to about 1000 mg, from about 0.4 to about 1000 mg, from about 0.5 to about 1000 mg, from about 0.6 to about 1000 mg, from about 0.7 to about 1000 mg, from about 0.8 to about 1000 mg, from about 0.9 to about 1000 mg, 1 to about 1000 mg, from about 2 to about 1000 mg, from about 3 to about 1000 mg, from about 4 to about 1000 mg, from about 5 to about 1000 mg, from about 6 to about 1000 mg, from about 7 to about 1000 mg, from about 8 to about 1000 mg, from about 9 to about 1000 mg, from about 10 to about 1000 mg, from about 15 to about 1000 mg, from about 20 to about 1000 mg, from about 25 to about 1000 mg, from about 30 to about 1000 mg, from about 35 to about 1000 mg, from about 40 to about 1000 mg, from about 45 to about 1000 mg, from about 50 to about 1000 mg, from about 55 to about 1000 mg, from about 60 to about 1000 mg, from about 65 to about 1000 mg, from about 70 to about 1000 mg, from about 75 to about 1000 mg, from about 80 to about 1000 mg, from about 85 to about 1000 mg, from about 90 to about 1000 mg, from about 95 to about 1000 mg, from about 100 to about 1000 mg, from about 150 to about 1000 mg, from about 200 to about 1000 mg, from about 250 to about 1000 mg, from about 300 to about 1000 mg, from about 350 to about 1000 mg, from about 400 to about 1000 mg, from about 450 to about 1000 mg, from about 500 to about 1000 mg, from about 550 to about 1000 mg, from about 600 to about 1000 mg, from about 650 to about 1000 mg, from about 700 to about 1000 mg, from about 750 to about 1000 mg, from about 800 to about 1000 mg, from about 850 to about 1000 mg, from about 900 to about 1000 mg, or from about 950 to about 1000 mg.

[0417] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from 0.1 to 1000 mg, from 0.2 to 1000 mg, from 0.3 to 1000 mg, from 0.4 to 1000 mg, from 0.5 to 1000 mg, from 0.6 to 1000 mg, from 0.7 to 1000 mg, from 0.8 to 1000 mg, from 0.9 to 1000 mg, 1 to 1000 mg, from 2 to 1000 mg, from 3 to 1000 mg, from 4 to 1000 mg, from 5 to 1000 mg, from 6 to 1000 mg, from 7 to 1000 mg, from 8 to 1000 mg, from 9 to 1000 mg, from 10 to 1000 mg, from 15 to 1000 mg, from 20 to 1000 mg, from 25 to 1000 mg, from 30 to 1000 mg, from 35 to 1000 mg, from 40 to 1000 mg, from 45 to 1000 mg, from 50 to 1000 mg, from 55 to 1000 mg, from 60 to 1000 mg, from 65 to 1000 mg, from 70 to 1000 mg, from 75 to 1000 mg, from 80 to 1000 mg, from 85 to 1000 mg, from 90 to 1000 mg, from 95 to 1000 mg, from 100 to 1000 mg, from 150 to 1000 mg, from 200 to 1000 mg, from 250 to 1000 mg, from 300 to 1000 mg, from 350 to 1000 mg, from 400 to 1000 mg, from 450 to 1000 mg, from 500 to 1000 mg, from 550 to 1000 mg, from 600 to 1000 mg, from 650 to 1000 mg,

from 700 to 1000 mg, from 750 to 1000 mg, from 800 to 1000 mg, from 850 to 1000 mg, from 900 to 1000 mg, or from 950 to 1000 mg.

[0418] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from about 0.1 to about 950 mg, from about 0.1 to about 900 mg, from about 0.1 to about 850 mg, from about 0.1 to about 800 mg, from about 0.1 to about 750 mg, from about 0.1 to about 700 mg, from about 0.1 to about 650 mg, from about 0.1 to about 600 mg, from about 0.1 to about 550 mg, from about 0.1 to about 500 mg, from about 0.1 to about 450 mg, from about 0.1 to about 400 mg, from about 0.1 to about 350 mg, from about 0.1 to about 300 mg, from about 0.1 to about 250 mg, from about 0.1 to about 200 mg, from about 0.1 to about 150 mg, from about 0.1 to about 100 mg, from about 0.1 to about 95 mg, from about 0.1 to about 90 mg, from about 0.1 to about 85 mg, from about 0.1 to about 80 mg, from about 0.1 to about 75 mg, from about 0.1 to about 70 mg, from about 0.1 to about 65 mg, from about 0.1 to about 60 mg, from about 0.1 to about 55 mg, from about 0.1 to about 50 mg, from about 0.1 to about 45 mg, from about 0.1 to about 40 mg, from about 0.1 to about 35 mg, from about 0.1 to about 30 mg, from about 0.1 to about mg, from about 0.1 to about 25 mg, from about 0.1 to about 20 mg, from about 0.1 to about 10 mg, from about 0.1 to about 9 mg, from about 0.1 to about 8 mg, from about 0.1 to about 7 mg, from about 0.1 to about 6 mg, from about 0.1 to about 5 mg, from about 0.1 to about 4 mg, from about 0.1 to about 3, from about 0.1 to about 2 mg, from about 0.1 to about 1 mg, from about 0.1 to about 0.9 mg, from about 0.1 to about 0.8 mg, from about 0.1 to about 0.7 mg, from about 0.1 to about 0.6 mg, from about 0.1 to about 0.5 mg, from about 0.1 to about 0.4 mg, from about 0.1 to about 0.3, or from about 0.1 to about 0.2 mg.

[0419] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from 0.1 to 950 mg, from 0.1 to 900 mg, from 0.1 to 850 mg, from 0.1 to 800 mg, from 0.1 to 750 mg, from 0.1 to 700 mg, from 0.1 to 650 mg, from 0.1 to 600 mg, from 0.1 to 550 mg, from 0.1 to 500 mg, from 0.1 to 450 mg, from 0.1 to 400 mg, from 0.1 to 350 mg, from 0.1 to 300 mg, from 0.1 to 250 mg, from 0.1 to 200 mg, from 0.1 to 150 mg, from 0.1 to 100 mg, from 0.1 to 95 mg, from 0.1 to 90 mg, from 0.1 to 85 mg, from 0.1 to 80 mg, from 0.1 to 75 mg, from 0.1 to 70 mg, from 0.1 to 65 mg, from 0.1 to 60 mg, from 0.1 to 55 mg, from 0.1 to 50 mg, from 0.1 to 45 mg, from 0.1 to 40 mg, from 0.1 to 35 mg, from 0.1 to 30 mg, from 0.1 to mg, from 0.1 to 25 mg, from 0.1 to 20 mg, from 0.1 to 10 mg, from 0.1 to 9 mg, from 0.1 to 8 mg, from 0.1 to 7 mg, from 0.1 to 6 mg, from 0.1 to 5 mg, from 0.1 to 4 mg, from 0.1 to 3, from 0.1 to 2 mg, from 0.1 to 1 mg, from 0.1 to 0.9 mg, from 0.1 to 0.8 mg, from 0.1 to 0.7 mg, from 0.1 to 0.6 mg, from 0.1 to 0.5 mg, from 0.1 to 0.4 mg, from 0.1 to 0.3, or from 0.1 to 0.2 mg.

[0420] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from about 1 to about 400 mg, from about 2 to about 400 mg, from about 3 to about 400 mg, from about 4 to about 400 mg, from about 5 to about 400 mg, from about 6 to about 400 mg,

from about 7 to about 400 mg, from about 8 to about 400 mg, from about 9 to about 400 mg, from about 10 to about 400 mg, from about 20 to about 400 mg, from about 30 to about 400 mg, from about 40 to about 400 mg, from about 50 to about 400 mg, from about 60 to about 400 mg, from about 70 to about 400 mg, from about 80 to about 400 mg, from about 90 to about 400 mg, from about 100 to about 400 mg, from about 110 to about 400 mg, from about 120 to about 400 mg, from about 130 to about 400 mg, from about140 to about 400 mg, from about 150 to about 400 mg, from about160 to about 400 mg, from about 170 to about 400 mg, from about 180 to about 400 mg, from about 190 to about 400 mg, from about 200 to about 400 mg, from about 210 to about 400 mg, from about 220 to about 400 mg, from about 230 to about 400 mg, from about 240 to about 400 mg, from about 250 to about 400 mg, from about 260 to about 400 mg, from about 270 to about 400 mg, from about 280 to about 400 mg, from about 290 to about 400 mg, from about 300 to about 400 mg, from about 310 to about 400 mg, from about 320 to about 400 mg, from about 330 to about 400 mg, from about 340 to about 400 mg, from about 350 to about 400 mg, from about 360 to about 400 mg, from about 370 to about 400 mg, from about 380 to about 400 mg, or from about 390 to about 400 mg.

[0421] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from 1 to 400 mg, from 2 to 400 mg, from 3 to 400 mg, from 4 to 400 mg, from 5 to 400 mg, from 6 to 400 mg, from 7 to 400 mg, from 8 to 400 mg, from 9 to 400 mg, from 10 to 400 mg, from 20 to 400 mg, from 30 to 400 mg, from 40 to 400 mg, from 50 to 400 mg, from 60 to 400 mg, from 70 to 400 mg, from 80 to 400 mg, from 90 to 400 mg, from 100 to 400 mg, from 110 to 400 mg, from 120 to 400 mg, from 130 to 400 mg, from about140 to 400 mg, from 150 to 400 mg, from about160 to 400 mg, from 170 to 400 mg, from 180 to 400 mg, from 190 to 400 mg, from 200 to 400 mg, from 210 to 400 mg, from 220 to 400 mg, from 230 to 400 mg, from 240 to 400 mg, from 250 to 400 mg, from 260 to 400 mg, from 270 to 400 mg, from 280 to 400 mg, from 290 to 400 mg, from 300 to 400 mg, from 310 to 400 mg, from 320 to 400 mg, from 330 to 400 mg, from 340 to 400 mg, from 350 to 400 mg, from 360 to 400 mg, from 370 to 400 mg, from 380 to 400 mg, or from 390 to 400 mg.

[0422] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from about 10 to about 390 mg, from about 10 to about 380 mg, from about 10 to about 370 mg, from about 10 to about 360 mg, from about 10 to about 350 mg, from about 10 to about 340 mg, from about 10 to about 330 mg, from about 10 to about 320 mg, from about 10 to about 310 mg, from about 10 to about 300 mg, from about 10 to about 290 mg, from about 10 to about 280 mg, from about 10 to about 270 mg, from about 10 to about 260 mg, from about 10 to about 250 mg, from about 10 to about 240 mg, from about 10 to about 230 mg, from about 10 to about 220 mg, from about 10 to about 210 mg, from about 10 to about 200 mg, from about 10 to about 190 mg, from about 10 to about 180 mg, from about 10 to about 170 mg, from about 10 to about 160 mg, from about 10 to about 150 mg, from about 10 to about 140 mg, from about 10 to about 130 mg, from about 10 to about 120 mg, from about 10 to about 110 mg, from about 10 to about 90 mg, from about 10 to about 80 mg, from about 10 to about 70

mg, from about 10 to about 60 mg, from about 10 to about 50 mg, from about 10 to about 40 mg, from about 10 to about 30 mg, or from about 10 to about 20 mg.

[0423] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of from 10 to 390 mg, from 10 to 380 mg, from 10 to 370 mg, from 10 to 360 mg, from 10 to 350 mg, from 10 to 340 mg, from 10 to 330 mg, from 10 to 320 mg, from 10 to 310 mg, from 10 to 300 mg, from 10 to 290 mg, from 10 to 280 mg, from 10 to 270 mg, from 10 to 260 mg, from 10 to 250 mg, from 10 to 240 mg, from 10 to 230 mg, from 10 to 220 mg, from 10 to 210 mg, from 10 to 200 mg, from 10 to 190 mg, from 10 to 180 mg, from 10 to 170 mg, from 10 to 160 mg, from 10 to 150 mg, from 10 to 140 mg, from 10 to 130 mg, from 10 to 120 mg, from 10 to 110 mg, from 10 to 90 mg, from 10 to 80 mg, from 10 to 70 mg, from 10 to 60 mg, from 10 to 50 mg, from 10 to 40 mg, from 10 to 30 mg, or from 10 to 20 mg.

[0424] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, about 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, about 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, about 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, about 101 mg, about 102 mg, about 103 mg, about 104 mg, about 105 mg, about 106 mg, about 107 mg, about 108 mg, about 109 mg, about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, about 120 mg, about 121 mg, about 122 mg, about 123 mg, about 124 mg, about 125 mg, about 126 mg, about 127 mg, about 128 mg, about 129 mg, about 130 mg, about 131 mg, about 132 mg, about 133 mg, about 134 mg, about 135 mg, about 136 mg, about 137 mg, about 138 mg, about 139 mg, about 140 mg, about 141 mg, about 142 mg, about 143 mg, about 144 mg, about 145 mg, about 146 mg, about 147 mg, about 148 mg, about 149 mg, about 150 mg, about 151 mg, about 152 mg, about 153 mg, about 154 mg, about 155 mg, about 156 mg, about 157 mg, about 158 mg, about 159 mg, about 160 mg, about 161 mg, about 162 mg, about 163 mg, about 164 mg, about 165 mg, about 166 mg, about 167 mg, about 168 mg, about 169 mg, about 170 mg, about 171 mg, about 172 mg, about 173 mg, about 174 mg,

about 175 mg, about 176 mg, about 177 mg, about 178 mg, about 179 mg, about 180 mg, about 181 mg, about 182 mg, about 183 mg, about 184 mg, about 185 mg, about 186 mg, about 187 mg, about 188 mg, about 189 mg, about 190 mg, about 191 mg, about 192 mg, about 193 mg, about 194 mg, about 195 mg, about 196 mg, about 197 mg, about 198 mg, about 199 mg, about 200 mg, about 201 mg, about 202 mg, about 203 mg, about 204 mg, about 205 mg, about 206 mg, about 207 mg, about 208 mg, about 209 mg, about 210 mg, about 211 mg, about 212 mg, about 213 mg, about 214 mg, about 215 mg, about 216 mg, about 217 mg, about 218 mg, about 219 mg, about 220 mg, about 221 mg, about 222 mg, about 223 mg, about 224 mg, about 225 mg, about 226 mg, about 227 mg, about 228 mg, about 229 mg, about 230 mg, about 231 mg, about 232 mg, about 233 mg, about 234 mg, about 235 mg, about 236 mg, about 237 mg, about 238 mg, about 239 mg, about 240 mg, about 241 mg, about 242 mg, about 243 mg, about 244 mg, about 245 mg, about 246 mg, about 247 mg, about 248 mg, about 249 mg, about 250 mg, about 251 mg, about 252 mg, about 253 mg, about 254 mg, about 255 mg, about 256 mg, about 257 mg, about 258 mg, about 259 mg, about 260 mg, about 261 mg, about 262 mg, about 263 mg, about 264 mg, about 265 mg, about 266 mg, about 267 mg, about 268 mg, about 269 mg, about 270 mg, about 271 mg, about 272 mg, about 273 mg, about 274 mg, about 275 mg, about 276 mg, about 277 mg, about 278 mg, about 279 mg, about 280 mg, about 281 mg, about 282 mg, about 283 mg, about 284 mg, about 285 mg, about 286 mg, about 287 mg, about 288 mg, about 289 mg, about 290 mg, about 291 mg, about 292 mg, about 293 mg, about 294 mg, about 295 mg, about 296 mg, about 297 mg, about 298 mg, about 299 mg, about 300 mg, about 301 mg, about 302 mg, about 303 mg, about 304 mg, about 305 mg, about 306 mg, about 307 mg, about 308 mg, about 309 mg, about 310 mg, about 311 mg, about 312 mg, about 313 mg, about 314 mg, about 315 mg, about 316 mg, about 317 mg, about 318 mg, about 319 mg, about 320 mg, about 321 mg, about 322 mg, about 323 mg, about 324 mg, about 325 mg, about 326 mg, about 327 mg, about 328 mg, about 329 mg, about 330 mg, about 331 mg, about 332 mg, about 333 mg, about 334 mg, about 335 mg, about 336 mg, about 337 mg, about 338 mg, about 339 mg, about 340 mg, about 341 mg, about 342 mg, about 343 mg, about 344 mg, about 345 mg, about 346 mg, about 347 mg, about 348 mg, about 349 mg, about 350 mg, about 351 mg, about 352 mg, about 353 mg, about 354 mg, about 355 mg, about 356 mg, about 357 mg, about 358 mg, about 359 mg, about 360 mg, about 361 mg, about 362 mg, about 363 mg, about 364 mg, about 365 mg, about 366 mg, about 367 mg, about 368 mg, about 369 mg, about 370 mg, about 371 mg, about 372 mg, about 373 mg, about 374 mg, about 375 mg, about 376 mg, about 377 mg, about 378 mg, about 379 mg, about 380 mg, about 381 mg, about 382 mg, about 383 mg, about 384 mg, about 385 mg, about 386 mg, about 387 mg, about 388 mg, about 389 mg, about 390 mg, about 391 mg, about 392 mg, about 393 mg, about 394 mg, about 395 mg, about 396 mg, about 397 mg, about 398 mg, about 399 mg, or about 400 mg.

[0425] In some embodiments, the method as described herein further comprises administering to the human subject a pharmaceutical composition comprising the compound as described herein at a maintenance dose of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41

mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg, 141 mg, 142 mg, 143 mg, 144 mg, 145 mg, 146 mg, 147 mg, 148 mg, 149 mg, 150 mg, 151 mg, 152 mg, 153 mg, 154 mg, 155 mg, 156 mg, 157 mg, 158 mg, 159 mg, 160 mg, 161 mg, 162 mg, 163 mg, 164 mg, 165 mg, 166 mg, 167 mg, 168 mg, 169 mg, 170 mg, 171 mg, 172 mg, 173 mg, 174 mg, 175 mg, 176 mg, 177 mg, 178 mg, 179 mg, 180 mg, 181 mg, 182 mg, 183 mg, 184 mg, 185 mg, 186 mg, 187 mg, 188 mg, 189 mg, 190 mg, 191 mg, 192 mg, 193 mg, 194 mg, 195 mg, 196 mg, 197 mg, 198 mg, 199 mg, 200 mg, 201 mg, 202 mg, 203 mg, 204 mg, 205 mg, 206 mg, 207 mg, 208 mg, 209 mg, 210 mg, 211 mg, 212 mg, 213 mg, 214 mg, 215 mg, 216 mg, 217 mg, 218 mg, 219 mg, 220 mg, 221 mg, 222 mg, 223 mg, 224 mg, 225 mg, 226 mg, 227 mg, 228 mg, 229 mg, 230 mg, 231 mg, 232 mg, 233 mg, 234 mg, 235 mg, 236 mg, 237 mg, 238 mg, 239 mg, 240 mg, 241 mg, 242 mg, 243 mg, 244 mg, 245 mg, 246 mg, 247 mg, 248 mg, 249 mg, 250 mg, 251 mg, 252 mg, 253 mg, 254 mg, 255 mg, 256 mg, 257 mg, 258 mg, 259 mg, 260 mg, 261 mg, 262 mg, 263 mg, 264 mg, 265 mg, 266 mg, 267 mg, 268 mg, 269 mg, 270 mg, 271 mg, 272 mg, 273 mg, 274 mg, 275 mg, 276 mg, 277 mg, 278 mg, 279 mg, 280 mg, 281 mg, 282 mg, 283 mg, 284 mg, 285 mg, 286 mg, 287 mg, 288 mg, 289 mg, 290 mg, 291 mg, 292 mg, 293 mg, 294 mg, 295 mg, 296 mg, 297 mg, 298 mg, 299 mg, 300 mg, 301 mg, 302 mg, 303 mg, 304 mg, 305 mg, 306 mg, 307 mg, 308 mg, 309 mg, 310 mg, 311 mg, 312 mg, 313 mg, 314 mg, 315 mg, 316 mg, 317 mg, 318 mg, 319 mg, 320 mg, 321 mg, 322 mg, 323 mg, 324 mg, 325 mg, 326 mg, 327 mg, 328 mg, 329 mg, 330 mg, 331 mg, 332 mg, 333 mg, 334 mg, 335 mg, 336 mg, 337 mg, 338 mg, 339 mg, 340 mg, 341 mg, 342 mg, 343 mg, 344 mg, 345 mg, 346 mg, 347 mg, 348 mg, 349 mg, 350 mg, 351 mg, 352 mg, 353 mg, 354 mg, 355 mg, 356 mg, 357 mg, 358 mg, 359 mg, 360 mg, 361 mg, 362 mg, 363 mg, 364 mg, 365 mg, 366 mg, 367 mg, 368 mg, 369 mg, 370 mg, 371 mg, 372 mg, 373 mg, 374 mg, 375 mg, 376 mg, 377 mg, 378 mg, 379 mg, 380 mg, 381 mg, 382 mg, 383 mg, 384 mg, 385 mg, 386 mg, 387 mg, 388 mg, 389 mg, 390 mg, 391 mg, 392 mg, 393 mg, 394 mg, 395 mg, 396 mg, 397 mg, 398 mg, 399 mg, or 400 mg.

Dosing Regimen: Loading Dose Schedule

[0426] In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising a second loading dose that is administered from 4 weeks to 12 weeks**,** from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5 weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks, from 6

weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the first loading dose after the first loading dose.

[0427] In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising a second loading dose that is administered from about 4 weeks to about 12 weeks**,** from about 4 weeks to about 11 weeks, from about 4 weeks to about 10 weeks, from about 4 weeks to about 9 weeks, from about 4 weeks to about 8 weeks, from about 4 weeks to about 7 weeks, from about 4 weeks to about 6 weeks, from about 4 weeks to about 5 weeks, from about 5 weeks to about 12 weeks, from about 5 weeks to about 11 weeks, from about 5 weeks to about 10 weeks, from about 5 weeks to about 9 weeks, from about 5 weeks to about 8 weeks, from about 5 weeks to about 7 weeks, from about 5 weeks to about 6 weeks, from about 6 weeks to about 12 weeks, from about 6 weeks to about 11 weeks, from about 6 weeks to about 10 weeks, from about 6 weeks to about 9 weeks, from about 6 weeks to about 8 weeks, from about 6 weeks to about 7 weeks, from about 7 weeks to about 12 weeks, from about 7 weeks to about 11 weeks, from about 7 weeks to about 10 weeks, from about 7 weeks to about 9 weeks, from about 7 weeks to about 8 weeks, from about 8 weeks to about 12 weeks, from about 8 weeks to about 11 weeks, from about 8 weeks to about 10 weeks, from about 8 weeks to about 9 weeks, from about 9 weeks to about 12 weeks, from about 9 weeks to about 11 weeks, from about 9 weeks to about 10 weeks, from about 10 weeks to about 12 weeks, from about 10 weeks to about 11 weeks, or from about 11 weeks to about 12 weeks after the first loading dose after the first loading dose.

[0428] In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising a third loading dose that is administered from 4 weeks to 12 weeks**,** from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5 weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks, from 6 weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the first loading dose after the second loading dose.

[0429] In some embodiments, the method or dosing regimen as described herein comprises administering to the human subject multiple doses of a pharmaceutical composition comprising a third

loading dose that is administered from about 4 weeks to about 12 weeks, from about 4 weeks to about 11 weeks, from about 4 weeks to about 10 weeks, from about 4 weeks to about 9 weeks, from about 4 weeks to about 8 weeks, from about 4 weeks to about 7 weeks, from about 4 weeks to about 6 weeks, from about 4 weeks to about 5 weeks, from about 5 weeks to about 12 weeks, from about 5 weeks to about 11 weeks, from about 5 weeks to about 10 weeks, from about 5 weeks to about 9 weeks, from about 5 weeks to about 8 weeks, from about 5 weeks to about 7 weeks, from about 5 weeks to about 6 weeks, from about 6 weeks to about 12 weeks, from about 6 weeks to about 11 weeks, from about 6 weeks to about 10 weeks, from about 6 weeks to about 9 weeks, from about 6 weeks to about 8 weeks, from about 6 weeks to about 7 weeks, from about 7 weeks to about 12 weeks, from about 7 weeks to about 11 weeks, from about 7 weeks to about 10 weeks, from about 7 weeks to about 9 weeks, from about 7 weeks to about 8 weeks, from about 8 weeks to about 12 weeks, from about 8 weeks to about 11 weeks, from about 8 weeks to about 10 weeks, from about 8 weeks to about 9 weeks, from about 9 weeks to about 12 weeks, from about 9 weeks to about 11 weeks, from about 9 weeks to about 10 weeks, from about 10 weeks to about 12 weeks, from about 10 weeks to about 11 weeks, or from about 11 weeks to about 12 weeks after the first loading dose after the second loading dose.

[0430] In some embodiments, the second loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14, weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, or 24 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 4 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 5 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 6 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 7 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 8 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 9 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 10 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 11 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 12 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 13 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 14 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 15 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 16 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 17 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 18 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 19 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 20 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 21 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 22 weeks after the first loading dose. In some

embodiments, the second loading dose is administered about 23 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 24 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 25 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 26 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 27 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 28 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 29 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 30 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 31 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 32 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 33 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 34 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 35 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 36 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 37 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 38 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 39 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 40 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 41 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 42 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 43 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 44 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 45 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 46 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 47 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 48 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 49 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 50 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 51 weeks after the first loading dose. In some embodiments, the second loading dose is administered about 52 weeks after the first loading dose.

[0431] In some embodiments, the third loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14, weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, or 24 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 4 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 5 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 6 weeks

after the second loading dose. In some embodiments, the third loading dose is administered about 7 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 8 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 9 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 10 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 11 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 12 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 13 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 14 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 15 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 16 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 17 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 18 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 19 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 20 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 21 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 22 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 23 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 24 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 25 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 26 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 27 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 28 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 29 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 30 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 31 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 32 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 33 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 34 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 35 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 36 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 37 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 38 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 39 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 40 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 41 weeks after the second loading dose. In some embodiments, the third loading dose is

administered about 42 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 43 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 44 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 45 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 46 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 47 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 48 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 49 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 50 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 51 weeks after the second loading dose. In some embodiments, the third loading dose is administered about 52 weeks after the second loading dose.

[0432] In some embodiments, the first loading dose, the second loading dose, and the third loading dose are administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14, weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, or 24 weeks apart from each other.

Dosing Regimen: Maintenance Dose Schedule

[0433] In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 20 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to

18 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 16 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 14 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 12 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 10 weeks after the dose immediately preceding the respective maintenance dose.

[0434] In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 11 months, from about 8 weeks to about 10 months, from about 8 weeks to about 8 months, from about 8 weeks to about 6 months, from about 8 weeks to about 20 weeks, from about 8 weeks to about 16 weeks, from about 8 weeks to about 14 weeks, from about 8 weeks to about 12 weeks, from about 8 weeks to about 10 weeks, from about 10 weeks to about 12 weeks, from about 12 weeks to about 16 weeks, from about 12 weeks to about 12 months, from about 12 weeks to about 11 months, from about 12 weeks to about 12 months, from about 12 weeks to about 8 months, from about 12 weeks to about 6 months, from about 12 weeks to about 20 weeks, from about 12 weeks to about 16 weeks, from about 12 weeks to about 14 weeks, from about 16 weeks to about 12 months, from about 16 weeks to about 11 months, from about 16 weeks to about 10 months, from about 16 weeks to about 8 months, from about 16 weeks to about 6 months, from about 16 weeks to about 20 weeks, from about 20 weeks to about 12 months, from about 20 weeks to about 11 months, from about 20 weeks to about 10 months, from about 20 weeks to about 8 months, from about 20 weeks to about 6 months, from about 6 months to about 12 months, from about 6 months to about 11 months, from about 6 months to about 10 months, from about 6 months to about 9 months, from about 6 months to about 8 months, from about 6 months to about 7 months, from about 7 months to about 12 months, from about 7 months to about 11 months, from about 7 months to about 10 months, from about 7 months to about 9 months, from about 7 months to about 8 months, from about 8 months to about 12 months, from about 8 months to about 11 months, from about 8 months to about 10 months, from about 8 months to about 9 months, from about 9 months to about 12 months, from about 9 months to about 11 months, from about 9 months to about 10 months, from about 10 months to about 12 months, from about 10 months to about 11 months, or from about 11 months to about 12 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 20 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 18

weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 16 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 14 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 12 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from about 8 weeks to about 10 weeks after the dose immediately preceding the respective maintenance dose.

[0435] In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 4 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 5 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 6 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 7 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 8 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 9 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 10 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 11 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 12 weeks after the dose immediately preceding the respective maintenance dose. In

some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 13 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 14 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 15 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 16 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 17 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 18 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 19 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 20 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 21 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 22 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 23 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 24 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 25 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 26 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 27 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 28 weeks after the dose immediately preceding

the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 29 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 30 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 31 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 32 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 33 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 34 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 35 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 36 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 37 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 38 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 39 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 40 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 41 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 42 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 43 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 44 weeks

after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 45 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 46 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 47 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 48 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 49 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 50 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 51 weeks after the dose immediately preceding the respective maintenance dose. In some embodiments, each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 52 weeks after the dose immediately preceding the respective maintenance dose.

[0436] In some embodiments, the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the second loading dose. In some embodiments, the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10

months, 11 months, or 12 months after the second loading dose. In some embodiments, the first maintenance dose is administered about 4 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 5 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 6 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 7 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 8 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 9 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 10 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 11 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 12 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 13 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 14 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 15 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 16 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 17 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 18 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 19 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 20 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 21 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 22 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 23 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 24 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 25 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 26 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 27 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 28 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 29 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 30 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 31 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 32 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 33 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 34 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 35 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 36 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 37 weeks after the second loading dose.

In some embodiments, the first maintenance dose is administered about 38 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 39 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 40 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 41 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 42 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 43 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 44 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 45 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 46 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 47 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 48 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 49 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 50 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 51 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered about 52 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 4 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 5 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 6 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 7 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 8 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 9 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 10 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 11 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 12 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 13 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 14 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 15 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 16 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 17 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 18 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 19 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 20 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 21 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 22 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 23 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 24 weeks after the second loading dose. In some embodiments, the first maintenance dose is

administered 25 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 26 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 27 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 28 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 29 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 30 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 31 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 32 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 33 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 34 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 35 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 36 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 37 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 38 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 39 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 40 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 41 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 42 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 43 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 44 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 45 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 46 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 47 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 48 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 49 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 50 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 51 weeks after the second loading dose. In some embodiments, the first maintenance dose is administered 52 weeks after the second loading dose.

[0437] In some embodiments, the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6

months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the third loading dose. In some embodiments, the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the third loading dose. In some embodiments, the first maintenance dose is administered about 4 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 5 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 6 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 7 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 8 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 9 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 10 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 11 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 12 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 13 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 14 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 15 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 16 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 17 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 18 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 19 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 20 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 21 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 22 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 23 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 24 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 25 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 26 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 27 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 28 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 29 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 30 weeks after the third loading dose. In some

embodiments, the first maintenance dose is administered about 31 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 32 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 33 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 34 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 35 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 36 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 37 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 38 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 39 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 40 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 41 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 42 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 43 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 44 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 45 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 46 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 47 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 48 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 49 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 50 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 51 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered about 52 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 4 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 5 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 6 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 7 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 8 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 9 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 10 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 11 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 12 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 13 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 14 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 15 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 16 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 17 weeks after the third loading dose. In some

embodiments, the first maintenance dose is administered 18 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 19 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 20 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 21 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 22 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 23 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 24 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 25 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 26 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 27 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 28 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 29 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 30 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 31 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 32 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 33 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 34 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 35 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 36 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 37 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 38 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 39 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 40 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 41 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 42 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 43 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 44 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 45 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 46 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 47 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 48 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 49 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 50 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 51 weeks after the third loading dose. In some embodiments, the first maintenance dose is administered 52 weeks after the third loading dose.

[0438] In some embodiments, the first maintenance dose is administered about 4 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 5 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 6 weeks after

the last loading dose. In some embodiments, the first maintenance dose is administered about 7 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 8 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 9 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 10 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 11 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 12 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 13 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 14 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 15 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 16 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 17 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 18 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 19 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 20 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 21 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 22 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 23 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 24 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 25 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 26 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 27 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 28 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 29 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 30 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 31 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 32 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 33 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 34 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 35 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 36 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 37 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 38 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 39 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 40 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 41 weeks after the last loading dose. In some embodiments, the first maintenance

dose is administered about 42 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 43 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 44 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 45 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 46 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 47 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 48 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 49 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 50 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 51 weeks after the last loading dose. In some embodiments, the first maintenance dose is administered about 52 weeks after the last loading dose.

[0439] In some embodiments, the one or more maintenance doses are administered over a lifetime of the human subject. In some embodiments, the method or the dosing regimen as described herein comprises administering the one or more maintenance doses to the human subject until an indication that a most recent maintenance dose is not tolerated by the human subject. In some embodiments, the method or the dosing regimen comprises administering the one or more maintenance doses to the human subject until an indication that a most recent maintenance dose is not effective in the human subject. In some embodiments, the one or more maintenance doses are administered to the human subject over a period of at least one year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35, years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0440] In some embodiments, the maintenance doses are administered at a same dose frequency or a substantially same dose frequency. In some embodiments, the maintenance doses are administered once every week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every ten weeks, once every, eleven weeks, once every twelve weeks, once every thirteen weeks, once every fourteen weeks, once every fifteen weeks, once every sixteen weeks, once every seventeen weeks, once every eighteen weeks, once very nineteen weeks, once every twenty weeks, once every 21 weeks, once every 22 weeks, once every 23 weeks, once every 24 weeks, once every 25 weeks, once every 26 weeks, once every 27 weeks, once every 28 weeks, once every 29 weeks, once every 30 weeks, once every 31 weeks, once every 32 weeks, once every 33 weeks, once every 34 weeks, once every 35 weeks, once every 36 weeks, once every 37 weeks, once every 38 weeks, once every 39 weeks, once every 40 weeks, once every 41 weeks, once every 42 weeks, once every 43 weeks, once every 44 weeks, once every 45 weeks, once every 46 weeks, once every 47 weeks, once every 48 weeks, once every 49 weeks, once every 50 weeks, once every 51 weeks, or once every 52 weeks.

[0441] In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24

months after administration of the last loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of the last loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 months after the last loading dose is administered. In some embodiments, the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 1 month after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 2 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 3 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 4 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 5 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, or 8 weeks after administration of a dose immediately prior. In some embodiments, dose frequency is maintained or reduced following an indication that the previous dose is effective. In some embodiments, dose frequency is increased following an indication that the previous dose is not effective.

[0442] In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the first loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of the first loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 months after the first loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the second loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of the second loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 months after the second loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the third loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of the third loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 months after the third loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the last loading dose. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of the last loading dose. In some

embodiments, a first maintenance dose of the one or more maintenance doses is administered about 1 month after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 2 months after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 3 months after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 months after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 5 months after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 6 months after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 1 week after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 2 weeks after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 3 weeks after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 4 weeks after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 5 weeks after the last loading dose is administered. In some embodiments, a first maintenance dose of the one or more maintenance doses is administered about 6 weeks after the last loading dose is administered.

[0443] In some embodiments, the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 1 month after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 2 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 3 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 4 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 5 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered about 6 months after administration of a dose immediately prior. In some embodiments, the one or more maintenance doses is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after administration of a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 1 month after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 2 months after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 3 months after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 4 months after the subject has been administered a dose immediately prior. In some embodiments, each

maintenance dose of the one or more maintenance doses is administered about 5 months after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 6 months after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 1 week after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 2 weeks after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 3 weeks after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 4 weeks after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 5 weeks after the subject has been administered a dose immediately prior. In some embodiments, each maintenance dose of the one or more maintenance doses is administered about 6 weeks after the subject has been administered a dose immediately prior. In some embodiments, dose frequency is maintained or reduced following an indication that the previous dose is effective. In some embodiments, dose frequency is increased following an indication that the previous dose is not effective.

[0444] In some embodiments, the time elapsed between the second loading dose and the third loading dose is half of the amount of time elapsed between the first loading dose and the second loading dose, and each maintenance dose is administered with twice the amount of time elapsed between the first and second loading doses. In some embodiments, 6 weeks elapse between the first loading dose and the second loading dose, 3 weeks elapse between the second and third loading dose, and 12 weeks elapse between each maintenance dose. In some embodiments, 8 weeks elapse between the first loading dose and the second loading dose, 4 weeks elapse between the second and third loading dose, and 16 weeks elapse between each maintenance dose. In some embodiments, 10 weeks elapse between the first loading dose and the second loading dose, 5 weeks elapse between the second and third loading dose, and 20 weeks elapse between each maintenance dose. In some embodiments, 12 weeks elapse between the first loading dose and the second loading dose, 6 weeks elapse between the second and third loading dose, and 24 weeks elapse between each maintenance dose.

Dosing Schedule Adjusted for Tolerability or Effectiveness and Additional Therapeutic Agents

[0445] In some embodiments, the method or dosing regimen as described herein further comprises assessing tolerability or effectiveness of the pharmaceutical composition. In some embodiments, the method or dosing regimen further comprises administering at least one additional therapeutic agent or therapy. In some embodiments, the at least one additional therapeutic agent or therapy is administered at the same time as the first loading dose, the second loading dose and/or the third loading dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered at the same time as the first maintenance dose and/or the one or more maintenance doses. In some embodiments, the at least one additional therapeutic agent or therapy is administered prior to administration of the first loading dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered after

administration of the first loading dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered after administration of the second loading dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered after administration of the third loading dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered after administration of the first maintenance dose. In some embodiments, the at least one additional therapeutic agent or therapy comprises Brivaracetam, Cannabidiol oral solution, Cenobamate, Clobazam, Clonazepam, Diazepam Nasal Spray, Diazepam Rectal, Divalproex Sodium, Divalproex Sodium-ER, Eslicarbazepine Acetate, Ethosuximide, Felbamate, Fenfluramine, Gabapentin, Levetiracetam, Levetiracetam XR, Lorazepam, Midazolam Nasal, Perampanel, Phenobarbital, Pregabalin, Primidone, Stiripentol, Tiagabine Hydrochloride, Topiramate, Topiramate XR, Valproic Acid, Vigabatrin, or Zonisamide. In some embodiments, the at least one additional therapeutic agent or therapy comprises fenfluramine.

[0446] In some embodiments, the method as described herein further comprises assessing tolerability or effectiveness of the pharmaceutical composition.

[0447] In some embodiments, an amount of compound in a subsequent dose is lower than an amount of compound in a previous dose following an indication that administration of the previous dose is not tolerated.

[0448] In some embodiments, an amount of compound in a subsequent loading dose is lower than an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is not tolerated. In some embodiments, an amount of compound in a subsequent maintenance dose is lower than an amount of compound in a previous maintenance dose following an indication that administration of the previous maintenance dose is not tolerated.

[0449] In some embodiments, an amount of compound in a subsequent loading dose is the same as the amount of compound in a previous loading dose following an indication that administration of the previous loading dose is effective. In some embodiments, an amount of compound in a subsequent maintenance dose is the same as an amount of compound in a previous maintenance dose following an indication that administration of the previous maintenance dose is effective.

[0450] In some embodiments, an amount of compound in a subsequent loading dose is higher than an amount of compound in the previous loading dose following an indication that administration of the previous dose is not effective. In some embodiments, an amount of compound in a subsequent maintenance dose is higher than an amount of compound in the previous maintenance dose following an indication that administration of the previous maintenance dose is not effective.

[0451] In some embodiments, an amount of compound in a subsequent loading dose is lower than an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is not tolerated. In some embodiments, an amount of compound in a subsequent maintenance dose is lower than an amount of compound in a previous maintenance dose following an indication that administration of the previous maintenance dose is not tolerated.

[0452] In some embodiments, an amount of compound in a subsequent loading dose is the same as the amount of compound in a previous loading dose following an indication that administration of the previous loading dose is tolerated. In some embodiments, an amount of compound in a subsequent maintenance dose is the same as an amount of compound in a previous maintenance dose following an indication that administration of the previous maintenance dose is tolerated.

[0453] In some embodiments, an amount of compound in a subsequent loading dose is higher than the amount of compound in a previous loading dose following an indication that administration of the previous loading dose is tolerated. In some embodiments, an amount of compound in a subsequent maintenance dose is higher than an amount of compound in a previous maintenance dose following an indication that administration of the previous maintenance dose is tolerated.

[0454] In some embodiments, an amount of compound in a subsequent maintenance dose is higher than an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is tolerated. In some embodiments, an amount of compound in a subsequent maintenance dose is the same as an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is effective. In some embodiments, an amount of compound in a subsequent maintenance dose is lower than an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is effective. In some embodiments, an amount of compound in a subsequent maintenance dose is higher than an amount of compound in a previous loading dose following an indication that administration of the previous loading dose is not effective. In some embodiments, subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the previous loading dose. In some embodiments, subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the previous maintenance dose.

[0455] In some embodiments, the subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after administration of the previous loading dose. In some embodiments, the subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days after administration of the previous loading dose. In some embodiments, the subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 weeks after administration of the previous loading dose. In some embodiments, the subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 months after administration of the previous loading dose. In some embodiments, the subsequent loading doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 years after administration of the previous loading dose.

[0456] In some embodiments, the subsequent loading doses are administered at the same interval. For example, every subsequent loading dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after administration of the

previous dose. In some embodiments, every subsequent loading dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days after administration of the previous loading dose. In some embodiments, every subsequent loading dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 weeks after administration of the previous loading dose. In some embodiments, every subsequent loading dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 months after administration of the previous loading dose.

[0457] In some embodiments, the subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after administration of the previous maintenance dose. In some embodiments, the subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days after administration of the previous maintenance dose. In some embodiments, the subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 weeks after administration of the previous maintenance dose. In some embodiments, the subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 months after administration of the previous maintenance dose. In some embodiments, the subsequent maintenance doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 years after administration of the previous maintenance dose.

[0458] In some embodiments, the subsequent maintenance doses are administered at the same interval. For example, every subsequent maintenance dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after administration of the previous dose. In some embodiments, every subsequent maintenance dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days after administration of the previous maintenance dose. In some embodiments, every subsequent maintenance dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 weeks after administration of the previous maintenance dose. In some embodiments, every subsequent maintenance dose is administered at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 months after administration of the previous maintenance dose.

[0459] In some embodiments, the subsequent doses are administered at the different intervals.

[0460] In some embodiments, the dose frequency is maintained or reduced following an indication that the previous dose is effective. In some embodiments, the dose frequency is increased following an indication that the previous dose is not effective. In some embodiments, the method further comprises administrating at least one additional therapeutic agent or therapy. In some embodiments, the at least one additional therapeutic agent or therapy is administered at the same time as the dose. In some

embodiments, the at least one additional therapeutic agent or therapy is administered prior to administration of the dose. In some embodiments, the at least one additional therapeutic agent or therapy is administered after administration of the dose.

Loading and Maintenance Doses

[0461] In some embodiments, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I) at least a first loading dose amount of from about 20 mg to about 80 mg and one or more maintenance doses, wherein the one or more maintenance doses contain the compound at an amount that is different from the first loading dose amount. In some embodiment, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (II) at a first loading dose amount of from about 30 mg to about 70 mg and one or more maintenance doses, wherein the one or more maintenance doses contain the compound at an amount that is different from the first loading dose amount. In some embodiment, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I) at least a first loading dose amount of from about 20 mg to about 80 mg and one or more maintenance doses, wherein the one or more maintenance doses contain the compound at an amount that is the same as the first loading dose amount. In some embodiment, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (II) at a first loading dose amount of from about 30 mg to about 70 mg and one or more maintenance doses, wherein the one or more maintenance doses contain the compound at an amount that is the same as the first loading dose amount.

[0462] In some embodiments, the first dose (also called first loading dose) is the first of one of more loading doses. In some embodiments, the first loading dose contains the compound at an amount of about 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 30 mg to about 40 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 35 mg to about 40 mg. In some embodiments, the first dose of the one or more loading doses contains the compound an amount of from about 30 mg to about 45 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 35 mg to about 45 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 30 mg to about 50 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 35 mg to about 50 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 30 mg to about 35 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 30 mg to about 80 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount

of from about 30 mg to about 70 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 30 mg to about 60 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 50 mg to about 70 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 50 mg to about 80 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 45 mg to about 80 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 45 mg to about 70 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of from about 45 mg to about 60 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 30 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 35 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 40 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 45 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 50 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 60 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 70 mg. In some embodiments, the first dose of the one or more loading doses contains the compound at an amount of about 80 mg.

[0463] In some embodiments, the method or dosing regimen comprises administering only one loading dose. In some embodiments, the method comprises administering two loading doses. In some embodiments, the method comprises administering three loading doses. In some embodiments, the method comprises administering four loading doses. In some embodiments, the method comprises administering five loading doses. In some embodiments, the method comprises administering at least two loading doses. In some embodiments, the method comprises administering at least three loading doses. In some embodiments, the method comprises administering at least four loading doses. In some embodiments, the method comprises administering from 2 to 5 loading doses. In some embodiments, the method comprises administering from 2 to 4 loading doses. In some embodiments, the method comprises administering from 2 to 3 loading doses. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 30 mg. In some embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 30 mg. In some embodiments, the method comprises administering four loading doses, wherein each loading dose contains the compound at an amount of about 30 mg. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 45 mg. In some embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 45 mg. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 60 mg. In some

embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 60 mg. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 70 mg. In some embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 70 mg. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 80 mg. In some embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 80 mg. In some embodiments, the method comprises administering two loading doses, wherein each loading dose contains the compound at an amount of about 90 mg. In some embodiments, the method comprises administering three loading doses, wherein each loading dose contains the compound at an amount of about 90 mg.

[0464] In some embodiments, the amount of compound in the one or more maintenance doses are higher than the amount of compound in last loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is higher than the amount of compound in the first loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is higher than the amount of compound in the second loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is higher than the amount of compound in the third loading dose. In some embodiments, the amount of compound in the one or more maintenance doses are lower than the amount of compound in last loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is lower than the amount of compound in the first loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is lower than the amount of compound in the second loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is lower than the amount of compound in the third loading dose. In some embodiments, the amount of compound in the one or more maintenance doses is lower than the amount in first maintenance dose. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, or 100 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 20 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 25 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 30 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 35 mg to about 45 mg. In some embodiments, the one or more maintenance

doses contain the compound at an amount of from about 40 mg to about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 45 mg to about 55 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 45 mg to about 60 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 45 mg to about 65 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 45 mg to about 70 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 45 mg to about 75 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 50 mg to about 60 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 50 mg to about 65 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 55 mg to about 65 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 50 mg to about 70 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 55 mg to about 70 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 60 mg to about 70 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 50 mg to about 75 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 55 mg to about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 60 mg to about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 65 mg to about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 70 mg to about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 75 mg to about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 20 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 25 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 30 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 35 mg to about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 20 mg to about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 25 mg to about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 30 mg to about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 30

mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 30 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 20 mg to about 30 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 25 mg to about 30 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 25 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 25 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 20 mg to about 25 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 10 mg to about 20 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of from about 15 mg to about 20 mg.

[0465] In some embodiments, the one or more maintenance doses contain the compound at an amount of about 20 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 25 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 30 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 35 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 40 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 45 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 50 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 55 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 60 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 65 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 70 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 75 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 80 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 85 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 90 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 95 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount of about 100 mg. In some embodiments, the one or more maintenance doses contain the compound at an amount effective to reduce seizure frequency and/or improve cognition and/or behavior for over one year of dosing compared to a subject not treated with the compound. In some embodiments, the one or more maintenance doses contain the compound at an amount effective to reduce seizure frequency and/or improve cognition and/or behavior for over one year of dosing compared to a subject administered the first dose but not administered the one or more maintenance doses.

[0466] In some embodiments, the method comprises administering at least two maintenance doses. In some embodiments, the method comprises administering at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 maintenance doses. In some embodiments, the method comprises administering two maintenance doses. In some embodiments, the method comprises administering three maintenance doses. In some embodiments, the method comprises administering four maintenance doses. In some embodiments, the method comprises administering 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 maintenance doses. In some embodiments, the method comprises administering at most 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 maintenance doses. In some embodiments, the maintenance doses are administered every month or every two, three, four, five, or six months. In some embodiments, the maintenance doses are administered every month. In some embodiments, the maintenance doses are administered every two months. In some embodiments, the maintenance doses are administered every three months. In some embodiments, the maintenance doses are administered every four months. In some embodiments, the maintenance doses are administered every five months. In some embodiments, the maintenance doses are administered every six months.

[0467] In some embodiments, the one or more maintenance doses contain the compound at an amount that is lower than the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount that is lower than the first dose amount following an indication that administration of the first dose is not tolerated. In some embodiments, the one or more maintenance doses contain the compound at an amount is lower than the first dose amount following an indication that administration of the first dose is effective. In some embodiments, the one or more maintenance doses contain the compound at an amount that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, or 80% lower than the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 40 mg, or 45 mg lower than the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount that is the same as the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount is the same as the first dose amount following an indication that administration of the first dose is effective. In some embodiments, the one or more maintenance doses contain the compound at an amount that is higher than the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount that is higher than the first dose amount following an indication that administration of the first dose is tolerated. In some embodiments, the one or more maintenance doses contain the compound at an amount that is higher than the first dose amount following an indication that administration of the first dose is not effective. In some embodiments, the one or more maintenance doses contain the compound at an amount that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, or 80% higher than the first loading dose amount. In some embodiments, the one or more maintenance doses contain the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 45 mg, 50 mg, 60 mg, 65 mg, or 70 mg higher than the first loading dose amount.

[0468] In some embodiments, the method or dosing regimen comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I) or (II), wherein the method comprises administering to the human subject the pharmaceutical composition at a first loading dose amount of from about 30 mg to about 80 mg and one or more maintenance doses at an amount of from about 30 mg to about 50 mg, wherein the one or more maintenance doses contain an amount that is different from the first loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose amount of from about 30 mg to about 70 mg and one or more maintenance doses at an amount of from about 30 mg to about 50 mg, wherein the one or more maintenance doses contain an amount that is different from the first loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose amount of from about 40 mg to about 70 mg and one or more maintenance doses at an amount of from about 30 mg to about 45 mg, wherein the one or more maintenance doses contain an amount that is different from the first loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of from about 45 mg to about 70 mg, and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 45 mg, wherein the one or more maintenance doses contain the compound at an amount that is different from the first loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of at least 45 mg and one or more maintenance doses that contain the compound at an amount of at least 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose amount of about 45 mg and one or more maintenance doses at an amount of about 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 50 mg and one or more maintenance doses that contain the compound at an amount of about 35 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 55 mg and one or more maintenance doses that contain the compound at an amount of about 40 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 60 mg and one or more maintenance doses that contain the compound at an amount of about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of about 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains

the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 60 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 50 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 40 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition at a first loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 35 mg. In some embodiments, the method or dosing regimen comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I) or (II), wherein the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of from about 30 mg to about 80 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 50 mg, wherein the one or more maintenance doses contain an amount that is different from the last loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of from about 30 mg to about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 50 mg, wherein the one or more maintenance doses contain an amount that is different from the last loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of from about 40 mg to about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 45 mg, wherein the one or more maintenance doses contain an amount that is different from the last loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of from about 45 mg to about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 45 mg, wherein the one or more maintenance doses contain an amount that is different from the last loading dose amount. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of at least 45 mg and one or more maintenance doses that contain the compound at an amount of at least 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 45 mg and one or more maintenance doses that contain the compound

at an amount of about 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 50 mg and one or more maintenance doses that contain the compound at an amount of about 35 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 55 mg and one or more maintenance doses that contain the compound at an amount of about 40 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 60 mg and one or more maintenance doses that contain the compound at an amount of about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of about 30 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 60 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 50 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 45 mg. In some embodiments, the method comprises administering to the human subject the pharmaceutical composition a last loading dose that contains the compound at an amount of about 70 mg and one or more maintenance doses that contain the compound at an amount of from about 30 mg to about 40 mg. The methods or dosing regimen disclosed herein can (i) reduce seizure frequency and/or (ii) improve non-seizure-related aspects after about 1 month, 3 months, 6 months, 9 months, or 1 year dosing of the maintenance dose as compared to a control, such as observed natural history of the disease. In some embodiments, the non-seizure-related aspects comprise cognitive or behavioral domains. In some embodiments, cognitive or behavioral domains comprise communication, daily living skills, socialization skills, and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills.

[0469] In some embodiment, the method as described herein comprises administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I), or in some cases, the chemical structure (II), wherein the method comprises administering to the human

subject the pharmaceutical composition comprising the compound at a first loading dose amount of from 30 to 70 mg and one or more maintenance doses, wherein the one or more maintenance doses contain an amount that is different from the first loading dose amount. In some embodiments, the pharmaceutical composition comprising the compound is administered into the intrathecal space of the human subject. In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid of the human subject. In some embodiments, the pharmaceutical composition is administered into the brain of the human subject. In some embodiments, the pharmaceutical composition is administered into the cerebrospinal fluid in the brain of the human subject. In some embodiments, the pharmaceutical composition is administered as a bolus injection. In some embodiments, the method comprises administering the pharmaceutical composition as a bolus injection over 1 to 60 minutes, 1 to 50 minutes, 1 to 40 minutes, 1 to 30 minutes, 1 to 20 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes. In some embodiments, the method comprises administering the pharmaceutical composition as a bolus injection using a spinal anesthesia needle. In some embodiments, the pharmaceutical composition is administered by infusion with a delivery pump. In some embodiments, the pharmaceutical composition is administered by intracerebroventricular injection. In some embodiments, the pharmaceutical composition is administered by intrathecal injection. In some embodiments, the pharmaceutical composition is administered by lumbar injection.

[0470] In some embodiments, the methods herein provide administering to the human subject a pharmaceutical composition comprising the compound according to chemical structure (I), or in some cases, the chemical structure (II), wherein the pharmaceutical composition comprises the compound at a first loading dose amount of from 30 to 50 mg and one or more maintenance doses, wherein the one or more maintenance doses contain the compound at an amount that is different from the first loading dose amount. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient, carrier, or diluent. In some embodiments, the pharmaceutical composition is a solution. In some embodiments, the compound is present in the pharmaceutical composition at a concentration of from about 0.1 mg/mL to about 250 mg/mL. In some embodiments, the compound is present in the first dose at a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, or 10 mg/mL. In some embodiments, the compound is present in the maintenance dose at a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, or 20 mg/mL.

[0471] In some embodiments, the pharmaceutical composition comprising the first dose is a solution. In some embodiments, the compound is dissolved or suspended in the solution and the first dose has volume of 5 mL or higher. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of from 5 to 50 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of from 5 to 25 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of from 5 to 10 mL. In

some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 5 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 6 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 7 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 8 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 9 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 10 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 11 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 12 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 13 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 14 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 15 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 17 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 20 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 25 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 30 mL.

[0472] In some embodiments, the pharmaceutical composition comprising the one or more maintenance doses is a solution. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 10 mL or higher. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of from 10 to 50 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of from 5 to 25 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of from 5 to 10 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 5 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 6 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 7 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 8 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 9 mL. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 10 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 11 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 12 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 13 mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 14 mL. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 15

mL. In some embodiments, the compound is dissolved or suspended in a solution and the first dose has volume of 17 mL. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 20 mL. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 25 mL. In some embodiments, the compound is dissolved or suspended in a solution and each of the one or more maintenance doses have a volume of 30 mL.

[0473] In some embodiments, the pharmaceutical composition is a solution. In some cases, the solution comprises a pharmaceutically acceptable excipient, carrier, or diluent. In some embodiments, the pharmaceutical composition comprises from 0.1 mL to 50 mL of a diluent, wherein the compound is solubilized or diluted in the diluent. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.5, 1, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45 or 50 mL of the diluent. In some embodiments, the pharmaceutical composition comprises 1 mL to 20 mL of the diluent, 2 mL to 10 mL of the diluent or 1 mL to 5 mL of the diluent. In some embodiments, the diluent comprises a cerebral spinal fluid (CSF) sample from the subject or an artificial cerebral spinal fluid (aCSF) solution. In some embodiments, the compound is solubilized or diluted in an isotonic solution. In some embodiments, the isotonic solution is a CSF sample from the subject. In some embodiments, the compound is solubilized or diluted in the pharmaceutical composition in a phosphate-buffered solution with at least pH 5.8. In some embodiments, the compound is solubilized or diluted in the pharmaceutical composition in a phosphate-buffered (pH 6.6 – 7.6) solution. In some embodiments, the buffer comprises 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na_2HPO_4, 0.1-50 mM NaH_2PO_4, 0.1-50 mM $CaCl_2$, 0.1-50 mM $MgCl_2$ or a combination thereof. In some embodiments, the buffer comprises 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$. In some embodiments, the buffer comprises 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof. In some embodiments, the buffer comprises carbohydrates. In some embodiments, the buffer comprises D-glucose. In some embodiments, the buffer comprises 1-100 mM D-glucose. In some embodiments, the buffer comprises an antioxidant. In some embodiments, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof. In some embodiments, the pharmaceutical formulation does not comprise a preservative. In other embodiments, the compound is solubilized or diluted in the pharmaceutical composition in a solution or diluent that lacks sodium phosphate. In some of these embodiments, the solution or diluent comprises 5-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$, and 0.1-50 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$. In some of these embodiments, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM; (c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM; (d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and (e) water. In some of these embodiments, the concentration of the compound is about 3

mg/mL, about 4.5 mg/mL, about 7 mg/mL, or about 33 mg/mL; the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM; the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM; the concentration of potassium chloride is about 3 mM; and the concentration of sodium chloride is about 150 mM. In some of these embodiments, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium ion (Ca^{2+}) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.1 mM to about 50 mM; (c) potassium ion (K^+) at a concentration of about 0.1 mM to about 20 mM; (d) sodium ion (Na^+) at a concentration of about 25 mM to about 250 mM; (e) chloride ion (Cl^-) at a concentration of about 25 mM to about 250 mM; and (f) water. In some cases, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM; (c) potassium ion (K^+) at a concentration of about 3 mM; (d) sodium ion (Na^+) at a concentration of about 160 mM; (e) chloride ion (Cl^-) at a concentration of about 160 mM; and (f) water. In some of these cases, the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4. In some cases, the pharmaceutical composition lacks phosphate ion.

Therapeutic Target Population

[0474] In some embodiments, the human subject is from about 6 months to about 1 year old, from about 1 to about 18, from about 2 to about 18, from about 3 to about 18, from about 4 to about 18, from about 5 to about 18, from about 6 to about 18, from about 7 to about 18, from about 8 to about 18, from about 9 to about 18, from about 10 to about 18, from about 11 to about 18, from about 12 to about 18, from about 13 to about 18, from about 14 to about 18, from about 15 to about 18, from about 16 to about 18, or from about 17 to about 18 years old. In some embodiments, the human subject is a human from about 1 to about 17, from about 1 to about 16, from about 1 to about 15, from about 1 to about 14, from about 1 to about 13, from about 1 to about 12, from about 1 to about 11, from about 1 to about 10, from about 1 to about 9, from about 1 to about 8, from about 1 to about 7, from about 1 to about 6, from about 1 to about 5, from about 1 to about 4, from about 1 to about 3, or from about 1 to about 2 years old. In some embodiments, the human subject is less than a year old or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 years old. In one nonlimiting embodiment, the human subject is from 2 to 12 years old. In another embodiment, the human subject is from 13 to 18 years old. In an embodiment, the human subject is at least 13 years old.

[0475] In some embodiments, the human subject is at most 100 years, 99 years, 98 years, 97 years, 96 years, 95 years, 94 years, 93 years, 92 years, 91 years, 90 years, 89 years, 88 years, 87 years, 86 years, 85 years, 84 years, 83 years, 82 years, 81 years, 80 years, 79 years, 78 years, 77 years, 76 years, 75 years, 74 years, 73 years, 72 years, 71 years, 70 years, 69 years, 68 years, 67 years, 66 years, 65 years, 64 years, 63 years, 62 years, 61 years, 60 years, 59 years, 58 years, 57 years, 56 years, 55 years, 54 years, 53 years, 52 years, 51 years, 50 years, 49 years, 48 years, 47 years, 46 years, 45 years, 44 years, 43 years, 42 years, 41 years, 40 years, 39 years, 38 years, 37 years, 36 years, 35 years, 30 years, 29 years, 28 years, 27 years, 26

years, 25 years, 24 years, 23 years, 22 years, 21 years, 20 years, 19 years, 18 years, 17 years, 16 years, 15 years, 14 years, 13 years, 12 years, 11 years, 10 years, 9 years, 8 years, 7 years, 6 years, 5 years, 4 years, 3 years, 2 years, 1 year old, or 6 months old.

[0476] In some embodiments, the human subject is less than a year old or less than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 years old.

[0477] In some embodiments, the human subject is at least 6 months old, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years old.

[0478] In some embodiments, the human subject is from 6 months to 35, 1 to 35, from 2 to 35, from 3 to 35, from 4 to 35, from 5 to 35, from 6 to 35, from 7 to 35, from 8 to 35, from 9 to 35, from 10 to 35, from 11 to 35, from 12 to 35, from 13 to 35, from 14 to 35, from 15 to 35, from 16 to 35, 17 to 35, from 18 to 35, from 19 to 35, from 20 to 35, from 21 to 35, from 22 to 35, from 23 to 35, from 24 to 35, from 25 to 35, from 26 to 35, from 27 to 35, from 28 to 35, from 29 to 35, from 30 to 35, from 31 to 35, from 32 to 35, from 33 to 35, or from 34 to 35 years old.

[0479] In some embodiments, the human subject is from 6 months to 1 year old, 1 to 100, from 2 to 100, from 3 to 100, from 4 to 100, from 5 to 100, from 6 to 100, from 7 to 100, from 8 to 100, from 9 to 100, from 10 to 100, from 11 to 100, from 12 to 100, from 13 to 100, from 14 to 100, from 15 to 100, from 16 to 100, from 17 to 100, from 18 to 100, from 19 to 100, from 20 to 100, from 21 to 100, from 22 to 100, from 23 to 100, from 24 to 100, from 25 to 100, from 26 to 100, from 27 to 100, from 28 to 100, from 29 to 100, from 30 to 100, from 31 to 100, from 32 to 100, from 33 to 100, from 34 to 100, from 35 to 100, from 36 to 100, from 37 to 100, from 38 to 100, from 39 to 100, from 40 to 100, from 41 to 100, from 42 to 100, from 43 to 100, from 44 to 100, from 45 to 100, from 46 to 100, from 47 to 100, from 48 to 100, from 49 to 100, from 50 to 100, from 51 to 100, from 52 to 100, from 53 to 100, from 54 to 100, from 55 to 100, from 56 to 100, from 57 to 100, from 58 to 100, from 59 to 100, from 60 to 100, from 61 to 100, from 62 to 100, from 63 to 100, from 64 to 100, from 65 to 100, from 66 to 100, from 67 to 100, from 68 to 100, from 69 to 100, from 70 to 100, from 71 to 100, from 72 to 100, from 73 to 100, from 74 to 100, from 75 to 100, from 76 to 100, from 77 to 100, from 78 to 100, from 79 to 100, from 80 to 100, from 81 to 100, from 82 to 100, from 83 to 100, from 84 to 100, from 85 to 100, from 86 to 100, from 87 to 100, from 88 to 100, from 89 to 100, from 90 to 100, from 91 to 100, from 92 to 100, from 93 to 100, from 94 to 100, from 95 to 100, from 96 to 100, from 97 to 100, from 98 to 100, or from 99 to 100 years old.

[0480] In some embodiments, the human subject is a human from 6 months to 1 year old, 1 to 35, from 1 to 34, from 1 to 33, from 1 to 32, from 1 to 31, from 1 to 30, from 1 to 29, from 1 to 28, from 1 to 27, from 1 to 26, from 1 to 25, from 1 to 24, from 1 to 23, from 1 to 22, from 1 to 21, from 1 to 20, from 1 to 19, from 1 to 18, from 1 to 17, from 1 to 16, from 1 to 15, from 1 to 14, from 1 to 13, from 1 to 12, from 1 to 11, from 1 to 10, from 1 to 9, from 1 to 8, from 1 to 7, from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, or from 1 to 2 years old.

[0481] In some embodiments, the human subject is a human from 6 months to 1 year old, 1 to 2, from 1 to 3, from 1 to 4, from 1 to 5, from 1 to 6, from 1 to 7, from 1 to 8, from 1 to 9, from 1 to 10, from 1 to 11, from 1 to 12, from 1 to 13, from 1 to 14, from 1 to 15, from 1 to 16, from 1 to 17, from 1 to 18, from 1 to 19, from 1 to 20, from 1 to 21, from 1 to 22, from 1 to 23, from 1 to 24, from 1 to 25, from 1 to 26, from 1 to 27, from 1 to 28, from 1 to 29, from 1 to 30, from 1 to 31, from 1 to 32, from 1 to 33, from 1 to 34, from 1 to 35, from 1 to 36, from 1 to 37, from 1 to 38, from 1 to 39, from 1 to 40, from 1 to 41, from 1 to 42, from 1 to 43, from 1 to 44, from 1 to 45, from 1 to 46, from 1 to 47, from 1 to 48, from 1 to 49, from 1 to 50, from 1 to 51, from 1 to 52, from 1 to 53, from 1 to 54, from 1 to 55, from 1 to 56, from 1 to 57, from 1 to 58, from 1 to 59, from 1 to 60, from 1 to 61, from 1 to 62, from 1 to 63, from 1 to 64, from 1 to 65, from 1 to 66, from 1 to 67, from 1 to 68, from 1 to 69, from 1 to 70, from 1 to 71, from 1 to 72, from 1 to 73, from 1 to 74, from 1 to 75, from 1 to 76, from 1 to 77, from 1 to 78, from 1 to 79, from 1 to 80, from 1 to 81, from 1 to 82, from 1 to 83, from 1 to 84, from 1 to 85, from 1 to 86, from 1 to 87, from 1 to 88, from 1 to 89, from 1 to 90, from 1 to 91, from 1 to 92, from 1 to 93, from 1 to 94, from 1 to 95, from 1 to 96, from 1 to 97, from 1 to 98, from 1 to 99, or from 1 to 100 years old.

[0482] In some embodiments, the human subject is a human from 2 to 35, from 2 to 34, from 2 to 33, from 2 to 32, from 2 to 31, from 2 to 30, from 2 to 29, from 2 to 28, from 2 to 27, from 2 to 26, from 2 to 25, from 2 to 24, from 2 to 23, from 2 to 22, from 2 to 21, from 2 to 20, from 2 to 19, from 2 to 18, from 2 to 17, from 2 to 16, from 2 to 15, from 2 to 14, from 2 to 13, from 2 to 12, from 2 to 11, from 2 to 10, from 2 to 9, from 2 to 8, from 2 to 7, from 2 to 6, from 2 to 5, from 2 to 4, or from 2 to 3 years old. In some embodiments, the human subject is a human from 3 to 35, from 3 to 34, from 3 to 33, from 3 to 32, from 3 to 31, from 3 to 30, from 3 to 29, from 3 to 28, from 3 to 27, from 3 to 26, from 3 to 25, from 3 to 24, from 3 to 23, from 3 to 22, from 3 to 21, from 3 to 20, from 3 to 19, from 3 to 18, from 3 to 17, from 3 to 16, from 3 to 15, from 3 to 14, from 3 to 13, from 3 to 12, from 3 to 11, from 3 to 10, from 3 to 9, from 3 to 8, from 3 to 7, from 3 to 6, from 3 to 5, or from 3 to 4 years old.

[0483] In some embodiments, the human subject is a human from 2 to 3, from 2 to 4, from 2 to 5, from 2 to 6, from 2 to 7, from 2 to 8, from 2 to 9, from 2 to 10, from 2 to 11, from 2 to 12, from 2 to 13, from 2 to 14, from 2 to 15, from 2 to 16, from 2 to 17, from 2 to 18, from 2 to 19, from 2 to 20, from 2 to 21, from 2 to 22, from 2 to 23, from 2 to 24, from 2 to 25, from 2 to 26, from 2 to 27, from 2 to 28, from 2 to 29, from 2 to 30, from 2 to 31, from 2 to 32, from 2 to 33, from 2 to 34, from 2 to 35, from 2 to 36, from 2 to 37, from 2 to 38, from 2 to 39, from 2 to 40, from 2 to 41, from 2 to 42, from 2 to 43, from 2 to 44, from 2 to 45, from 2 to 46, from 2 to 47, from 2 to 48, from 2 to 49, from 2 to 50, from 2 to 51, from 2 to 52, from 2 to 53, from 2 to 54, from 2 to 55, from 2 to 56, from 2 to 57, from 2 to 58, from 2 to 59, from 2 to 60, from 2 to 61, from 2 to 62, from 2 to 63, from 2 to 64, from 2 to 65, from 2 to 66, from 2 to 67, from 2 to 68, from 2 to 69, from 2 to 70, from 2 to 71, from 2 to 72, from 2 to 73, from 2 to 74, from 2 to 75, from 2 to 76, from 2 to 77, from 2 to 78, from 2 to 79, from 2 to 80, from 2 to 81, from 2 to 82, from 2 to 83, from 2 to 84, from 2 to 85, from 2 to 86, from 2 to 87, from 2 to 88, from 2 to 89, from 2 to 90, from 2 to 91, from 2 to 92, from 2 to 93, from 2 to 94, from 2 to 95, from 2 to 96, from 2 to 97, from 2 to 98, from 2 to 99, or from 2 to 100 years old.

[0484] In some embodiments, the human subject is a human from 3 to 4, from 3 to 5, from 3 to 6, from 3 to 7, from 3 to 8, from 3 to 9, from 3 to 10, from 3 to 11, from 3 to 12, from 3 to 13, from 3 to 14, from 3 to 15, from 3 to 16, from 3 to 17, from 3 to 18, from 3 to 19, from 3 to 20, from 3 to 21, from 3 to 22, from 3 to 23, from 3 to 24, from 3 to 25, from 3 to 26, from 3 to 27, from 3 to 28, from 3 to 29, from 3 to 30, from 3 to 31, from 3 to 32, from 3 to 33, from 3 to 34, from 3 to 35, from 3 to 36, from 3 to 37, from 3 to 38, from 3 to 39, from 3 to 40, from 3 to 41, from 3 to 42, from 3 to 43, from 3 to 44, from 3 to 45, from 3 to 46, from 3 to 47, from 3 to 48, from 3 to 49, from 3 to 50, from 3 to 51, from 3 to 52, from 3 to 53, from 3 to 54, from 3 to 55, from 3 to 56, from 3 to 57, from 3 to 58, from 3 to 59, from 3 to 60, from 3 to 61, from 3 to 62, from 3 to 63, from 3 to 64, from 3 to 65, from 3 to 66, from 3 to 67, from 3 to 68, from 3 to 69, from 3 to 70, from 3 to 71, from 3 to 72, from 3 to 73, from 3 to 74, from 3 to 75, from 3 to 76, from 3 to 77, from 3 to 78, from 3 to 79, from 3 to 80, from 3 to 81, from 3 to 82, from 3 to 83, from 3 to 84, from 3 to 85, from 3 to 86, from 3 to 87, from 3 to 88, from 3 to 89, from 3 to 90, from 3 to 91, from 3 to 92, from 3 to 93, from 3 to 94, from 3 to 95, from 3 to 96, from 3 to 97, from 3 to 98, from 3 to 99, or from 3 to 100 years old.

[0485] In some embodiments, the human subject is a human from 4 to 5, from 4 to 6, from 4 to 7, from 4 to 8, from 4 to 9, from 4 to 10, from 4 to 11, from 4 to 12, from 4 to 13, from 4 to 14, from 4 to 15, from 4 to 16, from 4 to 17, from 4 to 18, from 4 to 19, from 4 to 20, from 4 to 21, from 4 to 22, from 4 to 23, from 4 to 24, from 4 to 25, from 4 to 26, from 4 to 27, from 4 to 28, from 4 to 29, from 4 to 30, from 4 to 31, from 4 to 32, from 4 to 33, from 4 to 34, from 4 to 35, from 4 to 36, from 4 to 37, from 4 to 38, from 4 to 39, from 4 to 40, from 4 to 41, from 4 to 42, from 4 to 43, from 4 to 44, from 4 to 45, from 4 to 46, from 4 to 47, from 4 to 48, from 4 to 49, from 4 to 50, from 4 to 51, from 4 to 52, from 4 to 53, from 4 to 54, from 4 to 55, from 4 to 56, from 4 to 57, from 4 to 58, from 4 to 59, from 4 to 60, from 4 to 61, from 4 to 62, from 4 to 63, from 4 to 64, from 4 to 65, from 4 to 66, from 4 to 67, from 4 to 68, from 4 to 69, from 4 to 70, from 4 to 71, from 4 to 72, from 4 to 73, from 4 to 74, from 4 to 75, from 4 to 76, from 4 to 77, from 4 to 78, from 4 to 79, from 4 to 80, from 4 to 81, from 4 to 82, from 4 to 83, from 4 to 84, from 4 to 85, from 4 to 86, from 4 to 87, from 4 to 88, from 4 to 89, from 4 to 90, from 4 to 91, from 4 to 92, from 4 to 93, from 4 to 94, from 4 to 95, from 4 to 96, from 4 to 97, from 4 to 98, from 4 to 99, or from 4 to 100 years old.

[0486] In some embodiments, the human subject is a human from 4 to 35, from 4 to 34, from 4 to 33, from 4 to 32, from 4 to 31, from 4 to 30, from 4 to 29, from 4 to 28, from 4 to 27, from 4 to 26, from 4 to 25, from 4 to 24, from 4 to 23, from 4 to 22, from 4 to 21, from 4 to 20, from 4 to 19, from 4 to 18, from 4 to 17, from 4 to 16, from 4 to 15, from 4 to 14, from 4 to 13, from 4 to 12, from 4 to 11, from 4 to 10, from 4 to 9, from 4 to 8, from 4 to 7, from 4 to 6, or from 4 to 5 years old.

[0487] In some embodiments, the human subject is a human from 5 to 6, from 5 to 7, from 5 to 8, from 5 to 9, from 5 to 10, from 5 to 11, from 5 to 12, from 5 to 13, from 5 to 14, from 5 to 15, from 5 to 16, from 5 to 17, from 5 to 18, from 5 to 19, from 5 to 20, from 5 to 21, from 5 to 22, from 5 to 23, from 5 to 24, from 5 to 25, from 5 to 26, from 5 to 27, from 5 to 28, from 5 to 29, from 5 to 30, from 5 to 31, from 5 to 32, from 5 to 33, from 5 to 34, from 5 to 35, from 5 to 36, from 5 to 37, from 5 to 38, from 5 to 39, from

5 to 40, from 5 to 41, from 5 to 42, from 5 to 43, from 5 to 44, from 5 to 45, from 5 to 46, from 5 to 47, from 5 to 48, from 5 to 49, from 5 to 50, from 5 to 51, from 5 to 52, from 5 to 53, from 5 to 54, from 5 to 55, from 5 to 56, from 5 to 57, from 5 to 58, from 5 to 59, from 5 to 60, from 5 to 61, from 5 to 62, from 5 to 63, from 5 to 64, from 5 to 65, from 5 to 66, from 5 to 67, from 5 to 68, from 5 to 69, from 5 to 70, from 5 to 71, from 5 to 72, from 5 to 73, from 5 to 74, from 5 to 75, from 5 to 76, from 5 to 77, from 5 to 78, from 5 to 79, from 5 to 80, from 5 to 81, from 5 to 82, from 5 to 83, from 5 to 84, from 5 to 85, from 5 to 86, from 5 to 87, from 5 to 88, from 5 to 89, from 5 to 90, from 5 to 91, from 5 to 92, from 5 to 93, from 5 to 94, from 5 to 95, from 5 to 96, from 5 to 97, from 5 to 98, from 5 to 99, or from 5 to 100 years old.

[0488] In some embodiments, the human subject is a human from 5 to 35, from 5 to 34, from 5 to 33, from 5 to 32, from 5 to 31, from 5 to 30, from 5 to 29, from 5 to 28, from 5 to 27, from 5 to 26, from 5 to 25, from 5 to 24, from 5 to 23, from 5 to 22, from 5 to 21, from 5 to 20, from 5 to 19, from 5 to 18, from 5 to 17, from 5 to 16, from 5 to 15, from 5 to 14, from 5 to 13, from 5 to 12, from 5 to 11, from 5 to 10, from 5 to 9, from 5 to 8, from 5 to 7, or from 5 to 6 years old.

[0489] In some embodiments, the human subject is a human from 6 to 7, from 6 to 8, from 6 to 9, from 6 to 10, from 6 to 11, from 6 to 12, from 6 to 13, from 6 to 14, from 6 to 15, from 6 to 16, from 6 to 17, from 6 to 18, from 6 to 19, from 6 to 20, from 6 to 21, from 6 to 22, from 6 to 23, from 6 to 24, from 6 to 25, from 6 to 26, from 6 to 27, from 6 to 28, from 6 to 29, from 6 to 30, from 6 to 31, from 6 to 32, from 6 to 33, from 6 to 34, from 6 to 35, from 6 to 36, from 6 to 37, from 6 to 38, from 6 to 39, from 6 to 40, from 6 to 41, from 6 to 42, from 6 to 43, from 6 to 44, from 6 to 45, from 6 to 46, from 6 to 47, from 6 to 48, from 6 to 49, from 6 to 50, from 6 to 51, from 6 to 52, from 6 to 53, from 6 to 54, from 6 to 55, from 6 to 56, from 6 to 57, from 6 to 58, from 6 to 59, from 6 to 60, from 6 to 61, from 6 to 62, from 6 to 63, from 6 to 64, from 6 to 65, from 6 to 66, from 6 to 67, from 6 to 68, from 6 to 69, from 6 to 70, from 6 to 71, from 6 to 72, from 6 to 73, from 6 to 74, from 6 to 75, from 6 to 76, from 6 to 77, from 6 to 78, from 6 to 79, from 6 to 80, from 6 to 81, from 6 to 82, from 6 to 83, from 6 to 84, from 6 to 85, from 6 to 86, from 6 to 87, from 6 to 88, from 6 to 89, from 6 to 90, from 6 to 91, from 6 to 92, from 6 to 93, from 6 to 94, from 6 to 95, from 6 to 96, from 6 to 97, from 6 to 98, from 6 to 99, or from 6 to 100 years old.

[0490] In some embodiments, the human subject is a human from 6 to 35, from 6 to 34, from 6 to 33, from 6 to 32, from 6 to 31, from 6 to 30, from 6 to 29, from 6 to 28, from 6 to 27, from 6 to 26, from 6 to 25, from 6 to 24, from 6 to 23, from 6 to 22, from 6 to 21, from 6 to 20, from 6 to 19, from 6 to 18, from 6 to 17, from 6 to 16, from 6 to 15, from 6 to 14, from 6 to 13, from 6 to 12, from 6 to 11, from 6 to 10, from 6 to 9, from 6 to 8, or from 6 to 7 years old.

[0491] In some embodiments, the human subject is a human from 7 to 8, from 7 to 9, from 7 to 10, from 7 to 11, from 7 to 12, from 7 to 13, from 7 to 14, from 7 to 15, from 7 to 16, from 7 to 17, from 7 to 18, from 7 to 19, from 7 to 20, from 7 to 21, from 7 to 22, from 7 to 23, from 7 to 24, from 7 to 25, from 7 to 26, from 7 to 27, from 7 to 28, from 7 to 29, from 7 to 30, from 7 to 31, from 7 to 32, from 7 to 33, from 7 to 34, from 7 to 35, from 7 to 36, from 7 to 37, from 7 to 38, from 7 to 39, from 7 to 40, from 7 to 41, from 7 to 42, from 7 to 43, from 7 to 44, from 7 to 45, from 7 to 46, from 7 to 47, from 7 to 48, from 7 to

49, from 7 to 50, from 7 to 51, from 7 to 52, from 7 to 53, from 7 to 54, from 7 to 55, from 7 to 56, from 7 to 57, from 7 to 58, from 7 to 59, from 7 to 60, from 7 to 61, from 7 to 62, from 7 to 63, from 7 to 64, from 7 to 65, from 7 to 66, from 7 to 67, from 7 to 68, from 7 to 69, from 7 to 70, from 7 to 71, from 7 to 72, from 7 to 73, from 7 to 74, from 7 to 75, from 7 to 76, from 7 to 77, from 7 to 78, from 7 to 79, from 7 to 80, from 7 to 81, from 7 to 82, from 7 to 83, from 7 to 84, from 7 to 85, from 7 to 86, from 7 to 87, from 7 to 88, from 7 to 89, from 7 to 90, from 7 to 91, from 7 to 92, from 7 to 93, from 7 to 94, from 7 to 95, from 7 to 96, from 7 to 97, from 7 to 98, from 7 to 99, or from 7 to 100 years old.

[0492] In some embodiments, the human subject is a human from 7 to 35, from 7 to 34, from 7 to 33, from 7 to 32, from 7 to 31, from 7 to 30, from 7 to 29, from 7 to 28, from 7 to 27, from 7 to 26, from 7 to 25, from 7 to 24, from 7 to 23, from 7 to 22, from 7 to 21, from 7 to 20, from 7 to 19, from 7 to 18, from 7 to 17, from 7 to 16, from 7 to 15, from 7 to 14, from 7 to 13, from 7 to 12, from 7 to 11, from 7 to 10, from 7 to 9, or from 7 to 8 years old.

[0493] In some embodiments, the human subject is a human from 8 to 9, from 8 to 10, from 8 to 11, from 8 to 12, from 8 to 13, from 8 to 14, from 8 to 15, from 8 to 16, from 8 to 17, from 8 to 18, from 8 to 19, from 8 to 20, from 8 to 21, from 8 to 22, from 8 to 23, from 8 to 24, from 8 to 25, from 8 to 26, from 8 to 27, from 8 to 28, from 8 to 29, from 8 to 30, from 8 to 31, from 8 to 32, from 8 to 33, from 8 to 34, from 8 to 35, from 8 to 36, from 8 to 37, from 8 to 38, from 8 to 39, from 8 to 40, from 8 to 41, from 8 to 42, from 8 to 43, from 8 to 44, from 8 to 45, from 8 to 46, from 8 to 47, from 8 to 48, from 8 to 49, from 8 to 50, from 8 to 51, from 8 to 52, from 8 to 53, from 8 to 54, from 8 to 55, from 8 to 56, from 8 to 57, from 8 to 58, from 8 to 59, from 8 to 60, from 8 to 61, from 8 to 62, from 8 to 63, from 8 to 64, from 8 to 65, from 8 to 66, from 8 to 67, from 8 to 68, from 8 to 69, from 8 to 70, from 8 to 71, from 8 to 72, from 8 to 73, from 8 to 74, from 8 to 75, from 8 to 76, from 8 to 77, from 8 to 78, from 8 to 79, from 8 to 80, from 8 to 81, from 8 to 82, from 8 to 83, from 8 to 84, from 8 to 85, from 8 to 86, from 8 to 87, from 8 to 88, from 8 to 89, from 8 to 90, from 8 to 91, from 8 to 92, from 8 to 93, from 8 to 94, from 8 to 95, from 8 to 96, from 8 to 97, from 8 to 98, from 8 to 99, or from 8 to 100 years old.

[0494] In some embodiments, the human subject is a human from 8 to 35, from 8 to 34, from 8 to 33, from 8 to 32, from 8 to 31, from 8 to 30, from 8 to 29, from 8 to 28, from 8 to 27, from 8 to 26, from 8 to 25, from 8 to 24, from 8 to 23, from 8 to 22, from 8 to 21, from 8 to 20, from 8 to 19, from 8 to 18, from 8 to 17, from 8 to 16, from 8 to 15, from 8 to 14, from 8 to 13, from 8 to 12, from 8 to 11, from 8 to 10, or from 8 to 9 years old.

[0495] In some embodiments, the human subject is a human from 9 to 10, from 9 to 11, from 9 to 12, from 9 to 13, from 9 to 14, from 9 to 15, from 9 to 16, from 9 to 17, from 9 to 18, from 9 to 19, from 9 to 20, from 9 to 21, from 9 to 22, from 9 to 23, from 9 to 24, from 9 to 25, from 9 to 26, from 9 to 27, from 9 to 28, from 9 to 29, from 9 to 30, from 9 to 31, from 9 to 32, from 9 to 33, from 9 to 34, from 9 to 35, from 9 to 36, from 9 to 37, from 9 to 38, from 9 to 39, from 9 to 40, from 9 to 41, from 9 to 42, from 9 to 43, from 9 to 44, from 9 to 45, from 9 to 46, from 9 to 47, from 9 to 48, from 9 to 49, from 9 to 50, from 9 to 51, from 9 to 52, from 9 to 53, from 9 to 54, from 9 to 55, from 9 to 56, from 9 to 57, from 9 to 58, from 9 to 59, from 9 to 60, from 9 to 61, from 9 to 62, from 9 to 63, from 9 to 64, from 9 to 65, from 9 to

66, from 9 to 67, from 9 to 68, from 9 to 69, from 9 to 70, from 9 to 71, from 9 to 72, from 9 to 73, from 9 to 74, from 9 to 75, from 9 to 76, from 9 to 77, from 9 to 78, from 9 to 79, from 9 to 80, from 9 to 81, from 9 to 82, from 9 to 83, from 9 to 84, from 9 to 85, from 9 to 86, from 9 to 87, from 9 to 88, from 9 to 89, from 9 to 90, from 9 to 91, from 9 to 92, from 9 to 93, from 9 to 94, from 9 to 95, from 9 to 96, from 9 to 97, from 9 to 98, from 9 to 99, or from 9 to 100 years old.

[0496] In some embodiments, the human subject is a human from 10 to 11, from 10 to 12, from 10 to 13, from 10 to 14, from 10 to 15, from 10 to 16, from 10 to 17, from 10 to 18, from 10 to 19, from 10 to 20, from 10 to 21, from 10 to 22, from 10 to 23, from 10 to 24, from 10 to 25, from 10 to 26, from 10 to 27, from 10 to 28, from 10 to 29, from 10 to 30, from 10 to 31, from 10 to 32, from 10 to 33, from 10 to 34, from 10 to 35, from 10 to 36, from 10 to 37, from 10 to 38, from 10 to 39, from 10 to 40, from 10 to 41, from 10 to 42, from 10 to 43, from 10 to 44, from 10 to 45, from 10 to 46, from 10 to 47, from 10 to 48, from 10 to 49, from 10 to 50, from 10 to 51, from 10 to 52, from 10 to 53, from 10 to 54, from 10 to 55, from 10 to 56, from 10 to 57, from 10 to 58, from 10 to 59, from 10 to 60, from 10 to 61, from 10 to 62, from 10 to 63, from 10 to 64, from 10 to 65, from 10 to 66, from 10 to 67, from 10 to 68, from 10 to 69, from 10 to 70, from 10 to 71, from 10 to 72, from 10 to 73, from 10 to 74, from 10 to 75, from 10 to 76, from 10 to 77, from 10 to 78, from 10 to 79, from 10 to 80, from 10 to 81, from 10 to 82, from 10 to 83, from 10 to 84, from 10 to 85, from 10 to 86, from 10 to 87, from 10 to 88, from 10 to 89, from 10 to 90, from 10 to 91, from 10 to 92, from 10 to 93, from 10 to 94, from 10 to 95, from 10 to 96, from 10 to 97, from 10 to 98, from 10 to 99, or from 10 to 100 years old.

[0497] In some embodiments, the human subject is white, Asian, black, or African American. In a nonlimiting embodiment, the human subject is white. In one embodiment, the human subject is Asian. In another embodiment, the human subject is black or African American.

[0498] In some embodiments, the subject is characterized by having: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or (ix) any combination of (i) – (viii).

[0499] In some embodiments, the subject is characterized by having at least one or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet

Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least two or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least three or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least four or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of

adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least five or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least six or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having at least seven or more of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to

Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product. In some embodiments, the subject is characterized by having all eight of: (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; (ii) no past history of causal magnetic resonance imaging lesion; (iii) no other known etiology of any diseases or conditions except Dravet Syndrome; (iv) normal development at seizure onset; (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene; (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control; (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures is any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic; and (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product.

[0500] In some embodiments, the subject is additionally characterized by not having one or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin; or (m) any combination of (a) – (l). In some embodiments, the subject is characterized by not having one or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a

known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having two or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having three or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an

anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having four or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having five or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically,

significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having six or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having seven or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of

brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having eight or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having nine or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal

fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having ten or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having eleven or more of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper

limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin. In some embodiments, the subject is additionally characterized by not having all of the following: (a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr; (b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease; (c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin; (d) clinically, significantly unstable medical conditions other than epilepsy; (e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy; (f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation; (g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt; (h) clinically significant abnormal laboratory values prior to administering; (i) aspartate aminotransferase or alanine aminotransferase > 2.5-fold upper limit of normal, serum creatinine > upper limit of normal or platelet count < lower limit of normal; (j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering; (k) a psychiatric or behavioral disorder; and (l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin.

[0501] In some embodiments, the subject is additionally characterized by not having known pathogenic mutation in another gene that causes epilepsy. In some embodiments, the subject is additionally characterized by not having had clinically relevant symptoms or a clinically significant illness in the past 4 weeks other than epilepsy. In some embodiments, the subject is additionally characterized by not having specific mutations of *SCN1A* gene demonstrated to cause gain-of-function. In some embodiments, the subject is additionally characterized by currently not being treated with an anti-epileptic drug acting predominantly as a sodium channel blocker. In some embodiments, the subject is additionally characterized by not having clinically significant unstable medical condition(s) other than epilepsy.

[0502] In some embodiments, the subject has pediatric epilepsy, epileptic encephalopathies, refractory myoclonic epilepsy, or severe myoclonic epilepsy in infancy. In some embodiments, the subject has myoclonic epilepsies, generalized epilepsy, epilepsy, brain diseases, central nervous system diseases, nervous system diseases, or epileptic syndromes. In some embodiments, the methods of treatment as described herein comprise methods of treating or reducing the likelihood of developing a disease or condition, wherein the disease or condition is pediatric epilepsy, epileptic encephalopathies, refractory myoclonic epilepsy, or severe myoclonic epilepsy in infancy. In some embodiments, the methods of treatment as described herein comprise methods of treating or reducing the likelihood of developing a

disease or condition, wherein the disease or condition is myoclonic epilepsies, generalized epilepsy, epilepsy, brain diseases, central nervous system diseases, nervous system diseases, or epileptic syndromes. In some embodiment, the subject has seizures that are not controlled by current antiepileptic drug (AED) regimen. In some embodiment, the AED regimen comprises clobazam, cannabidiol, levetiracetam, stiripentol, or valproic acid/valproate.

[0503] The term "magnetic resonance imaging lesion," as used herein, refers to any damage or abnormal change in the tissue of an organism, caused by the magnetic resonance imaging. The term "magnetic resonance imaging," as used herein, refers to a form of medical imaging that measures the response of the atomic nuclei of body tissues to high-frequency radio waves when placed in a strong magnetic field, and that produces images of the internal organs.

[0504] The term "ketogenic diet," as used herein, refers to a high-fat, adequate-protein, low-carbohydrate diet that in medicine is used, for example, to treat refractory epilepsy in children. The diet forces the body to burn fats rather than carbohydrates.

[0505] The term "a vagal nerve stimulator" or "vagus nerve stimulation (VNS)" as used herein, refers to a medical treatment that involves delivering electrical impulses to the vagus nerve. It is, for example, used as an add-on treatment for certain types of intractable epilepsy and treatment-resistant depression.

[0506] The term "cannabinoid," as used herein, refers to a chemical found in *cannabis*. Exemplary cannabinoids include, but are not limited to, the phytocannabinoid tetrahydrocannabinol (THC) (Delta9-THC or Delta8-THC), and cannabidiol (CBD). Cannabinoids, as used herein, may be natural or synthetic chemicals.

[0507] The term "marijuana" or "cannabis," as used herein, refers to a psychoactive drug from the *Cannabis* plant used primarily for medical or recreational purposes. An exemplary main psychoactive component of cannabis is tetrahydrocannabinol (THC).

[0508] The term "sodium channel blocker," as used herein, refers to a drug which impair the conduction of sodium ions (Na+) through sodium channels. Examples of sodium channel blockers include, but are not limited to, alkaloids (*e.g.,* saxitoxin, neosaxitoxin, tetrodotoxin), local anesthetics (*e.g.,* lidocaine), anticonvulsants (*e.g.,* phenytoin, oxcarbazepine (derivative of carbamazepine)), and class Ia (*e.g.,* quinidine, procainamide and disopyramide), class Ib (*e.g.,* lidocaine, mexiletine, tocainide, and phenytoin) and class Ic (*e.g.,* encainide, flecainide, moricizine, and propafenone) antiarrhythmic agents.

[0509] The term "cerebrospinal fluid (CSF)," as used herein, refers to a clear, colorless body fluid found in the brain and spinal cord. CSF, for example, acts as a cushion or buffer, providing basic mechanical and immunological protection to the brain inside the skull, and plays a vital function in the cerebral autoregulation of cerebral blood flow. The term "artificial cerebrospinal fluid (aCSF)," as used herein, refers to a biological buffer solution that is commonly used as a vehicle solution for administration of agents to the central nervous system (CNS). aCSF, for instance, closely matches the electrolyte concentrations and physiological compatibility of endogenous CSF to enable a vital environment for neuronal tissue by maintaining the homeostasis, osmolarity, and pH at physiological levels.

[0510] The term "CSF drainage shunt," as used herein, refers to a system that drains excess fluid from the brain to another part of the body where the fluid is absorbed as part of the circulatory process. CSF shunts are, for example, used to treat hydrocephalus.

[0511] The term "electrocardiogram (EKG or ECG)," as used herein, refers to a test that measures the electrical activity of the heartbeat, *e.g.,* producing a graph of voltage versus time of the electrical activity of the heart. With each beat, an electrical impulse (or "wave") travels through the heart.

[0512] "Aspartate transaminase (AST)," also known as aspartate aminotransferase, AspAT/ASAT/AAT, or (serum) glutamic oxaloacetic transaminase (GOT, SGOT), as used herein, refers to a pyridoxal phosphate (PLP)-dependent transaminase enzyme (EC 2.6.1.1). AST includes any of the recombinant or naturally occurring forms of AST protein or variants or homologs thereof that maintain AST activity, (*e.g.,* within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% activity compared to AST). Exemplary AST activity includes, but are not limited to, playing a role in amino acid metabolism, for example, by catalyzing the reversible transfer of an α-amino group between aspartate and glutamate and, as such. In some aspects, the variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.,* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring AST protein. In some embodiments, the AST protein is substantially identical to the protein identified by the UniProt reference number P17174 or a variant or homolog having substantial identity thereto. In some embodiments, the AST protein is substantially identical to the protein identified by the UniProt reference number P00505 or a variant or homolog having substantial identity thereto.

[0513] "Alanine transaminase (ALT)," also known as alanine aminotransferase (ALAT), serum glutamate-pyruvate transaminase (SGPT), or serum glutamic-pyruvic transaminase (SGPT), as used herein, refers to a transaminase enzyme (EC 2.6.1.2). ALT includes any of the recombinant or naturally occurring forms of ALT protein or variants or homologs thereof that maintain ALT activity, (*e.g.,* within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% activity compared to ALT). Exemplary ALT activity includes, but are not limited to, catalyzing the two parts of the alanine cycle. In some aspects, the variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.,* a 50, 100, 150, or 200 continuous amino acid portion) compared to a naturally occurring ALT protein. In some embodiments, the ALT protein is substantially identical to the protein identified by the UniProt reference number P24298 or a variant or homolog having substantial identity thereto.

[0514] In some embodiments, serum AST level, serum ALT level, and their ratio (AST/ALT ratio) are measured clinically as biomarkers for liver health.

[0515] The term "laboratory vale," as used herein refers to the value obtained by laboratory tests or measurements. Exemplary, non-limiting laboratory tests or measurements may be related to hematology, coagulation, clinical chemistry, plasma, urinalysis, serum, serum or urine pregnancy, urine, or cerebrospinal fluid.

Brain Concentrations of Compound After Therapeutic Dose Administration

[0516] In some embodiments, brain concentration of the compound in the subject after administration of the pharmaceutical composition is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 μg/mL. In some embodiments, brain concentration of the compound in the subject after administration of the pharmaceutical composition is at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 μg/mL. In some embodiments, brain concentration of the compound in the subject after administration of the pharmaceutical composition is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 μg/mL.

[0517] In some embodiments, the compound as described herein in the mean brain without thalamus of the subject is maintained at a concentration between following intrathecal administration of the pharmaceutical composition following a dosing regimen as described herein. In some embodiments, the compound as described herein in the mean brain without thalamus of the subject is maintained at a concentration between 1 μg/g and 40 μg/g following intrathecal administration of the pharmaceutical composition comprising the first loading dose following a dosing regimen as described herein. In some embodiments, the compound is maintained at a concentration between 2 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 3 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 4 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 6 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 7 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 8 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 9 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 10 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 11 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the

compound is maintained at a concentration between 12 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 13 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 14 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 15 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 16 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 17 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 18 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 19 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 20 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 21 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 22 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 23 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 24 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 25 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 26 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 27 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 28 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 29 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 30 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 31 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 32 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 33 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 34 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 35 μg/g and 40 μg/g following intrathecal administration of the

first loading dose. In some embodiments, the compound is maintained at a concentration between 36 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 37 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 38 μg/g and 40 μg/g following intrathecal administration of the first loading dose. In some embodiments, the compound is maintained at a concentration between 39 μg/g and 40 μg/g following intrathecal administration of the first loading dose.

[0518] In some embodiments, the compound as described herein in the mean brain without thalamus of the subject is maintained at a concentration between 1 μg/g and 40 μg/g following intrathecal administration of the pharmaceutical composition comprising the second loading dose following a dosing regimen as described herein. In some embodiments, the compound is maintained at a concentration between 2 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 3 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 4 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 6 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 7 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 8 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 9 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 10 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 11 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 12 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 13 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 14 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 15 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 16 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 17 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 18 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a

concentration between 19 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 20 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 21 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 22 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 23 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 24 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 25 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 26 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 27 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 28 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 29 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 30 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 31 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 32 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 33 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 34 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 35 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 36 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 37 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 38 μg/g and 40 μg/g following intrathecal administration of the second loading dose. In some embodiments, the compound is maintained at a concentration between 39 μg/g and 40 μg/g following intrathecal administration of the second loading dose.

[0519] In some embodiments, the compound as described herein in the mean brain without thalamus of the subject is maintained at a concentration between 1 μg/g and 40 μg/g following intrathecal administration of the pharmaceutical composition comprising the third loading dose following a dosing regimen as described herein. In some embodiments, the compound is maintained at a concentration

between 2 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 3 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 4 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 6 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 7 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 8 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 9 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 10 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 11 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 12 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 13 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 14 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 15 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 16 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 17 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 18 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 19 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 20 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 21 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 22 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 23 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 24 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 25 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is

maintained at a concentration between 26 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 27 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 28 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 29 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 30 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 31 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 32 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 33 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 34 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 35 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 36 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 37 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 38 μg/g and 40 μg/g following intrathecal administration of the third loading dose. In some embodiments, the compound is maintained at a concentration between 39 μg/g and 40 μg/g following intrathecal administration of the third loading dose.

[0520] In some embodiments, the compound is maintained at a concentration of 1 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 2 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 3 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 4 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 5 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 6 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 7 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 8 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 9 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 10 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 11 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 12 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a

concentration of 13 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 14 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 15 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 16 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 17 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 18 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 19 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 20 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 21 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 22 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 23 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 24 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 25 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 26 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 27 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 28 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 29 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 30 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 31 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 32 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 33 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 34 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 35 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 36 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 37 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 38 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of 39 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 1 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 2 μg/g following administration of the first

loading dose. In some embodiments, the compound is maintained at a concentration of about 3 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 4 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 5 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 6 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 7 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 8 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 9 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 10 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 11 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 12 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 13 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 14 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 15 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 16 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 17 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 18 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 19 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 20 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 21 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 22 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 23 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 24 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 25 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 26 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 27 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 28 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 29 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 30 μg/g following administration of the first loading dose. In some embodiments, the compound is

maintained at a concentration of about 31 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 32 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 33 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 34 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 35 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 36 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 37 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 38 μg/g following administration of the first loading dose. In some embodiments, the compound is maintained at a concentration of about 39 μg/g following administration of the first loading dose.

[0521] In some embodiments, the compound is maintained at a concentration of 1 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 2 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 3 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 4 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 5 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 6 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 7 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 8 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 9 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 10 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 11 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 12 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 13 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 14 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 15 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 16 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 17 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 18 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 19 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a

concentration of 20 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 21 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 22 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 23 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 24 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 25 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 26 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 27 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 28 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 29 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 30 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 31 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 32 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 33 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 34 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 35 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 36 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 37 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 38 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of 39 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 1 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 2 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 3 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 4 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 5 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 6 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 7 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 8 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about

9 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 10 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 11 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 12 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 13 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 14 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 15 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 16 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 17 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 18 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 19 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 20 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 21 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 22 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 23 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 24 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 25 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 26 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 27 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 28 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 29 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 30 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 31 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 32 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 33 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 34 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 35 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 36 μg/g following

administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 37 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 38 μg/g following administration of the second loading dose. In some embodiments, the compound is maintained at a concentration of about 39 μg/g following administration of the second loading dose.

[0522] In some embodiments, the compound is maintained at a concentration of 1 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 2 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 3 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 4 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 5 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 6 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 7 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 8 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 9 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 10 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 11 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 12 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 13 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 14 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 15 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 16 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 17 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 18 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 19 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 20 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 21 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 22 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 23 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 24 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 25 μg/g following administration of the third loading dose. In some embodiments, the

compound is maintained at a concentration of 26 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 27 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 28 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 29 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 30 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 31 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 32 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 33 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 34 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 35 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 36 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 37 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 38 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of 39 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 1 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 2 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 3 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 4 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 5 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 6 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 7 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 8 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 9 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 10 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 11 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 12 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 13 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 14 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a

concentration of about 15 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 16 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 17 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 18 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 19 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 20 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 21 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 22 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 23 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 24 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 25 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 26 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 27 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 28 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 29 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 30 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 31 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 32 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 33 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 34 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 35 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 36 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 37 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 38 μg/g following administration of the third loading dose. In some embodiments, the compound is maintained at a concentration of about 39 μg/g following administration of the third loading dose.

[0523] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the concentration of the compound in the mean brain without thalamus of the subject is

maintained within the range of about 20% to 21%, 20% to 22%, 20% to 23%, 20% to 24%, 20% to 25%, 20% to 26%, 20% to 27%, 20% to 28%, 20% to 29%, 20% to 30%, 20% to 31%, 20% to 32%, 20% to 33%, 20% to 34%, 20% to 35%, 20% to 36%, 20% to 37%, 20% to 38%, 20% to 39%, 20% to 40%, 20% to 41%, 20% to 42%, 20% to 43%, 20% to 44%, 20% to 45%, 20% to 46%, 20% to 47%, 20% to 48%, 20% to 49%, 20% to 50%, 20% to 51%, 20% to 52%, 20% to 53%, 20% to 54%, 20% to 55%, 20% to 56%, 20% to 57%, 20% to 58%, 20% to 59%, 20% to 60%, 20% to 61%, 20% to 62%, 20% to 63%, 20% to 64%, 20% to 65%, 20% to 66%, 20% to 67%, 20% to 68%, 20% to 69%, 20% to 70%, 20% to 71%, 20% to 72%, 20% to 73%, 20% to 74%, 20% to 75%, 20% to 76%, 20% to 77%, 20% to 78%, 20% to 79%, 20% to 80%, 20% to 81%, 20% to 82%, 20% to 83%, 20% to 84%, 20% to 85%, 20% to 86%, 20% to 87%, 20% to 88%, 20% to 89%, 20% to 90%, 20% to 91%, 20% to 92%, 20% to 93%, 20% to 94%, 20% to 95%, 20% to 96%, 20% to 97%, 20% to 98%, 20% to 99%, 20% to 100%, 20% to 101%, 20% to 102%, 20% to 103%, 20% to 104%, 20% to 105%, 20% to 106%, 20% to 107%, 20% to 108%, 20% to 109%, 20% to 110%, 20% to 111%, 20% to 112%, 20% to 113%, 20% to 114%, 20% to 115%, 20% to 116%, 20% to 117%, 20% to 118%, 20% to 119%, 20% to 120%, 20% to 121%, 20% to 122%, 20% to 123%, 20% to 124%, 20% to 125%, 20% to 126%, 20% to 127%, 20% to 128%, 20% to 129%, 20% to 130%, 20% to 131%, 20% to 132%, 20% to 133%, 20% to 134%, 20% to 135%, 20% to 136%, 20% to 137%, 20% to 138%, 20% to 139%, 20% to 140%, 20% to 140%, 21% to 140%, 22% to 140%, 23% to 140%, 24% to 140%, 25% to 140%, 26% to 140%, 27% to 140%, 28% to 140%, 29% to 140%, 30% to 140%, 31% to 140%, 32% to 140%, 33% to 140%, 34% to 140%, 35% to 140%, 36% to 140%, 37% to 140%, 38% to 140%, 39% to 140%, 40% to 140%, 41% to 140%, 42% to 140%, 43% to 140%, 44% to 140%, 45% to 140%, 46% to 140%, 47% to 140%, 48% to 140%, 49% to 140%, 50% to 140%, 51% to 140%, 52% to 140%, 53% to 140%, 54% to 140%, 55% to 140%, 56% to 140%, 57% to 140%, 58% to 140%, 59% to 140%, 60% to 140%, 61% to 140%, 62% to 140%, 63% to 140%, 64% to 140%, 65% to 140%, 66% to 140%, 67% to 140%, 68% to 140%, 69% to 140%, 70% to 140%, 71% to 140%, 72% to 140%, 73% to 140%, 74% to 140%, 75% to 140%, 76% to 140%, 77% to 140%, 78% to 140%, 79% to 140%, 80% to 140%, 81% to 140%, 82% to 140%, 83% to 140%, 84% to 140%, 85% to 140%, 86% to 140%, 87% to 140%, 88% to 140%, 89% to 140%, 90% to 140%, 91% to 140%, 92% to 140%, 93% to 140%, 94% to 140%, 95% to 140%, 96% to 140%, 97% to 140%, 98% to 140%, 99% to 140%, 100% to 140%, 101% to 140%, 102% to 140%, 103% to 140%, 104% to 140%, 105% to 140%, 106% to 140%, 107% to 140%, 108% to 140%, 109% to 140%, 110% to 140%, 111% to 140%, 112% to 140%, 113% to 140%, 114% to 140%, 115% to 140%, 116% to 140%, 117% to 140%, 118% to 140%, 119% to 140%, 120% to 140%, 121% to 140%, 122% to 140%, 123% to 140%, 124% to 140%, 125% to 140%, 126% to 140%, 127% to 140%, 128% to 140%, 129% to 140%, 130% to 140%, 131% to 140%, 132% to 140%, 133% to 140%, 134% to 140%, 135% to 140%, 136% to 140%, 137% to 140%, 138% to 140%, or 139% to 140%, of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0524] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the concentration of the compound in the mean brain without thalamus of the subject is maintained within the range of about 20% to 21%, 20% to 22%, 20% to 23%, 20% to 24%, 20% to 25%, 20% to 26%, 20% to 27%, 20% to 28%, 20% to 29%, 20% to 30%, 20% to 31%, 20% to 32%, 20% to 33%, 20% to 34%, 20% to 35%, 20% to 36%, 20% to 37%, 20% to 38%, 20% to 39%, 20% to 40%, 20% to 41%, 20% to 42%, 20% to 43%, 20% to 44%, 20% to 45%, 20% to 46%, 20% to 47%, 20% to 48%, 20% to 49%, 20% to 50%, 20% to 51%, 20% to 52%, 20% to 53%, 20% to 54%, 20% to 55%, 20% to 56%, 20% to 57%, 20% to 58%, 20% to 59%, 20% to 60%, 20% to 61%, 20% to 62%, 20% to 63%, 20% to 64%, 20% to 65%, 20% to 66%, 20% to 67%, 20% to 68%, 20% to 69%, 20% to 70%, 20% to 71%, 20% to 72%, 20% to 73%, 20% to 74%, 20% to 75%, 20% to 76%, 20% to 77%, 20% to 78%, 20% to 79%, 20% to 80%, 20% to 81%, 20% to 82%, 20% to 83%, 20% to 84%, 20% to 85%, 20% to 86%, 20% to 87%, 20% to 88%, 20% to 89%, 20% to 90%, 20% to 91%, 20% to 92%, 20% to 93%, 20% to 94%, 20% to 95%, 20% to 96%, 20% to 97%, 20% to 98%, 20% to 99%, 20% to 100%, 20% to 101%, 20% to 102%, 20% to 103%, 20% to 104%, 20% to 105%, 20% to 106%, 20% to 107%, 20% to 108%, 20% to 109%, 20% to 110%, 20% to 111%, 20% to 112%, 20% to 113%, 20% to 114%, 20% to 115%, 20% to 116%, 20% to 117%, 20% to 118%, 20% to 119%, 20% to 120%, 20% to 121%, 20% to 122%, 20% to 123%, 20% to 124%, 20% to 125%, 20% to 126%, 20% to 127%, 20% to 128%, 20% to 129%, 20% to 130%, 20% to 131%, 20% to 132%, 20% to 133%, 20% to 134%, 20% to 135%, 20% to 136%, 20% to 137%, 20% to 138%, 20% to 139%, 20% to 140%, 21% to 140%, 22% to 140%, 23% to 140%, 24% to 140%, 25% to 140%, 26% to 140%, 27% to 140%, 28% to 140%, 29% to 140%, 30% to 140%, 31% to 140%, 32% to 140%, 33% to 140%, 34% to 140%, 35% to 140%, 36% to 140%, 37% to 140%, 38% to 140%, 39% to 140%, 40% to 140%, 41% to 140%, 42% to 140%, 43% to 140%, 44% to 140%, 45% to 140%, 46% to 140%, 47% to 140%, 48% to 140%, 49% to 140%, 50% to 140%, 51% to 140%, 52% to 140%, 53% to 140%, 54% to 140%, 55% to 140%, 56% to 140%, 57% to 140%, 58% to 140%, 59% to 140%, 60% to 140%, 61% to 140%, 62% to 140%, 63% to 140%, 64% to 140%, 65% to 140%, 66% to 140%, 67% to 140%, 68% to 140%, 69% to 140%, 70% to 140%, 71% to 140%, 72% to 140%, 73% to 140%, 74% to 140%, 75% to 140%, 76% to 140%, 77% to 140%, 78% to 140%, 79% to 140%, 80% to 140%, 81% to 140%, 82% to 140%, 83% to 140%, 84% to 140%, 85% to 140%, 86% to 140%, 87% to 140%, 88% to 140%, 89% to 140%, 90% to 140%, 91% to 140%, 92% to 140%, 93% to 140%, 94% to 140%, 95% to 140%, 96% to 140%, 97% to 140%, 98% to 140%, 99% to 140%, 100% to 140%, 101% to 140%, 102% to 140%, 103% to 140%, 104% to 140%, 105% to 140%, 106% to 140%, 107% to 140%, 108% to 140%, 109% to 140%, 110% to 140%, 111% to 140%, 112% to 140%, 113% to 140%, 114% to 140%, 115% to 140%, 116% to 140%, 117% to 140%, 118% to 140%, 119% to 140%, 120% to 140%, 121% to 140%, 122% to 140%, 123% to 140%, 124% to 140%, 125% to 140%, 126% to 140%, 127% to 140%, 128% to 140%, 129% to 140%, 130% to 140%, 131% to 140%, 132% to 140%, 133% to 140%,

134% to 140%, 135% to 140%, 136% to 140%, 137% to 140%, 138% to 140%, or 139% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0525] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the concentration of the compound in the mean brain without thalamus of the subject is maintained within the range of about 20% to 21%, 20% to 22%, 20% to 23%, 20% to 24%, 20% to 25%, 20% to 26%, 20% to 27%, 20% to 28%, 20% to 29%, 20% to 30%, 20% to 31%, 20% to 32%, 20% to 33%, 20% to 34%, 20% to 35%, 20% to 36%, 20% to 37%, 20% to 38%, 20% to 39%, 20% to 40%, 20% to 41%, 20% to 42%, 20% to 43%, 20% to 44%, 20% to 45%, 20% to 46%, 20% to 47%, 20% to 48%, 20% to 49%, 20% to 50%, 20% to 51%, 20% to 52%, 20% to 53%, 20% to 54%, 20% to 55%, 20% to 56%, 20% to 57%, 20% to 58%, 20% to 59%, 20% to 60%, 20% to 61%, 20% to 62%, 20% to 63%, 20% to 64%, 20% to 65%, 20% to 66%, 20% to 67%, 20% to 68%, 20% to 69%, 20% to 70%, 20% to 71%, 20% to 72%, 20% to 73%, 20% to 74%, 20% to 75%, 20% to 76%, 20% to 77%, 20% to 78%, 20% to 79%, 20% to 80%, 20% to 81%, 20% to 82%, 20% to 83%, 20% to 84%, 20% to 85%, 20% to 86%, 20% to 87%, 20% to 88%, 20% to 89%, 20% to 90%, 20% to 91%, 20% to 92%, 20% to 93%, 20% to 94%, 20% to 95%, 20% to 96%, 20% to 97%, 20% to 98%, 20% to 99%, 20% to 100%, 20% to 101%, 20% to 102%, 20% to 103%, 20% to 104%, 20% to 105%, 20% to 106%, 20% to 107%, 20% to 108%, 20% to 109%, 20% to 110%, 20% to 111%, 20% to 112%, 20% to 113%, 20% to 114%, 20% to 115%, 20% to 116%, 20% to 117%, 20% to 118%, 20% to 119%, 20% to 120%, 20% to 121%, 20% to 122%, 20% to 123%, 20% to 124%, 20% to 125%, 20% to 126%, 20% to 127%, 20% to 128%, 20% to 129%, 20% to 130%, 20% to 131%, 20% to 132%, 20% to 133%, 20% to 134%, 20% to 135%, 20% to 136%, 20% to 137%, 20% to 138%, 20% to 139%, 20% to 140%, 21% to 140%, 22% to 140%, 23% to 140%, 24% to 140%, 25% to 140%, 26% to 140%, 27% to 140%, 28% to 140%, 29% to 140%, 30% to 140%, 31% to 140%, 32% to 140%, 33% to 140%, 34% to 140%, 35% to 140%, 36% to 140%, 37% to 140%, 38% to 140%, 39% to 140%, 40% to 140%, 41% to 140%, 42% to 140%, 43% to 140%, 44% to 140%, 45% to 140%, 46% to 140%, 47% to 140%, 48% to 140%, 49% to 140%, 50% to 140%, 51% to 140%, 52% to 140%, 53% to 140%, 54% to 140%, 55% to 140%, 56% to 140%, 57% to 140%, 58% to 140%, 59% to 140%, 60% to 140%, 61% to 140%, 62% to 140%, 63% to 140%, 64% to 140%, 65% to 140%, 66% to 140%, 67% to 140%, 68% to 140%, 69% to 140%, 70% to 140%, 71% to 140%, 72% to 140%, 73% to 140%, 74% to 140%, 75% to 140%, 76% to 140%, 77% to 140%, 78% to 140%, 79% to 140%, 80% to 140%, 81% to 140%, 82% to 140%, 83% to 140%, 84% to 140%, 85% to 140%, 86% to 140%, 87% to 140%, 88% to 140%, 89% to 140%, 90% to 140%, 91% to 140%, 92% to 140%, 93% to 140%,

94% to 140%, 95% to 140%, 96% to 140%, 97% to 140%, 98% to 140%, 99% to 140%, 100% to 140%, 101% to 140%, 102% to 140%, 103% to 140%, 104% to 140%, 105% to 140%, 106% to 140%, 107% to 140%, 108% to 140%, 109% to 140%, 110% to 140%, 111% to 140%, 112% to 140%, 113% to 140%, 114% to 140%, 115% to 140%, 116% to 140%, 117% to 140%, 118% to 140%, 119% to 140%, 120% to 140%, 121% to 140%, 122% to 140%, 123% to 140%, 124% to 140%, 125% to 140%, 126% to 140%, 127% to 140%, 128% to 140%, 129% to 140%, 130% to 140%, 131% to 140%, 132% to 140%, 133% to 140%, 134% to 140%, 135% to 140%, 136% to 140%, 137% to 140%, 138% to 140%, or 139% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0526] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, the concentration of the compound in the mean brain without thalamus of the subject is maintained within the range of about 20% to 21%, 20% to 22%, 20% to 23%, 20% to 24%, 20% to 25%, 20% to 26%, 20% to 27%, 20% to 28%, 20% to 29%, 20% to 30%, 20% to 31%, 20% to 32%, 20% to 33%, 20% to 34%, 20% to 35%, 20% to 36%, 20% to 37%, 20% to 38%, 20% to 39%, 20% to 40%, 20% to 41%, 20% to 42%, 20% to 43%, 20% to 44%, 20% to 45%, 20% to 46%, 20% to 47%, 20% to 48%, 20% to 49%, 20% to 50%, 20% to 51%, 20% to 52%, 20% to 53%, 20% to 54%, 20% to 55%, 20% to 56%, 20% to 57%, 20% to 58%, 20% to 59%, 20% to 60%, 20% to 61%, 20% to 62%, 20% to 63%, 20% to 64%, 20% to 65%, 20% to 66%, 20% to 67%, 20% to 68%, 20% to 69%, 20% to 70%, 20% to 71%, 20% to 72%, 20% to 73%, 20% to 74%, 20% to 75%, 20% to 76%, 20% to 77%, 20% to 78%, 20% to 79%, 20% to 80%, 20% to 81%, 20% to 82%, 20% to 83%, 20% to 84%, 20% to 85%, 20% to 86%, 20% to 87%, 20% to 88%, 20% to 89%, 20% to 90%, 20% to 91%, 20% to 92%, 20% to 93%, 20% to 94%, 20% to 95%, 20% to 96%, 20% to 97%, 20% to 98%, 20% to 99%, 20% to 100%, 20% to 101%, 20% to 102%, 20% to 103%, 20% to 104%, 20% to 105%, 20% to 106%, 20% to 107%, 20% to 108%, 20% to 109%, 20% to 110%, 20% to 111%, 20% to 112%, 20% to 113%, 20% to 114%, 20% to 115%, 20% to 116%, 20% to 117%, 20% to 118%, 20% to 119%, 20% to 120%, 20% to 121%, 20% to 122%, 20% to 123%, 20% to 124%, 20% to 125%, 20% to 126%, 20% to 127%, 20% to 128%, 20% to 129%, 20% to 130%, 20% to 131%, 20% to 132%, 20% to 133%, 20% to 134%, 20% to 135%, 20% to 136%, 20% to 137%, 20% to 138%, 20% to 139%, 20% to 140%, 21% to 140%, 22% to 140%, 23% to 140%, 24% to 140%, 25% to 140%, 26% to 140%, 27% to 140%, 28% to 140%, 29% to 140%, 30% to 140%, 31% to 140%, 32% to 140%, 33% to 140%, 34% to 140%, 35% to 140%, 36% to 140%, 37% to 140%, 38% to 140%, 39% to 140%, 40% to 140%, 41% to 140%, 42% to 140%, 43% to 140%, 44% to

140%, 45% to 140%, 46% to 140%, 47% to 140%, 48% to 140%, 49% to 140%, 50% to 140%, 51% to 140%, 52% to 140%, 53% to 140%, 54% to 140%, 55% to 140%, 56% to 140%, 57% to 140%, 58% to 140%, 59% to 140%, 60% to 140%, 61% to 140%, 62% to 140%, 63% to 140%, 64% to 140%, 65% to 140%, 66% to 140%, 67% to 140%, 68% to 140%, 69% to 140%, 70% to 140%, 71% to 140%, 72% to 140%, 73% to 140%, 74% to 140%, 75% to 140%, 76% to 140%, 77% to 140%, 78% to 140%, 79% to 140%, 80% to 140%, 81% to 140%, 82% to 140%, 83% to 140%, 84% to 140%, 85% to 140%, 86% to 140%, 87% to 140%, 88% to 140%, 89% to 140%, 90% to 140%, 91% to 140%, 92% to 140%, 93% to 140%, 94% to 140%, 95% to 140%, 96% to 140%, 97% to 140%, 98% to 140%, 99% to 140%, 100% to 140%, 101% to 140%, 102% to 140%, 103% to 140%, 104% to 140%, 105% to 140%, 106% to 140%, 107% to 140%, 108% to 140%, 109% to 140%, 110% to 140%, 111% to 140%, 112% to 140%, 113% to 140%, 114% to 140%, 115% to 140%, 116% to 140%, 117% to 140%, 118% to 140%, 119% to 140%, 120% to 140%, 121% to 140%, 122% to 140%, 123% to 140%, 124% to 140%, 125% to 140%, 126% to 140%, 127% to 140%, 128% to 140%, 129% to 140%, 130% to 140%, 131% to 140%, 132% to 140%, 133% to 140%, 134% to 140%, 135% to 140%, 136% to 140%, 137% to 140%, 138% to 140%, or 139% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose and maintenance dose comprises 70 mg of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof and each maintenance dose comprises 45 mg of the compound of formula (I) or a salt thereof.

[0527] In some embodiments, the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, the concentration of the compound in the mean brain without thalamus of the subject is maintained within the range of about 20% to 21%, 20% to 22%, 20% to 23%, 20% to 24%, 20% to 25%, 20% to 26%, 20% to 27%, 20% to 28%, 20% to 29%, 20% to 30%, 20% to 31%, 20% to 32%, 20% to 33%, 20% to 34%, 20% to 35%, 20% to 36%, 20% to 37%, 20% to 38%, 20% to 39%, 20% to 40%, 20% to 41%, 20% to 42%, 20% to 43%, 20% to 44%, 20% to 45%, 20% to 46%, 20% to 47%, 20% to 48%, 20% to 49%, 20% to 50%, 20% to 51%, 20% to 52%, 20% to 53%, 20% to 54%, 20% to 55%, 20% to 56%, 20% to 57%, 20% to 58%, 20% to 59%, 20% to 60%, 20% to 61%, 20% to 62%, 20% to 63%, 20% to 64%, 20% to 65%, 20% to 66%, 20% to 67%, 20% to 68%, 20% to 69%, 20% to 70%, 20% to 71%, 20% to 72%, 20% to 73%, 20% to 74%, 20% to 75%, 20% to 76%, 20% to 77%, 20% to 78%, 20% to 79%, 20% to 80%, 20% to 81%, 20% to 82%, 20% to 83%, 20% to 84%, 20% to 85%, 20% to 86%, 20% to 87%, 20% to 88%, 20% to 89%, 20% to 90%, 20% to 91%, 20% to 92%, 20% to 93%, 20% to 94%,

20% to 95%, 20% to 96%, 20% to 97%, 20% to 98%, 20% to 99%, 20% to 100%, 20% to 101%, 20% to 102%, 20% to 103%, 20% to 104%, 20% to 105%, 20% to 106%, 20% to 107%, 20% to 108%, 20% to 109%, 20% to 110%, 20% to 111%, 20% to 112%, 20% to 113%, 20% to 114%, 20% to 115%, 20% to 116%, 20% to 117%, 20% to 118%, 20% to 119%, 20% to 120%, 20% to 121%, 20% to 122%, 20% to 123%, 20% to 124%, 20% to 125%, 20% to 126%, 20% to 127%, 20% to 128%, 20% to 129%, 20% to 130%, 20% to 131%, 20% to 132%, 20% to 133%, 20% to 134%, 20% to 135%, 20% to 136%, 20% to 137%, 20% to 138%, 20% to 139%, 20% to 140%, 21% to 140%, 22% to 140%, 23% to 140%, 24% to 140%, 25% to 140%, 26% to 140%, 27% to 140%, 28% to 140%, 29% to 140%, 30% to 140%, 31% to 140%, 32% to 140%, 33% to 140%, 34% to 140%, 35% to 140%, 36% to 140%, 37% to 140%, 38% to 140%, 39% to 140%, 40% to 140%, 41% to 140%, 42% to 140%, 43% to 140%, 44% to 140%, 45% to 140%, 46% to 140%, 47% to 140%, 48% to 140%, 49% to 140%, 50% to 140%, 51% to 140%, 52% to 140%, 53% to 140%, 54% to 140%, 55% to 140%, 56% to 140%, 57% to 140%, 58% to 140%, 59% to 140%, 60% to 140%, 61% to 140%, 62% to 140%, 63% to 140%, 64% to 140%, 65% to 140%, 66% to 140%, 67% to 140%, 68% to 140%, 69% to 140%, 70% to 140%, 71% to 140%, 72% to 140%, 73% to 140%, 74% to 140%, 75% to 140%, 76% to 140%, 77% to 140%, 78% to 140%, 79% to 140%, 80% to 140%, 81% to 140%, 82% to 140%, 83% to 140%, 84% to 140%, 85% to 140%, 86% to 140%, 87% to 140%, 88% to 140%, 89% to 140%, 90% to 140%, 91% to 140%, 92% to 140%, 93% to 140%, 94% to 140%, 95% to 140%, 96% to 140%, 97% to 140%, 98% to 140%, 99% to 140%, 100% to 140%, 101% to 140%, 102% to 140%, 103% to 140%, 104% to 140%, 105% to 140%, 106% to 140%, 107% to 140%, 108% to 140%, 109% to 140%, 110% to 140%, 111% to 140%, 112% to 140%, 113% to 140%, 114% to 140%, 115% to 140%, 116% to 140%, 117% to 140%, 118% to 140%, 119% to 140%, 120% to 140%, 121% to 140%, 122% to 140%, 123% to 140%, 124% to 140%, 125% to 140%, 126% to 140%, 127% to 140%, 128% to 140%, 129% to 140%, 130% to 140%, 131% to 140%, 132% to 140%, 133% to 140%, 134% to 140%, 135% to 140%, 136% to 140%, 137% to 140%, 138% to 140%, or 139% to 140% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose and maintenance dose comprises 70 mg of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof and each maintenance dose comprises 45 mg of the compound of formula (I) or a salt thereof.

[0528] In some embodiments, the compound provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the provides a maximum brain without thalamus concentration within the range of about 80% to 81%, 80% to 82%, 80% to 83%, 80% to 84%, 80% to 85%, 80% to 86%, 80% to 87%, 80% to 88%, 80% to 89%, 80% to 90%, 80% to 91%, 80% to 92%, 80% to 93%, 80% to 94%, 80% to 95%, 80% to 96%, 80% to 97%, 80%

to 98%, 80% to 99%, 80% to 100%, 80% to 101%, 80% to 102%, 80% to 103%, 80% to 104%, 80% to 105%, 80% to 106%, 80% to 107%, 80% to 108%, 80% to 109%, 80% to 110%, 80% to 111%, 80% to 112%, 80% to 113%, 80% to 114%, 80% to 115%, 80% to 116%, 80% to 117%, 80% to 118%, 80% to 119%, 80% to 120%, 80% to 121%, 80% to 122%, 80% to 123%, 80% to 124%, 80% to 125%, 81% to 125%, 82% to 125%, 83% to 125%, 84% to 125%, 85% to 125%, 86% to 125%, 87% to 125%, 88% to 125%, 89% to 125%, 90% to 125%, 91% to 125%, 92% to 125%, 93% to 125%, 94% to 125%, 95% to 125%, 96% to 125%, 97% to 125%, 98% to 125%, 99% to 125%, 100% to 125%, 101% to 125%, 102% to 125%, 103% to 125%, 104% to 125%, 105% to 125%, 106% to 125%, 107% to 125%, 108% to 125%, 109% to 125%, 110% to 125%, 111% to 125%, 112% to 125%, 113% to 125%, 114% to 125%, 115% to 125%, 116% to 125%, 117% to 125%, 118% to 125%, 119% to 125%, 120% to 125%, 121% to 125%, 122% to 125%, 123% to 125%, or 124% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0529] In some embodiments, the compound provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the provides a maximum brain without thalamus concentration within the range of about 80% to 81%, 80% to 82%, 80% to 83%, 80% to 84%, 80% to 85%, 80% to 86%, 80% to 87%, 80% to 88%, 80% to 89%, 80% to 90%, 80% to 91%, 80% to 92%, 80% to 93%, 80% to 94%, 80% to 95%, 80% to 96%, 80% to 97%, 80% to 98%, 80% to 99%, 80% to 100%, 80% to 101%, 80% to 102%, 80% to 103%, 80% to 104%, 80% to 105%, 80% to 106%, 80% to 107%, 80% to 108%, 80% to 109%, 80% to 110%, 80% to 111%, 80% to 112%, 80% to 113%, 80% to 114%, 80% to 115%, 80% to 116%, 80% to 117%, 80% to 118%, 80% to 119%, 80% to 120%, 80% to 121%, 80% to 122%, 80% to 123%, 80% to 124%, 80% to 125%, 81% to 125%, 82% to 125%, 83% to 125%, 84% to 125%, 85% to 125%, 86% to 125%, 87% to 125%, 88% to 125%, 89% to 125%, 90% to 125%, 91% to 125%, 92% to 125%, 93% to 125%, 94% to 125%, 95% to 125%, 96% to 125%, 97% to 125%, 98% to 125%, 99% to 125%, 100% to 125%, 101% to 125%, 102% to 125%, 103% to 125%, 104% to 125%, 105% to 125%, 106% to 125%, 107% to 125%, 108% to 125%, 109% to 125%, 110% to 125%, 111% to 125%, 112% to 125%, 113% to 125%, 114% to 125%, 115% to 125%, 116% to 125%, 117% to 125%, 118% to 125%, 119% to 125%, 120% to 125%, 121% to 125%, 122% to 125%, 123% to 125%, or 124% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0530] In some embodiments, the compound provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the third

loading dose of the compound of formula (I) or a salt thereof. In some embodiments, the provides a maximum brain without thalamus concentration within the range of about 80% to 81%, 80% to 82%, 80% to 83%, 80% to 84%, 80% to 85%, 80% to 86%, 80% to 87%, 80% to 88%, 80% to 89%, 80% to 90%, 80% to 91%, 80% to 92%, 80% to 93%, 80% to 94%, 80% to 95%, 80% to 96%, 80% to 97%, 80% to 98%, 80% to 99%, 80% to 100%, 80% to 101%, 80% to 102%, 80% to 103%, 80% to 104%, 80% to 105%, 80% to 106%, 80% to 107%, 80% to 108%, 80% to 109%, 80% to 110%, 80% to 111%, 80% to 112%, 80% to 113%, 80% to 114%, 80% to 115%, 80% to 116%, 80% to 117%, 80% to 118%, 80% to 119%, 80% to 120%, 80% to 121%, 80% to 122%, 80% to 123%, 80% to 124%, 80% to 125%, 81% to 125%, 82% to 125%, 83% to 125%, 84% to 125%, 85% to 125%, 86% to 125%, 87% to 125%, 88% to 125%, 89% to 125%, 90% to 125%, 91% to 125%, 92% to 125%, 93% to 125%, 94% to 125%, 95% to 125%, 96% to 125%, 97% to 125%, 98% to 125%, 99% to 125%, 100% to 125%, 101% to 125%, 102% to 125%, 103% to 125%, 104% to 125%, 105% to 125%, 106% to 125%, 107% to 125%, 108% to 125%, 109% to 125%, 110% to 125%, 111% to 125%, 112% to 125%, 113% to 125%, 114% to 125%, 115% to 125%, 116% to 125%, 117% to 125%, 118% to 125%, 119% to 125%, 120% to 125%, 121% to 125%, 122% to 125%, 123% to 125%, or 124% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof.

[0531] In some embodiments, the compound provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, the provides a maximum brain without thalamus concentration within the range of about 80% to 81%, 80% to 82%, 80% to 83%, 80% to 84%, 80% to 85%, 80% to 86%, 80% to 87%, 80% to 88%, 80% to 89%, 80% to 90%, 80% to 91%, 80% to 92%, 80% to 93%, 80% to 94%, 80% to 95%, 80% to 96%, 80% to 97%, 80% to 98%, 80% to 99%, 80% to 100%, 80% to 101%, 80% to 102%, 80% to 103%, 80% to 104%, 80% to 105%, 80% to 106%, 80% to 107%, 80% to 108%, 80% to 109%, 80% to 110%, 80% to 111%, 80% to 112%, 80% to 113%, 80% to 114%, 80% to 115%, 80% to 116%, 80% to 117%, 80% to 118%, 80% to 119%, 80% to 120%, 80% to 121%, 80% to 122%, 80% to 123%, 80% to 124%, 80% to 125%, 81% to 125%, 82% to 125%, 83% to 125%, 84% to 125%, 85% to 125%, 86% to 125%, 87% to 125%, 88% to 125%, 89% to 125%, 90% to 125%, 91% to 125%, 92% to 125%, 93% to 125%, 94% to 125%, 95% to 125%, 96% to 125%, 97% to 125%, 98% to 125%, 99% to 125%, 100% to 125%, 101% to 125%, 102% to 125%, 103% to 125%, 104% to 125%, 105% to 125%, 106% to 125%, 107% to 125%, 108% to 125%, 109% to 125%, 110% to 125%, 111% to 125%, 112% to 125%, 113% to 125%, 114% to 125%, 115% to 125%, 116% to 125%, 117% to 125%, 118% to 125%, 119% to 125%, 120% to 125%, 121% to 125%, 122% to 125%, 123% to 125%, or 124% to 125% of about 26 μg/g after intrathecal administration of the

first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose and maintenance dose comprises 70 mg of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof and each maintenance dose comprises 45 mg of the compound of formula (I) or a salt thereof.

[0532] In some embodiments, the compound provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, the provides a maximum brain without thalamus concentration within the range of about 80% to 81%, 80% to 82%, 80% to 83%, 80% to 84%, 80% to 85%, 80% to 86%, 80% to 87%, 80% to 88%, 80% to 89%, 80% to 90%, 80% to 91%, 80% to 92%, 80% to 93%, 80% to 94%, 80% to 95%, 80% to 96%, 80% to 97%, 80% to 98%, 80% to 99%, 80% to 100%, 80% to 101%, 80% to 102%, 80% to 103%, 80% to 104%, 80% to 105%, 80% to 106%, 80% to 107%, 80% to 108%, 80% to 109%, 80% to 110%, 80% to 111%, 80% to 112%, 80% to 113%, 80% to 114%, 80% to 115%, 80% to 116%, 80% to 117%, 80% to 118%, 80% to 119%, 80% to 120%, 80% to 121%, 80% to 122%, 80% to 123%, 80% to 124%, 80% to 125%, 81% to 125%, 82% to 125%, 83% to 125%, 84% to 125%, 85% to 125%, 86% to 125%, 87% to 125%, 88% to 125%, 89% to 125%, 90% to 125%, 91% to 125%, 92% to 125%, 93% to 125%, 94% to 125%, 95% to 125%, 96% to 125%, 97% to 125%, 98% to 125%, 99% to 125%, 100% to 125%, 101% to 125%, 102% to 125%, 103% to 125%, 104% to 125%, 105% to 125%, 106% to 125%, 107% to 125%, 108% to 125%, 109% to 125%, 110% to 125%, 111% to 125%, 112% to 125%, 113% to 125%, 114% to 125%, 115% to 125%, 116% to 125%, 117% to 125%, 118% to 125%, 119% to 125%, 120% to 125%, 121% to 125%, 122% to 125%, 123% to 125%, or 124% to 125% of about 26 μg/g after intrathecal administration of the first loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose and maintenance dose comprises 70 mg of the compound of formula (I) or a salt thereof. In some embodiments, each loading dose comprises 70 mg of the compound of formula (I) or a salt thereof and each maintenance dose comprises 45 mg of the compound of formula (I) or a salt thereof.

Dravet Syndrome and other related diseases

[0533] The terms “condition,” “diseases,” and “disorders” are used herein interchangeably in its broadest sense and include susceptibilities. In some embodiments, the disease or condition is Dravet Syndrome. In some embodiments, the method reduces or ameliorates at least one symptom of Dravet Syndrome in the human subject. In some embodiments, the symptom of Dravet Syndrome is a seizure. In

some embodiments, the administration reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration.

[0534] Dravet syndrome (DS), otherwise known as severe myoclonic epilepsy of infancy (SMEI), is an epileptic encephalopathy presenting in the first year of life. Dravet syndrome is an increasingly recognized epileptic encephalopathy in which the clinical diagnosis is supported by the finding of sodium channel gene mutations in approximately 70-80% of patients. DS is a severe and progressive developmental and epileptic encephalopathy that is characterized by high seizure frequency and severity, intellectual disability, and a high risk of sudden unexpected death in epilepsy. Mutations of ion channel genes play a major role in the pathogenesis of a range of epilepsy syndromes, resulting in some epilepsies being regarded as channelopathies. Voltage-gated sodium channels (VGSCs) play an essential role in neuronal excitability; therefore, it is not surprising that many mutations associated with DS have been identified in the gene encoding a VGSC subunit. The disease is described by, *e.g.,* Mulley, *et al.*, 2005, and the disease description at OMIM #607208 (Online Mendelian Inheritance in Man, Johns Hopkins University, 1966-2015), both incorporated by reference herein.

[0535] Between 70% and 80% of patients carry sodium channel 1 α subunit gene (*SCN1A*) abnormalities, and truncating mutations account for about 40%, and have a significant correlation with an earlier age of seizures onset. Sequencing mutations are found in about 70% of cases and comprise truncating (40%) and missense mutations (40%) with the remaining being splice-site changes. Most mutations are de novo, but familial mutations occur in 5-10% of cases and are usually missense in nature. The remaining SCN1A mutations comprise splice-site and missense mutations, most of which fall into the pore-forming region of the sodium channel. At present, over 500 mutations have been associated with DS and are randomly distributed along the gene (Mulley, *et al.*, Neurol. 2006, 67, 1094-1095).

[0536] The *SCN1A* gene is located in the cluster of sodium channel genes on human chromosome 2q24 and encodes the α-pore forming subunits known as $Na_V1.1$ of the neuronal voltage-gated sodium channel. The *SCN1A* gene spans approximately 100 kb of genomic DNA and comprises 26 exons. The $Na_V1.1$ protein consists of four domains, each with six-transmembrane segments. Two splice variants have been identified that result in a long and short isoform that differ in the presence or absence of 11 amino acids in the cytoplasmic loop between domains 1 and 2, in exon 11 (Miller, *et al.*, 1993-2015, and Mulley, *et al.*, 2005, 25, 535-542, of which entire content is incorporated herein by reference). In some aspects, the variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% nucleotide sequence identity across the whole sequence or a portion of the sequence (*e.g.,* a 50, 100, 150 or 200 continuous nucleotide portion) compared to a naturally occurring *SCN1A* gene. In some embodiments, the *SCN1A* gene is substantially identical to the gene identified by the Ensembl reference number ENSG00000144285 or a variant or homolog having substantial identity thereto.

[0537] Alternative splicing events in *SCN1A* gene can lead to non-productive mRNA transcripts which in turn can lead to aberrant protein expression, and therapeutic agents which can target the alternative splicing events in *SCN1A* gene can modulate the expression level of functional proteins in DS patients

and/or inhibit aberrant protein expression. Such therapeutic agents can be used to treat a condition characterized by $Na_V1.1$ protein deficiency.

[0538] One of the alternative splicing events that can lead to non-productive mRNA transcripts is the inclusion of an extra exon in the mRNA transcript that can induce nonsense-mediated mRNA decay. The present disclosure provides compositions and methods for modulating alternative splicing of SCN1A to increase the production of protein-coding mature mRNA, and thus, translated functional $Na_V1.1$ protein. These compositions and methods include compounds that can cause exon skipping and promote constitutive splicing of *SCN1A* pre-mRNA. In various embodiments, functional $Na_V1.1$ protein can be increased using the methods of the disclosure to treat a condition characterized by $Na_V1.1$ protein deficiency.

[0539] In some cases, the disease or condition is SMEB.

[0540] In some cases, the disease or condition is GEFS+.

[0541] In some cases, the disease or condition is a Febrile seizure (*e.g.,* Febrile seizures, familial, 3A).

[0542] In some cases, the disease or condition is autism (also known as autism spectrum disorder or ASD).

[0543] In some cases, the disease or condition is migraine (*e.g.,* migraine, familial hemiplegic, 3).

[0544] In some cases, the disease or condition is Alzheimer's disease.

[0545] In some embodiments, the disease or condition is SMEB. In some embodiments, the disease or condition is GEFS+. In some embodiments, the disease or condition is a Febrile seizure (*e.g.,* Febrile seizures, familial, 3A). In some embodiments, the disease or condition is autism (also known as autism spectrum disorder or ASD). In some embodiments, the disease or condition is migraine (*e.g.,* migraine, familial hemiplegic, 3). In some embodiments, the disease or condition is Alzheimer's disease. In some embodiments, the disease or condition is SCN2A encephalopathy. In some embodiments, the disease or condition is SCN8A encephalopathy. In some embodiments, the disease or condition is SCN5A arrhythmia.

[0546] In some embodiments, the disease or condition is induced by a mutation in $Na_V1.1$ (a protein encoded by the *SCN1A* gene). "$Na_V1.1$," also known as the sodium channel, voltage-gated, type I, alpha subunit (SCN1A), as used herein, refers to a protein which in humans is encoded by the *SCN1A* gene. $Na_V1.1$ includes any of the recombinant or naturally occurring forms of $Na_V1.1$ protein or variants or homologs thereof that maintain $Na_V1.1$ activity, (*e.g.,* within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% activity compared to $Na_V1.1$). In some aspects, the variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.,* a 50, 100, 150, or 200 continuous amino acid portion) compared to a naturally occurring $Na_V1.1$ protein. In some embodiments, the $Na_V1.1$ protein is substantially identical to the protein identified by the UniProt reference number P35498 or a variant or homolog having substantial identity thereto.

[0547] In some instances, the mutation is a loss-of-function mutation in $Na_V1.1$. In some cases, the loss-of-function mutation in $Na_V1.1$ comprises one or more mutations that decreases or impairs the function of

$Na_V1.1$ (*e.g.*, by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more) relative to the function of a wild-type $Na_V1.1$. In some cases, the loss-of-function mutation in $Na_V1.1$ comprises one or more mutations that result in a disease phenotype. Exemplary loss-of-function mutations include, but are not limited to, R859C, T875M, V1353L, I1656M, R1657C, A1685V, M1841T, and R1916G.

[0548] In other instances, the mutation is a gain-of-function mutation in $Na_V1.1$. In such cases, the gain-of-function mutation comprises one or more mutations that prolongs activation of $Na_V1.1$ (*e.g.*, by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more) relative to the function of a wild-type $Na_V1.1$. In such cases, the gain-of-function mutation in $Na_V1.1$ comprises one or more mutations that result in a disease phenotype. Exemplary gain-of-function mutations include, but are not limited to, D188V, W1204R, R1648H, and D1866Y.

[0549] In some embodiments, the disease or condition is an encephalopathy. In some cases, the encephalopathy is induced by a loss-of-function mutation in $Na_V1.1$.

[0550] In some embodiments, the encephalopathy is epileptic encephalopathy. Exemplary epileptic encephalopathies include, but are not limited to, Dravet Syndrome (DS) (also known as severe myoclonic epilepsy of infancy or SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); autism; malignant migrating partial seizures of infancy; or sick sinus syndrome 1. In some embodiments, the disease or condition is epileptic encephalopathy, optionally selected from Dravet Syndrome (DS) (also known as severe myoclonic epilepsy of infancy or SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); and sick sinus syndrome 1.

[0551] In some instances, GEFS+ is epilepsy, generalized, with febrile seizures plus, type 2.

[0552] In some instances, the Febrile seizure is Febrile seizures, familial, 3A.

[0553] In some instances, SMEB is SMEB without generalized spike wave (SMEB-SW), SMEB without myoclonic seizures (SMEB-M), SMEB lacking more than one feature of SMEI (SMEB-O), or intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC).

[0554] In some embodiments, GEFS+ is epilepsy, generalized, with febrile seizures plus, type 2. In some embodiments, the Febrile seizure is Febrile seizures, familial, 3A. In some embodiments, SMEB is SMEB without generalized spike wave (SMEB-SW), SMEB without myoclonic seizures (SMEB-M),

SMEB lacking more than one feature of SMEI (SMEB-O), or intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC).

[0555] In some embodiments, the diseases or conditions are induced by a loss-of-function mutation in $Na_V1.1$ include, but are not limited to, Dravet Syndrome (DS) (also known as SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); autism; or malignant migrating partial seizures of infancy.

[0556] In related embodiments, the method is a method of using a compound to decrease the expression of a protein or functional RNA. In some embodiments, a compound is used to decrease the expression of $Na_V1.1$ protein in cells of a subject having an NMD-inducing exon (NIE) containing pre-mRNA encoding $Na_V1.1$ protein. In some embodiments, the subject has a gain-of-function mutation in $Na_V1.1$, *e.g.,* migraine. In some embodiments, a compound is used to decrease the expression of $Na_V1.1$ protein in cells of a subject, the subject has a gain-of-function mutation in $Na_V1.1$, *e.g.,* migraine, familial hemiplegic, 3.

[0557] In some embodiments, the level of mRNA encoding $Na_V1.1$ protein is decreased 1.1 to 10-fold, when compared to the amount of mRNA encoding $Na_V1.1$ protein that is produced in a control cell, *e.g.,* one that is not treated with the antisense oligomer or one that is treated with an antisense oligomer that does not bind to the targeted portion of the SCN1A NIE containing pre-mRNA.

[0558] In some embodiments, the disease or condition is a $Na_V1.1$ genetic epilepsy. The $Na_V1.1$ genetic epilepsy can include a loss-of-function mutation in $Na_V1.1$ or a gain-of-function mutation in $Na_V1.1$. In some cases, the $Na_V1.1$ genetic epilepsy includes one or more hereditary mutations. In other cases, the $Na_V1.1$ genetic epilepsy includes one or more de novo mutations. In some cases, the $Na_V1.1$ genetic epilepsy includes Dravet Syndrome (DS) (also known as severe myoclonic epilepsy of infancy or SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); sudden unexpected death in epilepsy (SUDEP); or malignant migrating partial seizures of infancy. In some cases, the $Na_V1.1$ genetic epilepsy associated with a loss-of-function mutation in $Na_V1.1$ includes Dravet Syndrome (DS) (also known as severe myoclonic epilepsy of infancy or SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic

focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); sudden unexpected death in epilepsy (SUDEP); malignant migrating partial seizures of infancy.

[0559] In some embodiments, the disease or condition is associated with a haploinsufficiency of the *SCN1A* gene. Exemplary diseases or conditions associated with a haploinsufficiency of the *SCN1A* gene include, but are not limited to, Dravet Syndrome (DS) (also known as SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); or malignant migrating partial seizures of infancy. In some cases, the disease or condition is Dravet Syndrome (DS) (also known as SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); or malignant migrating partial seizures of infancy.

[0560] In some cases, the disease or condition is Dravet Syndrome (DS).

[0561] The term "epilepsy," as used herein, refers to a group of neurological disorders characterized by recurrent epileptic seizures. "Epileptic seizures," as used herein, refer to episodes that may vary from brief and nearly undetectable periods to long periods of vigorous shaking. Exemplary types of seizure include, but are not limited to, convulsive, non-convulsive, focal, and generalized seizures. Exemplary types of generalized seizures include, but are not limited to, tonic-clonic, tonic, clonic, myoclonic, absence, and atonic seizures.

[0562] In some embodiments, the disease or condition is induced by a gain-of-function mutation in $Na_V1.1$. Exemplary diseases or conditions associated with a gain-of-function mutation in $Na_V1.1$ include, but are not limited to, migraine. In some instances, the disease or condition induced by a gain-of-function mutation in $Na_V1.1$ is migraine. In some embodiments, the migraine is migraine, familial hemiplegic, 3.

[0563] In some embodiments, the method is a method of decreasing the expression of the $Na_V1.1$ protein by cells of a subject having a NIE containing pre-mRNA encoding the $Na_V1.1$ protein, and wherein the subject has a gain-of-function mutation in $Na_V1.1$. In such an embodiment, the subject has an allele from which the $Na_V1.1$ protein is produced in an elevated amount or an allele encoding a mutant SCN1A that

induces increased activity of $Na_V1.1$ in the cell. In some embodiments, the increased activity of $Na_V1.1$ is characterized by a prolonged or near persistent sodium current mediated by the mutant $Na_V1.1$ channel, a slowing of fast inactivation, a positive shift in steady-state inactivation, higher channel availability during repetitive stimulation, increased non-inactivated depolarization-induced persistent sodium currents, delayed entry into inactivation, accelerated recovery from fast inactivation, and/or rescue of folding defects by incubation at lower temperature or co-expression of interacting proteins. In any of these embodiments, the antisense oligomer binds to a targeted portion of the NIE containing pre-mRNA transcribed from the second allele, thereby inhibiting or blocking exon skipping of the pseudo-exon from the pre-mRNA, and causing a decrease in the level of mature mRNA encoding functional $Na_V1.1$ protein, and a decrease in the expression of the $Na_V1.1$ protein in the cells of the subject.

Assessments of Seizures

[0564] In some embodiments, the method or the dosing regimen of a compound described herein results in a reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration in a human subject. In some embodiments, the seizure frequency of the subject is reduced by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%. In a nonlimiting embodiment, the seizure frequency of the subject is reduced by at least about 50%. In one nonlimiting embodiment, the seizure frequency of the subject is reduced by at least about 60%. In another nonlimiting embodiment, the seizure frequency of the subject is reduced by at least about 70%. In one nonlimiting embodiment, the seizure frequency of the subject is reduced by at least about 80%. In one nonlimiting embodiment, the seizure frequency of the subject is reduced by at least about 90%. In one nonlimiting embodiment, the seizure frequency of the subject is reduced by about 100%. In some embodiments, the seizure intensity of the subject is reduced by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%. In a nonlimiting embodiment, the seizure intensity of the subject is reduced by at least about 50%. In one nonlimiting embodiment, the seizure intensity of the subject is reduced by at least about 60%. In another nonlimiting embodiment, the seizure intensity of the subject is reduced by at least about 70%. In one nonlimiting embodiment, the seizure intensity of the subject is reduced by at least about 80%. In one nonlimiting embodiment, the seizure intensity of the subject is reduced by at least about 90%. In one nonlimiting embodiment, the seizure intensity of the subject is reduced by about 100%. In some embodiments, the seizure duration of the subject is reduced by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%. In a nonlimiting embodiment, the seizure duration of the subject is reduced by at least about 50%. In one nonlimiting embodiment, the seizure duration of the subject is reduced by at least about 60%. In another nonlimiting embodiment, the seizure duration of the subject is reduced by at least about 70%. In one nonlimiting embodiment, the seizure duration of the subject is reduced by at least about 80%. In one nonlimiting embodiment, the seizure duration of the subject is reduced by at least about 90%. In one nonlimiting embodiment, the seizure duration of the subject is reduced by about 100%.

[0565] In some embodiments, the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer. In a nonlimiting embodiment, the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 6 months. In one nonlimiting embodiment, the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 12 months. In another nonlimiting embodiment, the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 24 months.

Assessments of Non-Seizure-Related Aspects

[0566] In some embodiments, the method or the dosing regimen of a compound described herein results in an improvement in a non-seizure-related aspect. In some embodiments, the non-seizure-related aspect comprises a cognitive or behavioral domain. In some embodiments, the cognitive or behavioral domain comprises communication, daily living skills, socialization, or motor skills. In some embodiments, the non-seizure-related aspect comprises a cognitive or behavioral subdomain such as receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, or fine motor skills. In some embodiments, the non-seizure-related aspect is determined according to a standardized assessment. In some embodiments, the cognitive or behavioral aspect is determined according to a standardized assessment. In some embodiments, the standardized assessment of a non-seizure related aspect comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C). n some embodiments, the standardized assessment of a non-seizure related aspect comprises a VABS-III and a CGI-C. n some embodiments, the standardized assessment of a non-seizure related aspect comprises a VABS-III and a CaGI-C. n some embodiments, the standardized assessment of a non-seizure related aspect comprises a CGI-C and a CaGI-C. n some embodiments, the standardized assessment of a non-seizure related aspect comprises a VABS-III, a CGI-C, and a CaGIC-C. In some embodiments, the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV). In some embodiments, the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, 9.000, 10.000, 11.000, 12.000, 13.000, 14.000, 15.000, 16.000, 17.000, 18.000, 19.000, or 20.000. In some embodiments, the standardized assessment comprises VABS-III and the positive change in GSV is about 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, 9.000, 10.000, 11.000, 12.000, 13.000, 14.000, 15.000, 16.000, 17.000, 18.000, 19.000, or 20.000. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 1. In some embodiments, the standardized assessment comprises VABS-III and an improvement

is an increase of GSV from about -3 to about 2. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -3 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 1. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 2. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of

GSV from about -2 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -2 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 1. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 2. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1

to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about -1 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 1. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 2. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 0 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 2. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 4. In some

embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 1 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 3. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 13. In some embodiments, the

standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 2 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 4. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 7. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 3 to about 20. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 5. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 6. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 7. In some embodiments, the standardized assessment

comprises VABS-III and an improvement is an increase of GSV from about 4 to about 8. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 9. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 10. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 11. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 12. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 13. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 14. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 15. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 16. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 17. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 18. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 19. In some embodiments, the standardized assessment comprises VABS-III and an improvement is an increase of GSV from about 4 to about 20.

[0567] In some embodiments, the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 7 to about 6, from about 7 to about 5, from about 7 to about 4, from about 7 to about 3, from about 7 to about 2, from about 7 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 6 to about 5, from about 6 to about 4, from about 6 to about 3, from about 6 to about 2, from about 6 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 5 to about 5, from about 5 to about 4, from about 5 to about 3, from about 5 to about 2, from about 5 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 4 to about 3, from about 4 to about 2, from about 4 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 3 to about 2, from about 3 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is decrease in a CGI-C score from about 2 to about 1. In some embodiments, the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 7 to about 6, from about 7 to about 5, from about 7 to about 4, from about 7 to about 3, from about 7 to about 2, from about 7 to about 1. In some

embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 6 to about 5, from about 6 to about 4, from about 6 to about 3, from about 6 to about 2, from about 6 to about 1. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 5 to about 5, from about 5 to about 4, from about 5 to about 3, from about 5 to about 2, from about 5 to about 1. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 4 to about 3, from about 4 to about 2, from about 4 to about 1. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 3 to about 2, from about 3 to about 1. In some embodiments, the standardized assessment comprises CAGI-C and the improvement is decrease in a CAGI-C score from about 2 to about 1. In some embodiments, the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1. In some embodiments, the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1. In some embodiments, the administration (a) reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration; and (b) results in an improvement in a non-seizure-related aspect.

[0568] In some embodiments, the improvement in the non-seizure-related aspect is sustained for at least 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer. In a nonlimiting embodiment, the improvement in the non-seizure-related aspect is sustained for at least 6 months. In one nonlimiting embodiment, the improvement in the non-seizure-related aspect is sustained for at least 12 months. In another nonlimiting embodiment, the improvement in the non-seizure-related aspect is sustained for at least 24 months.

[0569] In some embodiments, the method or the dosing regimen of a compound described herein results in no treatment-emergent serious adverse event (TESAE) in the human subject related to the administration of the compound of formula (I) or a salt thereof.

Compositions

[0570] In some embodiments, the ASO provided herein comprises a sequence with at least 83%, 88%, 94% or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO consists of a sequence with at least 83%, 88%, 94% or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO comprises a sequence with at least 83%, 88%, 94% or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**. In some embodiments, the ASO consists of a sequence with at least 83%, 88%, 94% or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0571] In some embodiments, the ASO comprises a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments,

the ASO consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO comprises a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**. In some embodiments, the ASO consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0572] In some embodiments, the ASO as described herein comprises at least one modified sugar moiety.

[0573] In some embodiments, the ASO as described herein comprises T-methoxyethyl sugar moiety. In some embodiments, the T-methoxyethyl sugar moiety is a T-2'-methoxyethyl sugar moiety. In some embodiments, the ASO as described herein comprises a 2'-O-methoxyethyl moiety. In some embodiments, the ASO as described herein comprises a thymidine comprising a 2'-O-methoxyethyl moiety. In some embodiments, each nucleobase of the ASO as described herein comprises a 2'-O-methoxyethyl moiety.

[0574] In some embodiments, the ASO as described herein consists of from 8 to 50 nucleobases. In some embodiments, the ASO as described herein consists of from 16 to 20 nucleobases. In some embodiments, the ASO as described herein consists of from 12 to 20 nucleobases. In some embodiments, the ASO as described herein consists of from 8 to 20 nucleobases.

[0575] In some embodiments, the ASO as described herein consists of from 5 to 100, from 6 to 100, from 7 to 100, from 8 to 100, from 9 to 100, from 10 to 100, from 11 to 100, from 12 to 100, from 13 to 100, from 14 to 100, from 15 to 100, from 16 to 100, from 17 to 100, from 18 to 100, from 19 to 100, from 20 to 100, from 21 to 100, from 22 to 100, from 23 to 100, from 24 to 100, from 25 to 100, from 30 to 100, from 35 to 100, from 40 to 100, from 45 to 100, from 50 to 100, from 55 to 100, from 60 to 100, from 65 to 100, from 70 to 100, from 75 to 100, from 80 to 100, from 85 to 100, or from 90 to 100 nucleobases. In some embodiments, the ASO as described herein consists of from 5 to 100, 5 to 95, 5 to 90, 5 to 85, 5 to 80, 5 to 75, 5 to 70, 5 to 65, 5 to 60, 5 to 55, 5 to 50, 5 to 45, 5 to 40, 5 to 35, 5 to 30, 5 to 25, 5 to 20, 5 to 15, or 5 to 10 nucleobases. In some embodiments, the ASO as described herein consists of from 8 to 50, from 8 to 45, from 8 to 40, from 8 to 35, from 8 to 30, from 8 to 29, from 8 to 28, from 8 to 27, from 8 to 26, from 8 to 25, from 8 to 24, from 8 to 23, from 8 to 22, from 8 to 21, from 8 to 20, from 8 to 19, from 8 to 18, from 8 to 17, or from 8 to 16 nucleobases. In some embodiments, the ASO as described herein consists of from 9 to 20, from 10 to 20, from 11 to 20, from 12 to 20, from 13 to 20, from 14 to 20, from 15 to 20, from 16 to 20, from 17 to 20, or from 18 to 20 nucleobases. In some

embodiments, the ASO as described herein consists of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleobases.

[0576] In some embodiments, the ASO as described herein comprises a 5'-methylcytosine (5'-MeC). In some embodiments, each cytosine of the ASO as described herein is a 5'-methylcytosine (5'-MeC).

[0577] In some embodiments, the ASO as described herein comprises a phosphorothioate linkage. In some embodiments, each internucleoside linkage of the ASO as described herein is a phosphorothioate linkage.

[0578] In some embodiments, the ASO as described herein comprises a locked nucleic acid (LNA).

[0579] In some embodiments, the ASO as described herein comprises least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 LNAs. In some embodiments, the ASO as described herein comprises 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 LNAs. In some embodiments, the ASO as described herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 LNAs.

[0580] In some embodiments, the 5' end nucleotide of the ASO as described herein is an LNA. In some embodiments, the 3' end nucleotide of the ASO as described herein is an LNA. In some embodiments, the 5' and 3' end nucleotides of the ASO as described herein are LNAs.

ASO (Antisense Oligomer)

[0581] Provided herein is a composition comprising a compound that is an antisense oligomer that induces exon skipping by binding to a targeted portion of a SCN1A NIE containing pre-mRNA. As used herein, the terms "ASO" and "antisense oligomer" are used interchangeably and refer to an oligomer such as a polynucleotide, comprising nucleobases that hybridizes to a target nucleic acid (*e.g.,* a SCN1A NIE containing pre-mRNA) sequence by Watson-Crick base pairing or wobble base pairing (G-U). The ASO may have exact sequence complementary to the target sequence or near complementarity (*e.g.,* sufficient complementarity to bind the target sequence and enhancing splicing at a splice site). ASOs are designed so that they bind (hybridize) to a target nucleic acid (*e.g.,* a targeted portion of a pre-mRNA transcript) and remain hybridized under physiological conditions. Typically, if they hybridize to a site other than the intended (targeted) nucleic acid sequence, they hybridize to a limited number of sequences that are not a target nucleic acid (to a few sites other than a target nucleic acid). Design of an ASO can take into consideration the occurrence of the nucleic acid sequence of the targeted portion of the pre-mRNA transcript or a sufficiently similar nucleic acid sequence in other locations in the genome or cellular pre-mRNA or transcriptome, such that the likelihood the ASO will bind other sites and cause "off-target" effects is limited. Any antisense oligomers known in the art, for example in PCT Application No. PCT/US2014/054151, published as WO 2015/035091, titled "Reducing Nonsense-Mediated mRNA Decay," incorporated by reference herein, can be used to practice the methods described herein.

[0582] In some embodiments, ASOs "specifically hybridize" to or are "specific" to a target nucleic acid or a targeted portion of a NIE containing pre-mRNA. Typically, such hybridization occurs with a T_m substantially greater than 37 °C, preferably at least 50 °C, and typically between 60 °C, to approximately 90 °C. Such hybridization preferably corresponds to stringent hybridization conditions. At a given ionic

strength and pH, the T_m is the temperature at which 50% of a target sequence hybridizes to a complementary oligonucleotide.

[0583] Oligomers, such as oligonucleotides, are "complementary" to one another when hybridization occurs in an antiparallel configuration between two single-stranded polynucleotides. A double-stranded polynucleotide can be "complementary" to another polynucleotide, if hybridization can occur between one of the strands of the first polynucleotide and the second. Complementarity (the degree to which one polynucleotide is complementary with another) is quantifiable in terms of the proportion (*e.g.,* the percentage) of bases in opposing strands that are expected to form hydrogen bonds with each other, according to generally accepted base-pairing rules. The sequence of an antisense oligomer (ASO) need not be 100% complementary to that of its target nucleic acid to hybridize. In certain embodiments, ASOs can comprise at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence complementarity to a target region within the target nucleic acid sequence to which they are targeted. For example, an ASO in which 18 of 20 nucleobases of the oligomeric compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining non-complementary nucleobases may be clustered together or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. Percent complementarity of an ASO with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul, *et al.*, J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 7, 649-656, of which entire content is incorporated herein by reference).

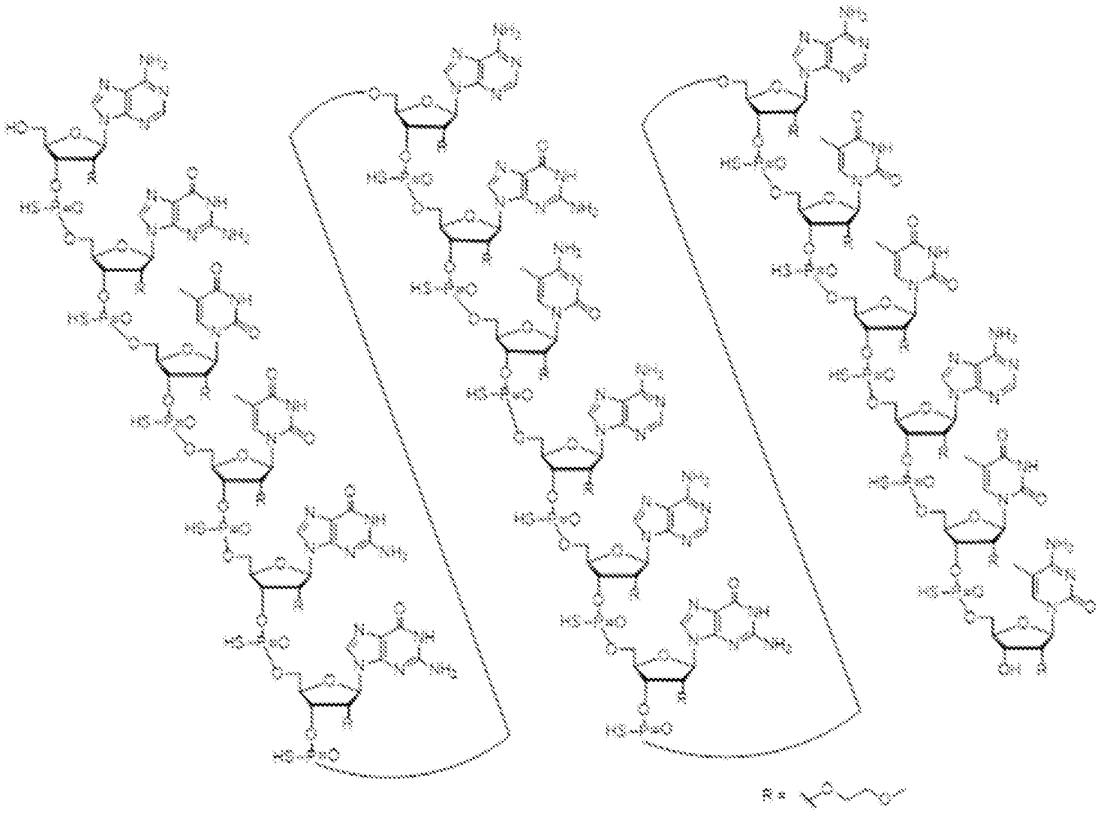
[0584] An ASO need not hybridize to all nucleobases in a target sequence and the nucleobases to which it does hybridize may be contiguous or noncontiguous. ASOs may hybridize over one or more segments of a pre-mRNA transcript, such that intervening or adjacent segments are not involved in the hybridization event (*e.g.,* a loop structure or hairpin structure may be formed). In certain embodiments, an ASO hybridizes to noncontiguous nucleobases in a target pre-mRNA transcript. For example, an ASO can hybridize to nucleobases in a pre-mRNA transcript that are separated by one or more nucleobase(s) to which the ASO does not hybridize.

[0585] In some cases, an ASO described herein is *all-P-ambo*-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-

methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine, or a salt thereof.

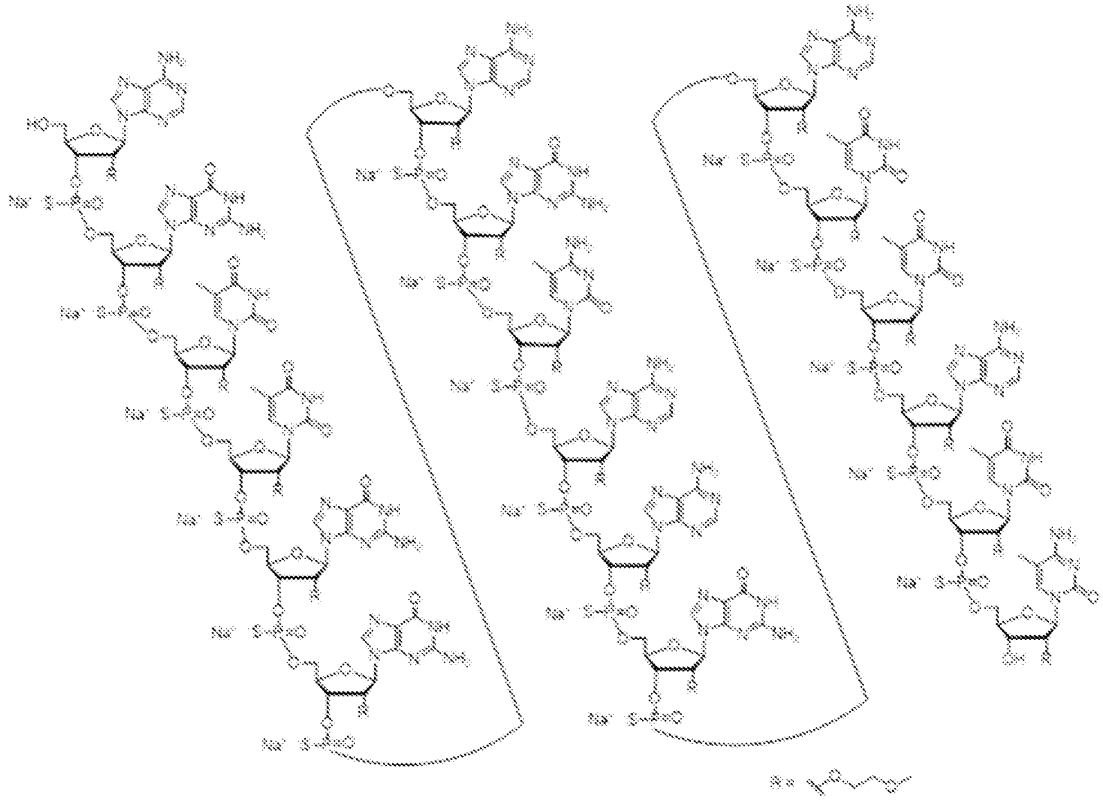
[0586] In some cases, an ASO described herein is a sodium salt of *all-P-ambo*-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine.

[0587] In some cases, a compound (*e.g.,* an ASO) described herein is compound (I) having the structure depicted in formula (I) (free acid):



(I), or a salt thereof.

[0588] In some cases, a compound (*e.g.,* an ASO) described herein is compound (II) having the structure depicted in formula (II) (sodium salt):



(II).

[0589] In any of the structural formulae (graphic representation of a chemical compound) presented herein, where two curved lines and a straight line in between them are used to connect a phosphorus atom ("P") and an oxygen atom ("O"), the two curved lines and the straight line therebetween should be seen as a single integral segment, representing the covalent bond between the phosphorus atom and the oxygen atom, which is part of a backbone linkage (*e.g.,* phosphodiester linkage or phosphorothioate linkage) between two neighboring nucleotides. Any of the vertices (corners) in any of those structural formulae where a curved line and a straight line join does not represent carbon atom or presence of -CH2- at the relevant location in the compound the structural formula represents.

[0590] The compounds described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) comprise nucleobases that are complementary to nucleobases present in a targeted portion of a NIE containing pre-mRNA. The term ASO embodies oligonucleotides and any other oligomeric molecule that comprises nucleobases capable of hybridizing to a complementary nucleobase on a target mRNA but does not comprise a sugar moiety, such as a peptide nucleic acid (PNA). The ASOs may comprise naturally occurring nucleotides, nucleotide analogs, modified nucleotides, or any combination of two or three of the preceding. The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" includes nucleotides with modified or substituted sugar groups and/or having a modified backbone. In some embodiments, all of the nucleotides of the ASO are

modified nucleotides. Chemical modifications of ASOs or components of ASOs that are compatible with the methods and compositions described herein will be evident to one of skill in the art and can be found, for example, in U.S. Pat. 8,258,109 B2, U.S. Pat. No. 5,656,612, U.S. Patent Publication No. 2012/0190728, and Dias and Stein, Mol. Cancer Ther. 2002, 347-355, herein incorporated by reference in their entirety.

[0591] One or more nucleobases of an ASO (*e.g.,* compound (I) or a salt thereof, or compound (II)) may be any naturally occurring, unmodified nucleobase such as adenine, guanine, cytosine, thymine and uracil, or any synthetic or modified nucleobase that is sufficiently similar to an unmodified nucleobase such that it is capable of hydrogen bonding with a nucleobase present on a target pre-mRNA. Examples of modified nucleobases include, without limitation, hypoxanthine, xanthine, 7-methylguanine, 5, 6-dihydrouracil, 5-methylcytosine, and 5-hydroxymethoylcytosine.

[0592] The compounds described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) also comprise a backbone structure that connects the components of an oligomer. The term "backbone structure" and "oligomer linkages" may be used interchangeably and refer to the connection between monomers of the ASO. In naturally occurring oligonucleotides, the backbone comprises a 3'-5' phosphodiester linkage connecting sugar moieties of the oligomer. The backbone structure or oligomer linkages of the ASOs described herein may include (but are not limited to) phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoramidate, and the like. See, *e.g.,* LaPlanche, *et al.*, Nucleic Acids Res. 14:9081 (1986); Stec, *et al.*, J. Am. Chem. Soc. 106:6077 (1984), Stein, *et al.*, Nucleic Acids Res. 16:3209 (1988), Zon, *et al.*, Anti-Cancer Drug Design 6:539 (1991); Zon, *et al.*, Oligonucleotides and Analogues: A Practical Approach, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec, *et al.*, U.S. Pat. No. 5,151,510; Uhlmann and Peyman, Chemical Reviews 90:543 (1990), of which entire content is incorporated herein by reference. In some embodiments, the backbone structure of the ASO does not contain phosphorous but rather contains peptide bonds, for example in a peptide nucleic acid (PNA), or linking groups including carbamate, amides, and linear and cyclic hydrocarbon groups. In some embodiments, the backbone modification is a phosphorothioate linkage. In some embodiments, the backbone modification is a phosphoramidate linkage.

[0593] In some embodiments, the stereochemistry at each of the phosphorus internucleotide linkages of the ASO backbone is random. In some embodiments, the stereochemistry at each of the phosphorus internucleotide linkages of the ASO backbone is controlled and is not random. For example, U.S. Pat. App. Pub. No. 2014/0194610, "Methods for the Synthesis of Functionalized Nucleic Acids," incorporated herein by reference, describes methods for independently selecting the handedness of chirality at each phosphorous atom in a nucleic acid oligomer. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in **Tables 5** and **6**, comprises an ASO having phosphorus internucleotide linkages that are not random. In some embodiments, a composition used in the methods of the invention comprises a pure diastereomeric ASO. In some embodiments, a composition used in the methods of the invention comprises an ASO that has

diastereomeric purity of at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, about 100%, about 90% to about 100%, about 91% to about 100%, about 92% to about 100%, about 93% to about 100%, about 94% to about 100%, about 95% to about 100%, about 96% to about 100%, about 97% to about 100%, about 98% to about 100%, or about 99% to about 100%.

[0594] In some embodiments, the ASO (*e.g.*, compound (I) or a salt thereof, or compound (II)) has a nonrandom mixture of *R*p and *S*p configurations at its phosphorus internucleotide linkages. For example, it has been suggested that a mix of *R*p and *S*p in antisense oligonucleotides or antisense oligomers helps to achieve a balance between good activity and nuclease stability (Wan, *et al.*, 2014, "Synthesis, biophysical properties and biological activity of second-generation antisense oligonucleotides containing chiral phosphorothioate linkages," Nucleic Acids Research 42(22): 13456-13468, incorporated herein by reference). In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-114, comprises about 5-100% *R*p, at least about 5% *R*p, at least about 10% *R*p, at least about 15% *R*p, at least about 20% *R*p, at least about 25% *R*p, at least about 30% *R*p, at least about 35% *R*p, at least about 40% *R*p, at least about 45% *R*p, at least about 50% *R*p, at least about 55% *R*p, at least about 60% *R*p, at least about 65% *R*p, at least about 70% *R*p, at least about 75% *R*p, at least about 80% *R*p, at least about 85% *R*p, at least about 90% *R*p, or at least about 95% *R*p, with the remainder *S*p, or about 100% *R*p. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-114, comprises about 10% to about 100% *R*p, about 15% to about 100% *R*p, about 20% to about 100% *R*p, about 25% to about 100% *R*p, about 30% to about 100% *R*p, about 35% to about 100% *R*p, about 40% to about 100% *R*p, about 45% to about 100% *R*p, about 50% to about 100% *R*p, about 55% to about 100% *R*p, about 60% to about 100% *R*p, about 65% to about 100% *R*p, about 70% to about 100% *R*p, about 75% to about 100% *R*p, about 80% to about 100% *R*p, about 85% to about 100% *R*p, about 90% to about 100% *R*p, or about 95% to about 100% *R*p, about 20% to about 80% *R*p, about 25% to about 75% *R*p, about 30% to about 70% *R*p, about 40% to about 60% *R*p, or about 45% to about 55% *R*p, with the remainder *S*p.

[0595] In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-114, comprises about 5-100% *S*p, at least about 5% *S*p, at least about 10% *S*p, at least about 15% *S*p, at least about 20% *S*p, at least about 25% *S*p, at least about 30% *S*p, at least about 35% *S*p, at least about 40% *S*p, at least about 45% *S*p, at least about 50% *S*p, at least about 55% *S*p, at least about 60% *S*p, at least about 65% *S*p, at least about 70% *S*p, at least about 75% *S*p, at least about 80% *S*p, at least about 85% *S*p, at least about 90% *S*p, or at least about 95% *S*p, with the remainder *R*p, or about 100% *S*p. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-114, comprises about 10% to about 100% *S*p, about 15% to about 100% *S*p, about 20% to about 100% *S*p, about 25% to about 100% *S*p, about 30% to about 100% *S*p, about 35% to about 100% *S*p, about 40% to about 100% *S*p, about 45% to about 100% *S*p, about 50% to about 100% *S*p, about 55% to about 100%

Sp, about 60% to about 100% *Sp*, about 65% to about 100% *Sp*, about 70% to about 100% *Sp*, about 75% to about 100% *Sp*, about 80% to about 100% *Sp*, about 85% to about 100% *Sp*, about 90% to about 100% *Sp*, or about 95% to about 100% *Sp*, about 20% to about 80% *Sp*, about 25% to about 75% *Sp*, about 30% to about 70% *Sp*, about 40% to about 60% *Sp*, or about 45% to about 55% *Sp*, with the remainder *Rp*.

[0596] In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-67, 210-256 or 304-1099, comprises about 5-100% *Rp*, at least about 5% *Rp*, at least about 10% *Rp*, at least about 15% *Rp*, at least about 20% *Rp*, at least about 25% *Rp*, at least about 30% *Rp*, at least about 35% *Rp*, at least about 40% *Rp*, at least about 45% *Rp*, at least about 50% *Rp*, at least about 55% *Rp*, at least about 60% *Rp*, at least about 65% *Rp*, at least about 70% *Rp*, at least about 75% *Rp*, at least about 80% *Rp*, at least about 85% *Rp*, at least about 90% *Rp*, or at least about 95% *Rp*, with the remainder *Sp*, or about 100% *Rp*. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-67, 210-256 or 304-1099, comprises about 10% to about 100% *Rp*, about 15% to about 100% *Rp*, about 20% to about 100% *Rp*, about 25% to about 100% *Rp*, about 30% to about 100% *Rp*, about 35% to about 100% *Rp*, about 40% to about 100% *Rp*, about 45% to about 100% *Rp*, about 50% to about 100% *Rp*, about 55% to about 100% *Rp*, about 60% to about 100% *Rp*, about 65% to about 100% *Rp*, about 70% to about 100% *Rp*, about 75% to about 100% *Rp*, about 80% to about 100% *Rp*, about 85% to about 100% *Rp*, about 90% to about 100% *Rp*, or about 95% to about 100% *Rp*, about 20% to about 80% *Rp*, about 25% to about 75% *Rp*, about 30% to about 70% *Rp*, about 40% to about 60% *Rp*, or about 45% to about 55% *Rp*, with the remainder *Sp*.

[0597] In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-67, 210-256 or 304-1099, comprises about 5-100% *Sp*, at least about 5% *Sp*, at least about 10% *Sp*, at least about 15% *Sp*, at least about 20% *Sp*, at least about 25% *Sp*, at least about 30% *Sp*, at least about 35% *Sp*, at least about 40% *Sp*, at least about 45% *Sp*, at least about 50% *Sp*, at least about 55% *Sp*, at least about 60% *Sp*, at least about 65% *Sp*, at least about 70% *Sp*, at least about 75% *Sp*, at least about 80% *Sp*, at least about 85% *Sp*, at least about 90% *Sp*, or at least about 95% *Sp*, with the remainder *Rp*, or about 100% *Sp*. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in SEQ ID NOs: 21-67, 210-256 or 304-1099, comprises about 10% to about 100% *Sp*, about 15% to about 100% *Sp*, about 20% to about 100% *Sp*, about 25% to about 100% *Sp*, about 30% to about 100% *Sp*, about 35% to about 100% *Sp*, about 40% to about 100% *Sp*, about 45% to about 100% *Sp*, about 50% to about 100% *Sp*, about 55% to about 100% *Sp*, about 60% to about 100% *Sp*, about 65% to about 100% *Sp*, about 70% to about 100% *Sp*, about 75% to about 100% *Sp*, about 80% to about 100% *Sp*, about 85% to about 100% *Sp*, about 90% to about 100% *Sp*, or about 95% to about 100% *Sp*, about 20% to about 80% *Sp*, about 25% to about 75% *Sp*, about 30% to about 70% *Sp*, about 40% to about 60% *Sp*, or about 45% to about 55% *Sp*, with the remainder *Rp*.

[0598] In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B,**

6, 7A, and **7B**, comprises about 5-100% *R*p, at least about 5% *R*p, at least about 10% *R*p, at least about 15% *R*p, at least about 20% *R*p, at least about 25% *R*p, at least about 30% *R*p, at least about 35% *R*p, at least about 40% *R*p, at least about 45% *R*p, at least about 50% *R*p, at least about 55% *R*p, at least about 60% *R*p, at least about 65% *R*p, at least about 70% *R*p, at least about 75% *R*p, at least about 80% *R*p, at least about 85% *R*p, at least about 90% *R*p, or at least about 95% *R*p, with the remainder *S*p, or about 100% *R*p. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, comprises about 10% to about 100% *R*p, about 15% to about 100% *R*p, about 20% to about 100% *R*p, about 25% to about 100% *R*p, about 30% to about 100% *R*p, about 35% to about 100% *R*p, about 40% to about 100% *R*p, about 45% to about 100% *R*p, about 50% to about 100% *R*p, about 55% to about 100% *R*p, about 60% to about 100% *R*p, about 65% to about 100% *R*p, about 70% to about 100% *R*p, about 75% to about 100% *R*p, about 80% to about 100% *R*p, about 85% to about 100% *R*p, about 90% to about 100% *R*p, or about 95% to about 100% *R*p, about 20% to about 80% *R*p, about 25% to about 75% *R*p, about 30% to about 70% *R*p, about 40% to about 60% *R*p, or about 45% to about 55% *R*p, with the remainder *S*p.

[0599] In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, comprises about 5-100% *S*p, at least about 5% *S*p, at least about 10% *S*p, at least about 15% *S*p, at least about 20% *S*p, at least about 25% *S*p, at least about 30% *S*p, at least about 35% *S*p, at least about 40% *S*p, at least about 45% *S*p, at least about 50% *S*p, at least about 55% *S*p, at least about 60% *S*p, at least about 65% *S*p, at least about 70% *S*p, at least about 75% *S*p, at least about 80% *S*p, at least about 85% *S*p, at least about 90% *S*p, or at least about 95% *S*p, with the remainder *R*p, or about 100% *S*p. In some embodiments, an ASO used in the methods of the invention, including, but not limited to, any of the ASOs set forth herein in any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**, comprises about 10% to about 100% *S*p, about 15% to about 100% *S*p, about 20% to about 100% *S*p, about 25% to about 100% *S*p, about 30% to about 100% *S*p, about 35% to about 100% *S*p, about 40% to about 100% *S*p, about 45% to about 100% *S*p, about 50% to about 100% *S*p, about 55% to about 100% *S*p, about 60% to about 100% *S*p, about 65% to about 100% *S*p, about 70% to about 100% *S*p, about 75% to about 100% *S*p, about 80% to about 100% *S*p, about 85% to about 100% *S*p, about 90% to about 100% *S*p, or about 95% to about 100% *S*p, about 20% to about 80% *S*p, about 25% to about 75% *S*p, about 30% to about 70% *S*p, about 40% to about 60% *S*p, or about 45% to about 55% *S*p, with the remainder *R*p.

[0600] In some embodiments, an ASO used in the methods of the invention, having the structure of formula (I) or (II), comprises about 5-100% *S*p, at least about 5% *S*p, at least about 10% *S*p, at least about 15% *S*p, at least about 20% *S*p, at least about 25% *S*p, at least about 30% *S*p, at least about 35% *S*p, at least about 40% *S*p, at least about 45% *S*p, at least about 50% *S*p, at least about 55% *S*p, at least about 60% *S*p, at least about 65% *S*p, at least about 70% *S*p, at least about 75% *S*p, at least about 80% *S*p, at least about 85% *S*p, at least about 90% *S*p, or at least about 95% *S*p, with the remainder *R*p, or about

100% *S*p. In some embodiments, an ASO used in the methods of the invention, having the structure of formula (I) or (II), comprises about 10% to about 100% *S*p, about 15% to about 100% *S*p, about 20% to about 100% *S*p, about 25% to about 100% *S*p, about 30% to about 100% *S*p, about 35% to about 100% *S*p, about 40% to about 100% *S*p, about 45% to about 100% *S*p, about 50% to about 100% *S*p, about 55% to about 100% *S*p, about 60% to about 100% *S*p, about 65% to about 100% *S*p, about 70% to about 100% *S*p, about 75% to about 100% *S*p, about 80% to about 100% *S*p, about 85% to about 100% *S*p, about 90% to about 100% *S*p, or about 95% to about 100% *S*p, about 20% to about 80% *S*p, about 25% to about 75% *S*p, about 30% to about 70% *S*p, about 40% to about 60% *S*p, or about 45% to about 55% *S*p, with the remainder *R*p.

[0601] Any of the compounds (*e.g.,* ASOs) described herein may contain a sugar moiety that comprises ribose or deoxyribose, as present in naturally occurring nucleotides, or a modified sugar moiety or sugar analog, including a morpholine ring. Non-limiting examples of modified sugar moieties include 2' substitutions such as 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'MOE), 2'-O-aminoethyl, 2'F, 2'-N-methyl-acetamide (2'-NMA); N3'->P5' phosphoramidate, 2' dimethylaminooxyethoxy, 2' dimethylaminoethoxyethoxy, 2'-guanidinidium, 2'-O-guanidinium ethyl, carbamate modified sugars, and bicyclic modified sugars. In some embodiments, the sugar moiety modification is selected from 2'-O-Me, 2'F, 2'MOE, and 2'-NMA. As used herein, "2'-NMA" means a -O-CH2-C(=O)-NH-CH3 group in place of the 2'-OH group of a ribosyl sugar moiety. In some embodiments, the sugar moiety modification is an extra bridge bond, such as in a locked nucleic acid (LNA). In some embodiments the sugar analog contains a morpholine ring, such as phosphorodiamidate morpholino (PMO). In some embodiments, the sugar moiety comprises a ribofuranosyl or 2' deoxyribofuranosyl modification. In some embodiments, the sugar moiety comprises 2'4'-constrained 2'O-methyloxyethyl (cMOE) modifications. In some embodiments, the sugar moiety comprises cEt 2', 4' constrained 2'-O ethyl BNA modifications. In some embodiments, the sugar moiety comprises tricycloDNA (tcDNA) modifications. In some embodiments, the sugar moiety comprises ethylene nucleic acid (ENA) modifications. In some embodiments, the sugar moiety comprises MCE modifications. Modifications are known in the art and described in the literature, *e.g.,* by Jarver, *et al.*, 2014, Nucleic Acid Therapeutics 24(1): 37-47, incorporated by reference for this purpose herein. "A Chemical View of Oligonucleotides for Exon Skipping and Related Drug Applications," Nucleic Acid Therapeutics 24(1): 37-47, incorporated by reference for this purpose herein.

[0602] In some embodiments, each monomer of the ASO is modified in the same way, for example each linkage of the backbone of the ASO comprises a phosphorothioate linkage or each ribose sugar moiety comprises a 2'O-methyl modification. Such modifications that are present on each of the monomer components of an ASO are referred to as "uniform modifications." In some examples, a combination of different modifications may be desired, for example, an ASO may comprise a combination of phosphorodiamidate linkages and sugar moieties comprising morpholine rings (morpholinos). Combinations of different modifications to an ASO are referred to as "mixed modifications" or "mixed chemistries."

[0603] In some embodiments, the ASO comprises one or more backbone modifications. In some embodiments, the ASO comprises one or more sugar moiety modification. In some embodiments, the ASO comprises one or more backbone modifications and one or more sugar moiety modifications. In some embodiments, the ASO comprises a 2'MOE modification and a phosphorothioate backbone. In some embodiments, the ASO comprises a phosphorodiamidate morpholino (PMO). In some embodiments, the ASO comprises a peptide nucleic acid (PNA). Any of the ASOs or any component of an ASO (*e.g.,* a nucleobase, sugar moiety, backbone) described herein may be modified in order to achieve desired properties or activities of the ASO or reduce undesired properties or activities of the ASO. For example, an ASO or one or more components of any ASO may be modified to enhance binding affinity to a target sequence on a pre-mRNA transcript; reduce binding to any non-target sequence; reduce degradation by cellular nucleases (*i.e.,* RNase H); improve uptake of the ASO into a cell and/or into the nucleus of a cell; alter the pharmacokinetics or pharmacodynamics of the ASO; and/or modulate the half-life of the ASO.

[0604] In some embodiments, the ASOs are comprised of 2'-O-(2-methoxyethyl) (MOE) phosphorothioate-modified nucleotides. ASOs comprised of such nucleotides are especially well-suited to the methods disclosed herein; oligomers having such modifications have been shown to have significantly enhanced resistance to nuclease degradation and increased bioavailability, making them suitable, for example, for oral delivery in some embodiments described herein. See *e.g.,* Geary, *et al.*, J Pharmacol Exp Ther. 2001; 296(3):890-7; Geary, *et al.*, J Pharmacol Exp Ther. 2001; 296(3):898-904, of which entire content is incorporated herein by reference.

[0605] Methods of synthesizing ASOs will be known to one of skill in the art. Alternatively or in addition, ASOs may be obtained from a commercial source.

[0606] Unless specified otherwise, the left-hand end of single-stranded nucleic acid (*e.g.,* pre-mRNA transcript, oligonucleotide, ASO, *etc.*) sequences is the 5' end and the left-hand direction of single or double-stranded nucleic acid sequences is referred to as the 5' direction. Similarly, the right-hand end or direction of a nucleic acid sequence (single- or double-stranded) is the 3' end or direction. Generally, a region or sequence that is 5' to a reference point in a nucleic acid is referred to as "upstream," and a region or sequence that is 3' to a reference point in a nucleic acid is referred to as "downstream." Generally, the 5' direction or end of an mRNA is where the initiation or start codon is located, while the 3' end or direction is where the termination codon is located. In some aspects, nucleotides that are upstream of a reference point in a nucleic acid may be designated by a negative number, while nucleotides that are downstream of a reference point may be designated by a positive number. For example, a reference point (*e.g.,* an exon-exon junction in mRNA) may be designated as the "zero" site, and a nucleotide that is directly adjacent and upstream of the reference point is designated "minus one," *e.g.,* "-1," while a nucleotide that is directly adjacent and downstream of the reference point is designated "plus one," *e.g.,* "+1."

[0607] In some embodiments, the ASOs are complementary to (and bind to) a targeted portion of a SCN1A NIE containing pre-mRNA that is downstream (in the 3' direction) of the 5' splice site (or 3' end

of the NIE) of the included exon in a SCN1A NIE containing pre-mRNA (*e.g.,* the direction designated by positive numbers relative to the 5' splice site). In some embodiments, the ASOs are complementary to a targeted portion of the SCN1A NIE containing pre-mRNA that is within the region about +1 to about +500 relative to the 5' splice site (or 3' end) of the included exon. In some embodiments, the ASOs may be complementary to a targeted portion of a SCN1A NIE containing pre-mRNA that is within the region between nucleotides +6 and +496 relative to the 5' splice site (or 3' end) of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region about +1 to about +500, about +1 to about +490, about +1 to about +480, about +1 to about +470, about +1 to about +460, about +1 to about +450, about +1 to about +440, about +1 to about +430, about +1 to about +420, about +1 to about +410, about +1 to about +400, about +1 to about +390, about +1 to about +380, about +1 to about +370, about +1 to about +360, about +1 to about +350, about +1 to about +340, about +1 to about +330, about +1 to about +320, about +1 to about +310, about +1 to about +300, about +1 to about +290, about +1 to about +280, about +1 to about +270, about +1 to about +260, about +1 to about +250, about +1 to about +240, about +1 to about +230, about +1 to about +220, about +1 to about +210, about +1 to about +200, about +1 to about +190, about +1 to about +180, about +1 to about +170, about +1 to about +160, about +1 to about +150, about +1 to about +140, about +1 to about +130, about +1 to about +120, about +1 to about +110, about +1 to about +100, about +1 to about +90, about +1 to about +80, about +1 to about +70, about +1 to about +60, about +1 to about +50, about +1 to about +40, about +1 to about +30, or about +1 to about +20 relative to 5' splice site (or 3' end) of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region from about +1 to about +100, from about +100 to about +200, from about +200 to about +300, from about +300 to about +400, or from about +400 to about +500 relative to 5' splice site (or 3' end) of the included exon.

[0608] In some embodiments, the ASOs are complementary to (and bind to) a targeted portion of a SCN1A NIE containing pre-mRNA that is upstream (in the 5' direction) of the 5' splice site (or 3' end) of the included exon in a SCN1A NIE containing pre-mRNA (*e.g.,* the direction designated by negative numbers relative to the 5' splice site). In some embodiments, the ASOs are complementary to a targeted portion of the SCN1A NIE containing pre-mRNA that is within the region about -4 to about -270 relative to the 5' splice site (or 3' end) of the included exon. In some embodiments, the ASOs may be complementary to a targeted portion of a SCN1A NIE containing pre-mRNA that is within the region between nucleotides -1 and -264 relative to the 5' splice site (or 3' end) of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region about -1 to about -270, about -1 to about -260, about -1 to about -250, about -1 to about -240, about -1 to about -230, about -1 to about -220, about -1 to about -210, about -1 to about -200, about -1 to about -190, about -1 to about -180, about -1 to about -170, about -1 to about -160, about -1 to about -150, about -1 to about -140, about -1 to about -130, about -1 to about -120, about -1 to about -110, about -1 to about -100, about -1 to about -90, about -1 to about -80, about -1 to about -70, about -1 to about -60, about -1 to about -50, about -1 to about -40, about -1 to about -30, or about -1 to about -20 relative to 5' splice site (or 3' end) of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the

region from about -1 to about -50, from about -50 to about -100, from about -100 to about -150, from about -150 to about -200, or from about -200 to about -250 relative to 5' splice site (or 3' end) of the included exon.

[0609] In some embodiments, the ASOs are complementary to a targeted region of a SCN1A NIE containing pre-mRNA that is upstream (in the 5' direction) of the 3' splice site (or 5' end) of the included exon in a SCN1A NIE containing pre-mRNA (*e.g.,* in the direction designated by negative numbers). In some embodiments, the ASOs are complementary to a targeted portion of the SCN1A NIE containing pre-mRNA that is within the region about -1 to about -500 relative to the 3' splice site (or 5' end) of the included exon. In some embodiments, the ASOs are complementary to a targeted portion of the SCN1A NIE containing pre-mRNA that is within the region -1 to -496 relative to the 3' splice site of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region about -1 to about -500, about -1 to about -490, about -1 to about -480, about -1 to about -470, about -1 to about -460, about -1 to about -450, about -1 to about -440, about -1 to about -430, about -1 to about -420, about -1 to about -410, about -1 to about -400, about -1 to about -390, about -1 to about -380, about -1 to about -370, about -1 to about -360, about -1 to about -350, about -1 to about -340, about -1 to about -330, about -1 to about -320, about -1 to about -310, about -1 to about -300, about -1 to about -290, about -1 to about -280, about -1 to about -270, about -1 to about -260, about -1 to about -250, about -1 to about -240, about -1 to about -230, about -1 to about -220, about -1 to about -210, about -1 to about -200, about -1 to about -190, about -1 to about -180, about -1 to about -170, about -1 to about -160, about -1 to about -150, about -1 to about -140, about -1 to about -130, about -1 to about -120, about -1 to about -110, about -1 to about -100, about -1 to about -90, about -1 to about -80, about -1 to about -70, about -1 to about -60, about -1 to about -50, about -1 to about -40, or about -1 to about -30 relative to 3' splice site of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region from about -1 to about -100, from about -100 to about -200, from about -200 to about -300, from about -300 to about -400, or from about -400 to about -500 relative to 3' splice site of the included exon.

[0610] In some embodiments, the ASOs are complementary to a targeted region of a SCN1A NIE containing pre-mRNA that is downstream (in the 3' direction) of the 3' splice site (5' end) of the included exon in a SCN1A NIE containing pre-mRNA (*e.g.,* in the direction designated by positive numbers). In some embodiments, the ASOs are complementary to a targeted portion of the SCN1A NIE containing pre-mRNA that is within the region of about +1 to about +100 relative to the 3' splice site of the included exon. In some aspects, the ASOs are complementary to a targeted portion that is within the region about +1 to about +90, about +1 to about +80, about +1 to about +70, about +1 to about +60, about +1 to about +50, about +1 to about +40, about +1 to about +30, about +1 to about +20, or about +1 to about +10 relative to 3' splice site of the included exon.

[0611] In some embodiments, the targeted portion of the SCN1A NIE containing pre-mRNA is within the region +100 relative to the 5' splice site (3' end) of the included exon to -100 relative to the 3' splice site (5' end) of the included exon. In some embodiments, the targeted portion of the SCN1A NIE

containing pre-mRNA is within the NIE. In some embodiments, the targeted portion of the SCN1A NIE containing pre-mRNA comprises a pseudo-exon and intron boundary.

[0612] The ASOs may be of any length suitable for specific binding and effective enhancement of splicing. In some embodiments, the ASOs consist of 8 to 50 nucleobases. For example, the ASO may be 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 40, 45, or 50 nucleobases in length. In some embodiments, the ASOs consist of more than 50 nucleobases. In some embodiments, the ASO is from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, 12 to 15 nucleobases, 13 to 50 nucleobases, 13 to 40 nucleobases, 13 to 35 nucleobases, 13 to 30 nucleobases, 13 to 25 nucleobases, 13 to 20 nucleobases, 14 to 50 nucleobases, 14 to 40 nucleobases, 14 to 35 nucleobases, 14 to 30 nucleobases, 14 to 25 nucleobases, 14 to 20 nucleobases, 15 to 50 nucleobases, 15 to 40 nucleobases, 15 to 35 nucleobases, 15 to 30 nucleobases, 15 to 25 nucleobases, 15 to 20 nucleobases, 20 to 50 nucleobases, 20 to 40 nucleobases, 20 to 35 nucleobases, 20 to 30 nucleobases, 20 to 25 nucleobases, 25 to 50 nucleobases, 25 to 40 nucleobases, 25 to 35 nucleobases, or 25 to 30 nucleobases in length. In some embodiments, the ASOs are 18 nucleotides in length. In some embodiments, the ASOs are 15 nucleotides in length. In some embodiments, the ASOs are 25 nucleotides in length.

[0613] In some embodiments, two or more ASOs with different chemistries but complementary to the same targeted portion of the NIE containing pre-mRNA are used. In some embodiments, two or more ASOs that are complementary to different targeted portions of the NIE containing pre-mRNA are used.

[0614] In some embodiments, the antisense oligomers of the present disclosure (*e.g.,* compound (I) or a salt thereof, or compound (II)) are chemically linked to one or more moieties or conjugates, *e.g.,* a targeting moiety or other conjugate that enhances the activity or cellular uptake of the oligonucleotide. Such moieties include, but are not limited to, a lipid moiety, *e.g.,* as a cholesterol moiety, a cholesteryl moiety, an aliphatic chain, *e.g.,* dodecandiol or undecyl residues, a polyamine or a polyethylene glycol chain, or adamantane acetic acid. Oligonucleotides comprising lipophilic moieties and preparation methods have been described in the published literature. In some embodiments, the antisense oligomer is conjugated with a moiety including, but not limited to, an abasic nucleotide, a polyether, a polyamine, a polyamide, a peptide, a carbohydrate, *e.g.,* N-acetylgalactosamine (GalNAc), N-Ac-Glucosamine (GluNAc), or mannose (*e.g.,* mannose-6-phosphate), a lipid, or a polyhydrocarbon compound. Conjugates can be linked to one or more of any nucleotides comprising the antisense oligomer at any of several positions on the sugar, base, or phosphate group, as understood in the art and described in the literature, *e.g.,* using a linker. Linkers can include a bivalent or trivalent branched linker. In some

embodiments, the conjugate is attached to the 3' end of the antisense oligomer. Methods of preparing oligonucleotide conjugates are described, *e.g.,* in U.S. Pat. No. 8,450,467, "Carbohydrate conjugates as delivery agents for oligonucleotides," incorporated by reference herein.

[0615] In some embodiments, the nucleic acid to be targeted by an ASO is a SCN1A NIE containing pre-mRNA expressed in a cell, such as a eukaryotic cell. In some embodiments, the term "cell" may refer to a population of cells. In some embodiments, the cell is in a subject. In some embodiments, the cell is isolated from a subject. In some embodiments, the cell is *ex vivo*. In some embodiments, the cell is a condition or disease-relevant cell or a cell line. In some embodiments, the cell is *in vitro* (*e.g.,* in cell culture).

[0616] In some embodiments, the compound is the salt of a nucleotide. In some embodiments, the compound is the salt of a nucleotide, fully phosphorothioate-linked oligonucleotide. In some embodiments, the compound is the salt of a nucleotide in which the salt binds to the phosphate-link. In some embodiments, the compound is the salt of a nucleotide, fully phosphorothioate-linked oligonucleotide in which the salt binds to the phosphate-link. In some embodiments, the compound is the sodium salt of a nucleotide. In some embodiments, the compound is the sodium salt of a nucleotide, fully phosphorothioate-linked oligonucleotide. In some embodiments, the compound is the sodium salt of a nucleotide in which the sodium salt binds to the phosphate-link. In some embodiments, the compound is the sodium salt of a nucleotide, fully phosphorothioate-linked oligonucleotide in which the sodium salt binds to the phosphate-link. In some embodiments, the compound is the potassium salt of a nucleotide. In some embodiments, the compound is the potassium salt of a nucleotide, fully phosphorothioate-linked oligonucleotide. In some embodiments, the compound is the potassium salt of a nucleotide in which the potassium salt binds to the phosphate-link. In some embodiments, the compound is the potassium salt of a nucleotide, fully phosphorothioate-linked oligonucleotide in which the potassium salt binds to the phosphate-link. In some cases, the compound is compound (I) or a salt thereof. In some cases, the compound is compound (II).

[0617] In some embodiment, the compound is the monosodium salt of a 2-nucleotide (2-mer). In some embodiment, the compound is the disodium salt of a 3-nucleotide (3-mer). In some embodiment, the compound is the trisodium salt of a 4-nucleotide (4-mer). In some embodiment, the compound is the tetrasodium salt of a 5-nucleotide (5-mer). In some embodiment, the compound is the pentasodium salt of a 6-nucleotide (6-mer). In some embodiment, the compound is the hexasodium salt of a 7-nucleotide (7-mer). In some embodiment, the compound is the heptasodium salt of an 8-nucleotide (8-mer). In some embodiment, the compound is the octasodium salt of a 9-nucleotide (9-mer). In some embodiment, the compound is the nonasodium salt of a 10-nucleotide (10-mer). In some embodiment, the compound is the decasodium salt of a 11-nucleotide (11-mer). In some embodiment, the compound is the undecasodium salt of a 12-nucleotide (12-mer). In some embodiment, the compound is the dodecasodium salt of a 13-nucleotide (13-mer). In some embodiment, the compound is the tridecasodium salt of a 14-nucleotide (14-mer). In some embodiment, the compound is the tetradecasodium salt of a 15-nucleotide (15-mer). In some embodiment, the compound is the pentadecasodium salt of a 16-nucleotide (16-mer). In some

embodiment, the compound is the hexadecasodium salt of a 17-nucleotide (17-mer). In some embodiment, the compound is the heptadecasodium salt of an 18-nucleotide (18-mer). In some embodiment, the compound is the octadecasodium salt of a 19-nucleotide (19-mer). In some embodiment, the compound is the nonadecasodium salt of a 20-nucleotide (20-mer). In some embodiment, the compound is the icosasodium salt of a 21-nucleotide (21-mer). In some embodiment, the compound is the henicosasodium salt of a 22-nucleotide (22-mer). In some embodiment, the compound is the docosasodium salt of a 23-nucleotide (23-mer). In some embodiment, the compound is the tricosasodium salt of a 24-nucleotide (24-mer). In some embodiment, the compound is the tetracosasodium salt of a 25-nucleotide (25-mer). In some embodiment, the compound is the pentacosasodium salt of a 26-nucleotide (26-mer). In some embodiment, the compound is the hexacosasodium salt of a 27-nucleotide (27-mer). In some embodiment, the compound is the heptacosasodium salt of a 28-nucleotide (28-mer). In some embodiment, the compound is the octacosasodium salt of a 29-nucleotide (29-mer). In some embodiment, the compound is the nonacosasodium salt of a 30-nucleotide (30-mer). In some embodiment, the compound is the triacontasodium salt of a 31-nucleotide (31-mer). In some embodiment, the compound is the hentriacontasodium salt of a 32-nucleotide (32-mer). In some embodiment, the compound is the dotriacontasodium salt of a 33-nucleotide (33-mer). In some embodiment, the compound is the tritriacontasodium salt of a 34-nucleotide (34-mer). In some embodiment, the compound is the tetratriacontasodium salt of a 35-nucleotide (35-mer). In some embodiment, the compound is the pentatriacontasodium salt of a 36-nucleotide (36-mer). In some embodiment, the compound is the hexatriacontasodium salt of a 37-nucleotide (37-mer). In some embodiment, the compound is the heptatriacontasodium salt of a 38-nucleotide (38-mer). In some embodiment, the compound is the octatriacontasodium salt of a 39-nucleotide (39-mer). In some embodiment, the compound is the nonatriacontasodium salt of a 40-nucleotide (40-mer). In some embodiment, the compound is the tetracontasodium salt of a 41-nucleotide (41-mer). In some embodiment, the compound is the hentetracontasodium salt of a 42-nucleotide (42-mer). In some embodiment, the compound is the dotetracontasodium salt of a 43-nucleotide (43-mer). In some embodiment, the compound is the tritetracontasodium salt of a 44-nucleotide (44-mer). In some embodiment, the compound is the tetratetracontasodium salt of a 45-nucleotide (45-mer). In some embodiment, the compound is the pentatetracontasodium salt of a 46-nucleotide (46-mer). In some embodiment, the compound is the hexatetracontasodium salt of a 47-nucleotide (47-mer). In some embodiment, the compound is the heptatetracontasodium salt of a 48-nucleotide (48-mer). In some embodiment, the compound is the octatetracontasodium salt of a 49-nucleotide (49-mer). In some embodiment, the compound is the nonatetracontasodium salt of a 50-nucleotide (50-mer). In some embodiment, the compound is the pentacontasodium salt of a 51-nucleotide (51-mer).

[0618] In some embodiment, the compound is the monosodium salt of a 2-nucleotide (2-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the disodium salt of a 3-nucleotide (3-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound

is the trisodium salt of a 4-nucleotide (4-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetrasodium salt of a 5-nucleotide (5-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentasodium salt of a 6-nucleotide (6-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexasodium salt of a 7-nucleotide (7-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptasodium salt of an 8-nucleotide (8-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octasodium salt of a 9-nucleotide (9-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonasodium salt of a 10-nucleotide (10-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the decasodium salt of a 11-nucleotide (11-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the undecasodium salt of a 12-nucleotide (12-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dodecasodium salt of a 13-nucleotide (13-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tridecasodium salt of a 14-nucleotide (14-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetradecasodium salt of a 15-nucleotide (15-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentadecasodium salt of a 16-nucleotide (16-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexadecasodium salt of a 17-nucleotide (17-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptadecasodium salt of an 18-nucleotide (18-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octadecasodium salt of a 19-nucleotide (19-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonadecasodium salt of a 20-nucleotide (20-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the icosasodium salt of a 21-nucleotide (21-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the henicosasodium salt of a 22-nucleotide (22-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the docosasodium salt of a 23-nucleotide (23-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tricosasodium salt of a 24-nucleotide (24-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetracosasodium salt of a 25-nucleotide (25-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentacosasodium salt of a 26-nucleotide (26-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexacosasodium salt of a 27-nucleotide (27-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptacosasodium salt of a 28-nucleotide (28-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octacosasodium salt of a 29-nucleotide (29-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonacosasodium salt of a 30-nucleotide (30-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the triacontasodium salt of a 31-nucleotide (31-mer), fully phosphorothioate-linked oligonucleotide. In some

embodiment, the compound is the hentriacontasodium salt of a 32-nucleotide (32-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dotriacontasodium salt of a 33-nucleotide (33-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tritriacontasodium salt of a 34-nucleotide (34-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetratriacontasodium salt of a 35-nucleotide (35-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentatriacontasodium salt of a 36-nucleotide (36-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexatriacontasodium salt of a 37-nucleotide (37-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptatriacontasodium salt of a 38-nucleotide (38-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octatriacontasodium salt of a 39-nucleotide (39-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonatriacontasodium salt of a 40-nucleotide (40-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetracontasodium salt of a 41-nucleotide (41-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hentetracontasodium salt of a 42-nucleotide (42-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dotetracontasodium salt of a 43-nucleotide (43-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tritetracontasodium salt of a 44-nucleotide (44-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetratetracontasodium salt of a 45-nucleotide (45-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentatetracontasodium salt of a 46-nucleotide (46-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexatetracontasodium salt of a 47-nucleotide (47-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptatetracontasodium salt of a 48-nucleotide (48-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octatetracontasodium salt of a 49-nucleotide (49-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonatetracontasodium salt of a 50-nucleotide (50-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentacontasodium salt of a 51-nucleotide (51-mer), fully phosphorothioate-linked oligonucleotide.

[0619] In some embodiment, the compound is the monopotassium salt of a 2-nucleotide (2-mer). In some embodiment, the compound is the dipotassium salt of a 3-nucleotide (3-mer). In some embodiment, the compound is the tripotassium salt of a 4-nucleotide (4-mer). In some embodiment, the compound is the tetrapotassium salt of a 5-nucleotide (5-mer). In some embodiment, the compound is the pentapotassium salt of a 6-nucleotide (6-mer). In some embodiment, the compound is the hexapotassium salt of a 7-nucleotide (7-mer). In some embodiment, the compound is the heptapotassium salt of an 8-nucleotide (8-mer). In some embodiment, the compound is the octapotassium salt of a 9-nucleotide (9-mer). In some embodiment, the compound is the nonapotassium salt of a 10-nucleotide (10-mer). In some embodiment, the compound is the decapotassium salt of a 11-nucleotide (11-mer). In some embodiment,

the compound is the undecapotassium salt of a 12-nucleotide (12-mer). In some embodiment, the compound is the dodecapotassium salt of a 13-nucleotide (13-mer). In some embodiment, the compound is the tridecapotassium salt of a 14-nucleotide (14-mer). In some embodiment, the compound is the tetradecapotassium salt of a 15-nucleotide (15-mer). In some embodiment, the compound is the pentadecapotassium salt of a 16-nucleotide (16-mer). In some embodiment, the compound is the hexadecapotassium salt of a 17-nucleotide (17-mer). In some embodiment, the compound is the heptadecapotassium salt of an 18-nucleotide (18-mer). In some embodiment, the compound is the octadecapotassium salt of a 19-nucleotide (19-mer). In some embodiment, the compound is the nonadecapotassium salt of a 20-nucleotide (20-mer). In some embodiment, the compound is the icosapotassium salt of a 21-nucleotide (21-mer). In some embodiment, the compound is the henicosapotassium salt of a 22-nucleotide (22-mer). In some embodiment, the compound is the docosapotassium salt of a 23-nucleotide (23-mer). In some embodiment, the compound is the tricosapotassium salt of a 24-nucleotide (24-mer). In some embodiment, the compound is the tetracosapotassium salt of a 25-nucleotide (25-mer). In some embodiment, the compound is the pentacosapotassium salt of a 26-nucleotide (26-mer). In some embodiment, the compound is the hexacosapotassium salt of a 27-nucleotide (27-mer). In some embodiment, the compound is the heptacosapotassium salt of a 28-nucleotide (28-mer). In some embodiment, the compound is the octacosapotassium salt of a 29-nucleotide (29-mer). In some embodiment, the compound is the nonacosapotassium salt of a 30-nucleotide (30-mer). In some embodiment, the compound is the triacontapotassium salt of a 31-nucleotide (31-mer). In some embodiment, the compound is the hentriacontapotassium salt of a 32-nucleotide (32-mer). In some embodiment, the compound is the dotriacontapotassium salt of a 33-nucleotide (33-mer). In some embodiment, the compound is the tritriacontapotassium salt of a 34-nucleotide (34-mer). In some embodiment, the compound is the tetratriacontapotassium salt of a 35-nucleotide (35-mer). In some embodiment, the compound is the pentatriacontapotassium salt of a 36-nucleotide (36-mer). In some embodiment, the compound is the hexatriacontapotassium salt of a 37-nucleotide (37-mer). In some embodiment, the compound is the heptatriacontapotassium salt of a 38-nucleotide (38-mer). In some embodiment, the compound is the octatriacontapotassium salt of a 39-nucleotide (39-mer). In some embodiment, the compound is the nonatriacontapotassium salt of a 40-nucleotide (40-mer). In some embodiment, the compound is the tetracontapotassium salt of a 41-nucleotide (41-mer). In some embodiment, the compound is the hentetracontapotassium salt of a 42-nucleotide (42-mer). In some embodiment, the compound is the dotetracontapotassium salt of a 43-nucleotide (43-mer). In some embodiment, the compound is the tritetracontapotassium salt of a 44-nucleotide (44-mer). In some embodiment, the compound is the tetratetracontapotassium salt of a 45-nucleotide (45-mer). In some embodiment, the compound is the pentatetracontapotassium salt of a 46-nucleotide (46-mer). In some embodiment, the compound is the hexatetracontapotassium salt of a 47-nucleotide (47-mer). In some embodiment, the compound is the heptatetracontapotassium salt of a 48-nucleotide (48-mer). In some embodiment, the compound is the octatetracontapotassium salt of a 49-nucleotide (49-mer). In some embodiment, the compound is the

nonatetracontapotassium salt of a 50-nucleotide (50-mer). In some embodiment, the compound is the pentacontapotassium salt of a 51-nucleotide (51-mer).

[0620] In some embodiment, the compound is the monopotassium salt of a 2-nucleotide (2-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dipotassium salt of a 3-nucleotide (3-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tripotassium salt of a 4-nucleotide (4-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetrapotassium salt of a 5-nucleotide (5-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentapotassium salt of a 6-nucleotide (6-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexapotassium salt of a 7-nucleotide (7-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptapotassium salt of an 8-nucleotide (8-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octapotassium salt of a 9-nucleotide (9-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonapotassium salt of a 10-nucleotide (10-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the decapotassium salt of a 11-nucleotide (11-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the undecapotassium salt of a 12-nucleotide (12-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dodecapotassium salt of a 13-nucleotide (13-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tridecapotassium salt of a 14-nucleotide (14-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetradecapotassium salt of a 15-nucleotide (15-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentadecapotassium salt of a 16-nucleotide (16-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexadecapotassium salt of a 17-nucleotide (17-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptadecapotassium salt of an 18-nucleotide (18-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octadecapotassium salt of a 19-nucleotide (19-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonadecapotassium salt of a 20-nucleotide (20-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the icosapotassium salt of a 21-nucleotide (21-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the henicosapotassium salt of a 22-nucleotide (22-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the docosapotassium salt of a 23-nucleotide (23-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tricosapotassium salt of a 24-nucleotide (24-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetracosapotassium salt of a 25-nucleotide (25-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentacosapotassium salt of a 26-nucleotide (26-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexacosapotassium salt of a 27-nucleotide (27-mer), fully phosphorothioate-linked oligonucleotide. In

some embodiment, the compound is the heptacosapotassium salt of a 28-nucleotide (28-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octacosapotassium salt of a 29-nucleotide (29-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonacosapotassium salt of a 30-nucleotide (30-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the triacontapotassium salt of a 31-nucleotide (31-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hentriacontapotassium salt of a 32-nucleotide (32-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dotriacontapotassium salt of a 33-nucleotide (33-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tritriacontapotassium salt of a 34-nucleotide (34-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetratriacontapotassium salt of a 35-nucleotide (35-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentatriacontapotassium salt of a 36-nucleotide (36-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexatriacontapotassium salt of a 37-nucleotide (37-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptatriacontapotassium salt of a 38-nucleotide (38-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octatriacontapotassium salt of a 39-nucleotide (39-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonatriacontapotassium salt of a 40-nucleotide (40-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetracontapotassium salt of a 41-nucleotide (41-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hentetracontapotassium salt of a 42-nucleotide (42-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the dotetracontapotassium salt of a 43-nucleotide (43-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tritetracontapotassium salt of a 44-nucleotide (44-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the tetratetracontapotassium salt of a 45-nucleotide (45-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentatetracontapotassium salt of a 46-nucleotide (46-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the hexatetracontapotassium salt of a 47-nucleotide (47-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the heptatetracontapotassium salt of a 48-nucleotide (48-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the octatetracontapotassium salt of a 49-nucleotide (49-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the nonatetracontapotassium salt of a 50-nucleotide (50-mer), fully phosphorothioate-linked oligonucleotide. In some embodiment, the compound is the pentacontapotassium salt of a 51-nucleotide (51-mer), fully phosphorothioate-linked oligonucleotide.

SCN1A

[0621] The *SCN1A* gene can encode SCN1A (sodium channel, voltage-gated, type I, alpha subunit) protein, which can also be referred to as alpha-subunit of voltage-gated sodium channel $Na_V1.1$. Also described above, SCN1A mutations in DS are spread across the entire protein. More than 100 novel mutations have been identified throughout the gene with the more debilitating arising de novo. These comprise of truncations (47%), missense (43%), deletions (3%), and splice site mutations (7%). The percentage of subjects carrying SCN1A mutations varies between 33 and 100%. The majority of mutations are novel changes (88%).

[0622] In some embodiments, the methods described herein are used to modulate, *e.g.,* increase or decrease, the production of a functional $Na_V1.1$ protein. As used herein, the term "functional" refers to the amount of activity or function of a $Na_V1.1$ protein that is necessary to eliminate any one or more symptoms of a treated condition, *e.g.,* Dravet syndrome; Epilepsy, generalized, with febrile seizures plus, type 2; Febrile seizures, familial, 3A; Autism; Epileptic encephalopathy, early infantile, 13; Sick sinus syndrome 1; Alzheimer's disease; or SUDEP. In some embodiments, the methods are used to increase the production of a partially functional $Na_V1.1$ protein. As used herein, the term "partially functional" refers to any amount of activity or function of the $Na_V1.1$ protein that is less than the amount of activity or function that is necessary to eliminate or prevent any one or more symptoms of a disease or condition. In some embodiments, a partially functional protein or RNA will have at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% less activity relative to the fully functional protein or RNA.

[0623] In some embodiments, the method is a method of increasing the expression of the $Na_V1.1$ protein by cells of a subject having a NIE containing pre-mRNA encoding the $Na_V1.1$ protein, wherein the subject has Dravet syndrome characterized by a deficient amount of activity of $Na_V1.1$ protein, and wherein the deficient amount of the $Na_V1.1$ protein is characterized by haploinsufficiency of the $Na_V1.1$ protein. In such an embodiment, the subject has a first allele encoding a functional $Na_V1.1$ protein, and a second allele from which the $Na_V1.1$ protein is not produced. In another such embodiment, the subject has a first allele encoding a functional $Na_V1.1$ protein, and a second allele encoding a nonfunctional $Na_V1.1$ protein. In another such embodiment, the subject has a first allele encoding a functional $Na_V1.1$ protein, and a second allele encoding a partially functional $Na_V1.1$ protein. In some embodiments, the subject expresses a partially functional $Na_V1.1$ protein from one allele, wherein the partially functional $Na_V1.1$ protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, or a partial gene deletion. In some embodiments, the subject expresses a nonfunctional $Na_V1.1$ protein from one allele, wherein the nonfunctional $Na_V1.1$ protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, a partial gene deletion, in one allele. In some embodiments, the subject has a SCN1A whole gene deletion, in one allele. In any of these embodiments, the antisense oligomer binds to a targeted portion of the NIE containing pre-mRNA transcribed from the second allele, thereby inducing exon skipping of the pseudo-exon from the pre-mRNA and causing an increase in the level of mature

mRNA encoding functional $Na_V1.1$ protein, and an increase in the expression of the $Na_V1.1$ protein in the cells of the subject.

[0624] In some embodiments of the present invention, a subject can have a mutation in SCN1A. Mutations in *SCN1A* can be spread throughout said gene. $Na_V1.1$ protein can consist of four domains. Said SCN1A domains can have transmembrane segments. Mutations in said $Na_V1.1$ protein may arise throughout said protein. Said $Na_V1.1$ protein may consist of at least two isoforms. Mutations in SCN1A may comprise of R931C, R946C, M934I, R1648C, or R1648H. In some cases, mutations may be observed in a C-terminus of a $Na_V1.1$ protein. Mutations in a $Na_V1.1$ protein may also be found in loops between segments 5 and 6 of the first three domains of said $Na_V1.1$ protein. In some cases, mutations may be observed in an N-terminus of a $Na_V1.1$ protein. Exemplary mutations within SCN1A include, but are not limited to, R222X, R712X, I227S, R1892X, W952X, R1245X, R1407X, W1434R, c.4338+1G>A, 51516X, L1670fsX1678, or K1846fsX1856. Mutations that can be targeted with the present invention may also encode a pore of an ion channel.

[0625] In some embodiments, the methods and compositions described herein can be used to treat DS. In other embodiments, the methods and compositions described herein can be used to treat severe myoclonic epilepsy of infancy (SMEI). In other embodiments, the methods and compositions described herein can be used to treat borderline Dravet syndrome; Epilepsy, generalized, with febrile seizures plus, type 2; Febrile seizures, familial, 3A; Migraine, familial hemiplegic, 3; Autism; Epileptic encephalopathy, early infantile, 13; Sick sinus syndrome 1; Alzheimer's disease or SUDEP.

[0626] In related embodiments, the method is a method of using a compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) to increase the expression of a protein or functional RNA. In some embodiments, a compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) is used to increase the expression of $Na_V1.1$ protein in cells of a subject having a NIE containing pre-mRNA encoding $Na_V1.1$ protein, wherein the subject has a deficiency, *e.g.,* Dravet Syndrome (DS) (also known as SMEI); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; early infantile SCN1A encephalopathy; early infantile epileptic encephalopathy (EIEE); or autism, in the amount or function of a $Na_V1.1$ protein. In some embodiments, a compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) is used to increase the expression of $Na_V1.1$ protein in cells of a subject, wherein the subject has a deficiency, *e.g.,* Epileptic encephalopathy, early infantile, 13; in the amount or function of a SCN8A protein. In some embodiments, a compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) is used to increase the expression of $Na_V1.1$ protein in cells of a subject, wherein the subject has a deficiency, *e.g.,* Sick sinus syndrome 1; in the amount or function of a SCN5A protein.

[0627] In some embodiment, the methods and compositions described herein can also be used to treat borderline SMEI. Additionally, the methods and compositions described herein can be used to treat generalized epilepsy with febrile seizures plus (GEFS+). GEFS+ may be associated with mutations in epilepsy-associated ion channel subunits such as SCN1B or GABRG2. The methods and compositions described herein can also be used to treat sodium channelopathies. Sodium channelopathies may be associated with mutations in SCN1A. Sodium channelopathies may also be associated with subunits of SCN1A, such as the beta subunit, SCN1B. In some cases, additional diseases associated with SCN1A mutations may also be treated with the present disclosure. Related SCN1A diseases associated with SCN1A mutations include, but are not limited to, atypical myotonia congenita, hyperkalemic periodic paralysis, and paramyotonia congenita.

[0628] In some embodiments, a subject having any SCN1A mutation known in the art and described in the literature (*e.g.,* by Hamdan, *et al.*, 2009, N. Engl. Med. 360 (6) pp. 599, Mulley, *et al.*, 2005, Hum. Muta. 25, 535-542, of which entire content is incorporated herein by reference) can be treated using the methods and compositions described herein. In some embodiments, the mutation is within any SCN1A intron or exon.

[0629] In some embodiments, the NIE containing pre-mRNA transcript that encodes the protein that is causative of the disease or condition is targeted by the ASOs described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)). In some embodiments, a NIE containing pre-mRNA transcript that encodes a protein that is not causative of the disease is targeted by the ASOs. For example, a disease that is the result of a mutation or deficiency of a first protein in a particular pathway may be ameliorated by targeting a NIE containing pre-mRNA that encodes a second protein, thereby increasing production of the second protein. In some embodiments, the function of the second protein is able to compensate for the mutation or deficiency of the first protein (which is causative of the disease or condition).

[0630] In some embodiments, the subject has: m(a) a first mutant allele from which (i) the $Na_V1.1$ protein is produced at a reduced level compared to production from a wild-type allele, (ii) the $Na_V1.1$ protein is produced in a form having reduced function compared to an equivalent wild-type protein, or (iii) the $Na_V1.1$ protein or functional RNA is not produced; and (b) a second mutant allele from which (i) the $Na_V1.1$ protein is produced at a reduced level compared to production from a wild-type allele, (ii) the $Na_V1.1$ protein is produced in a form having reduced function compared to an equivalent wild-type protein, or(iii) the $Na_V1.1$ protein is not produced, and wherein the NIE containing pre-mRNA is transcribed from the first allele and/or the second allele. In these embodiments, the compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) binds to a targeted portion of the NIE containing pre-mRNA transcribed from the first allele or the second allele, thereby inducing exon skipping of the pseudo-exon from the NIE containing pre-mRNA, and causing an increase in the level of mRNA encoding $Na_V1.1$ protein and an increase in the expression of the target protein or functional RNA in the cells of the subject. In these embodiments, the target protein or functional RNA having an increase in expression level resulting from the exon skipping of the pseudo-exon from the NIE containing pre-mRNA is either in a form having reduced function compared to the equivalent wild-type protein

(partially functional), or having full function compared to the equivalent wild-type protein (fully functional).

[0631] In some embodiments, the level of mRNA encoding $Na_V1.1$ protein is increased 1.1 to 10-fold, when compared to the amount of mRNA encoding $Na_V1.1$ protein that is produced in a control cell, *e.g.,* one that is not treated with the antisense oligomer or one that is treated with an antisense oligomer that does not bind to the targeted portion of the SCN1A NIE containing pre-mRNA.

[0632] In some embodiments, a subject treated using the methods of the present disclosure expresses a mutant $Na_V1.1$ protein from one allele, wherein the mutant $Na_V1.1$ protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, or a partial gene deletion, and wherein the mutant $Na_V1.1$ protein causes an elevated activity level of $Na_V1.1$. In some embodiments, a subject treated using the methods of the present disclosure expresses an elevated amount of $Na_V1.1$ protein from one allele due to a frameshift mutation, a nonsense mutation, a missense mutation, or a partial gene deletion.

[0633] In some embodiments, a subject treated using the methods of the present disclosure expresses a partially functional $Na_V1.1$ protein from one allele, wherein the partially functional $Na_V1.1$ protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, or a partial gene deletion. In some embodiments, a subject treated using the methods of the disclosure expresses a nonfunctional $Na_V1.1$ protein from one allele, wherein the nonfunctional $Na_V1.1$ protein is caused by a frameshift mutation, a nonsense mutation, a missense mutation, a partial gene deletion, in one allele. In some embodiments, a subject treated using the methods of the disclosure has a SCN1A whole gene deletion, in one allele.

[0634] In some embodiments, the method is a method of decreasing the expression of the $Na_V1.1$ protein by cells of a subject having a NIE containing pre-mRNA encoding the $Na_V1.1$ protein, and wherein the subject has a gain-of-function mutation in $Na_V1.1$. In such an embodiment, the subject has an allele from which the $Na_V1.1$ protein is produced in an elevated amount or an allele encoding a mutant SCN1A that induces increased activity of $Na_V1.1$ in the cell. In some embodiments, the increased activity of $Na_V1.1$ is characterized by a prolonged or near persistent sodium current mediated by the mutant $Na_V1.1$ channel, a slowing of fast inactivation, a positive shift in steady-state inactivation, higher channel availability during repetitive stimulation, increased non-inactivated depolarization-induced persistent sodium currents, delayed entry into inactivation, accelerated recovery from fast inactivation, and/or rescue of folding defects by incubation at lower temperature or co-expression of interacting proteins.

Target Transcripts

[0635] Splicing of the identified SCN1A NIE pre-mRNA species to produce functional mature *Scn1a* mRNA can be induced using a therapeutic agent such as a compound (*e.g.,* an ASO) that stimulates exon skipping of an NIE. Induction of exon skipping can result in inhibition of an NMD pathway. The resulting mature *Scn1a* mRNA can be translated normally without activating NMD pathway, thereby increasing the amount of $Na_V1.1$ protein in the patient's cells and alleviating symptoms of a condition associated with SCN1A deficiency, such as Dravet Syndrome (DS); Epilepsy, generalized, with febrile

seizures plus, type 2; Febrile seizures, familial, 3A; Autism; Epileptic encephalopathy, early infantile, 13; Sick sinus syndrome 1; Alzheimer's disease; or SUDEP.

[0636] In various embodiments, the present disclosure provides a therapeutic agent which can target *SCN1A* pre-mRNA transcripts to modulate, *e.g.,* enhance or inhibit, splicing or protein expression level. The therapeutic agent can be a small molecule, polynucleotide, or polypeptide. In some embodiments, the therapeutic agent is a compound (*e.g.,* compound (I) or a salt thereof, or compound (II)). Various regions or sequences on the *SCN1A* pre-mRNA can be targeted by a therapeutic agent, such as an ASO. In some embodiments, the compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) targets a *SCN1A* pre-mRNA transcript containing an NIE. In some embodiments, the compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) targets a sequence within an NIE of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence upstream (or 5') from the 5' end of an NIE (3'ss) of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence downstream (or 3') from the 3' end of an NIE (5'ss) of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence that is within an intron flanking on the 5' end of the NIE of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence that is within an intron flanking the 3' end of the NIE of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence comprising an NIE-intron boundary of a *SCN1A* pre-mRNA transcript. An NIE-intron boundary can refer to the junction of an intron sequence and an NIE region. The intron sequence can flank the 5' end of the NIE, or the 3' end of the NIE. In some embodiments, the compound targets a sequence within an exon of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence within an intron of a *SCN1A* pre-mRNA transcript. In some embodiments, the compound targets a sequence comprising both a portion of an intron and a portion of an exon.

[0637] In some embodiments, a therapeutic agent described herein modulates binding of a factor involved in splicing of the pre-mRNA containing an NMD exon. In some embodiments, a therapeutic agent described herein interferes with binding of a factor involved in splicing of the pre-mRNA containing an NMD exon. In some embodiments, a therapeutic agent described herein prevents binding of a factor involved in splicing of the pre-mRNA containing an NMD exon. In some embodiments, a therapeutic agent targets a targeted portion located in an intronic region between two canonical exonic regions of the pre-mRNA containing an NMD exon and encoding $Na_V1.1$, and wherein the intronic region contains the NMD exon. In some embodiments, a therapeutic agent targets a targeted portion at least partially overlaps with the NMD exon. In some embodiments, a therapeutic agent targets a targeted portion that is at least partially overlaps with an intron upstream of the NMD exon. In some embodiments, a therapeutic agent targets a targeted portion within the NMD exon.

[0638] In some embodiments, a therapeutic agent targets a targeted portion comprising at least about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon. In some embodiments, a therapeutic agent targets a targeted portion comprising at most about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon. In some embodiments, a

therapeutic agent targets a targeted portion comprising about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon.

[0639] In some embodiments, a therapeutic agent targets a targeted portion proximal to the NMD exon.

[0640] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from the 5' end of the NIE. In some embodiments, the compound targets a sequence from about 1 to about 20 nucleotides, about 20 to about 50 nucleotides, about 50 to about 100 nucleotides, about 100 to about 150 nucleotides, about 150 to about 200 nucleotides, about 200 to about 250 nucleotides, about 250 to about 300, about 250 to about 300 nucleotides, about 350 to about 400 nucleotides, about 450 to about 500 nucleotides, about 550 to about 600 nucleotides, about 650 to about 700 nucleotides, about 750 to about 800 nucleotides, about 850 to about 900 nucleotides, about 950 to about 1000 nucleotides, about 1050 to about 1100 nucleotides, about 1150 to about 1200 nucleotides, about 1250 to about 1300 nucleotides, about 1350 to about 1400 nucleotides, or about 1450 to about 1500 nucleotides upstream (or 5') from the 5' end of the NIE region. In some embodiments, the compound may target a sequence more than 300 nucleotides upstream from the 5' end of the NIE. In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides downstream (or 3') from the 3' end of the NIE. In some embodiments, the compound targets a sequence about 1 to about 20 nucleotides, about 20 to about 50 nucleotides, about 50 to about 100 nucleotides, about 100 to about 150 nucleotides, about 150 to about 200 nucleotides, about 200 to about 250 nucleotides, about 250 to about 300 nucleotides, about 350 to about 400 nucleotides, about 450 to about 500 nucleotides, about 550 to about 600 nucleotides, about 650 to about 700 nucleotides, about 750 to about 800 nucleotides, about 850 to about 900 nucleotides, about 950 to about 1000 nucleotides, about 1050 to about 1100 nucleotides, about 1150 to about 1200 nucleotides, about 1250 to about 1300 nucleotides, about 1350 to about 1400 nucleotides, or about 1450 to about 1500 nucleotides downstream from the 3' end of the NIE. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from the 3' end of the NIE.

[0641] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from the 5' end of the NIE. In some embodiments, the compound targets a sequence at least about 1 nucleotide, at least about 10 nucleotides, at least about 20 nucleotides, at least about 50 nucleotides, at least about 80 nucleotides, at least about 85 nucleotides, at least about 90 nucleotides, at least about 95 nucleotides, at least about 96 nucleotides, at least about 97 nucleotides, at least about 98 nucleotides, at least about 99 nucleotides, at least about 100 nucleotides, at least about 101 nucleotides, at least about 102 nucleotides, at least about 103 nucleotides, at least about 104 nucleotides, at least about 105 nucleotides, at least about 110 nucleotides, at least about 120 nucleotides, at least about 150 nucleotides, at least about 200 nucleotides, at least about 300 nucleotides, at least about 400 nucleotides, at least about 500 nucleotides, at least about 600 nucleotides, at least about 700 nucleotides, at least about 800 nucleotides, at least about 900 nucleotides, or at least about 1000 nucleotides upstream (or 5') from the 5' end of the NIE region. In some embodiments, the compound targets a sequence about 4 to about 300 nucleotides downstream (or 3') from the 3' end of the NIE. In some embodiments, the compound

targets a sequence at least about 1 nucleotide, at least about 10 nucleotides, at least about 20 nucleotides, at least about 50 nucleotides, at least about 80 nucleotides, at least about 85 nucleotides, at least about 90 nucleotides, at least about 95 nucleotides, at least about 96 nucleotides, at least about 97 nucleotides, at least about 98 nucleotides, at least about 99 nucleotides, at least about 100 nucleotides, at least about 101 nucleotides, at least about 102 nucleotides, at least about 103 nucleotides, at least about 104 nucleotides, at least about 105 nucleotides, at least about 110 nucleotides, at least about 120 nucleotides, at least about 150 nucleotides, at least about 200 nucleotides, at least about 300 nucleotides, at least about 400 nucleotides, at least about 500 nucleotides, at least about 600 nucleotides, at least about 700 nucleotides, at least about 800 nucleotides, at least about 900 nucleotides, or at least about 1000 nucleotides downstream from the 3' end of the NIE. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from the 3' end of the NIE.

[0642] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from the 5' end of the NIE. In some embodiments, the compound targets a sequence at most about 10 nucleotides, at most about 20 nucleotides, at most about 50 nucleotides, at most about 80 nucleotides, at most about 85 nucleotides, at most about 90 nucleotides, at most about 95 nucleotides, at most about 96 nucleotides, at most about 97 nucleotides, at most about 98 nucleotides, at most about 99 nucleotides, at most about 100 nucleotides, at most about 101 nucleotides, at most about 102 nucleotides, at most about 103 nucleotides, at most about 104 nucleotides, at most about 105 nucleotides, at most about 110 nucleotides, at most about 120 nucleotides, at most about 150 nucleotides, at most about 200 nucleotides, at most about 300 nucleotides, at most about 400 nucleotides, at most about 500 nucleotides, at most about 600 nucleotides, at most about 700 nucleotides, at most about 800 nucleotides, at most about 900 nucleotides, at most about 1000 nucleotides, at most about 1100 nucleotides, at most about 1200 nucleotides, at most about 1300 nucleotides, at most about 1400 nucleotides, or at most about 1500 nucleotides upstream (or 5') from the 5' end of the NIE region. In some embodiments, the compound targets a sequence about 4 to about 300 nucleotides downstream (or 3') from the 3' end of the NIE. In some embodiments, the compound targets a sequence at most about 10 nucleotides, at most about 20 nucleotides, at most about 50 nucleotides, at most about 80 nucleotides, at most about 85 nucleotides, at most about 90 nucleotides, at most about 95 nucleotides, at most about 96 nucleotides, at most about 97 nucleotides, at most about 98 nucleotides, at most about 99 nucleotides, at most about 100 nucleotides, at most about 101 nucleotides, at most about 102 nucleotides, at most about 103 nucleotides, at most about 104 nucleotides, at most about 105 nucleotides, at most about 110 nucleotides, at most about 120 nucleotides, at most about 150 nucleotides, at most about 200 nucleotides, at most about 300 nucleotides, at most about 400 nucleotides, at most about 500 nucleotides, at most about 600 nucleotides, at most about 700 nucleotides, at most about 800 nucleotides, at most about 900 nucleotides, or at most about 1000 nucleotides, at most about 1100 nucleotides, at most about 1200 nucleotides, at most about 1300 nucleotides, at most about 1400 nucleotides, or at most about 1500 nucleotides downstream from the 3' end of the NIE. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from the 3' end of the NIE.

[0643] In some embodiments, the NIE as described herein is located between GRCh37/hg19: chr2:166,863,740 and GRCh37/hg19: chr2:166,863,803, as depicted in **FIG. 1D**. In some embodiments, the 5' end of the NIE is located at GRCh37/hg19: chr2:166,863,803. In some embodiments, the 3' end of the NIE is located at GRCh37/hg19: chr2:166,863,740.

[0644] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence about 1 to about 20 nucleotides, about 20 to about 50 nucleotides, about 50 to about 100 nucleotides, about 100 to about 150 nucleotides, about 150 to about 200 nucleotides, about 200 to about 250 nucleotides, about 250 to about 300, about 250 to about 300 nucleotides, about 350 to about 400 nucleotides, about 450 to about 500 nucleotides, about 550 to about 600 nucleotides, about 650 to about 700 nucleotides, about 750 to about 800 nucleotides, about 850 to about 900 nucleotides, about 950 to about 1000 nucleotides, about 1050 to about 1100 nucleotides, about 1150 to about 1200 nucleotides, about 1250 to about 1300 nucleotides, about 1350 to about 1400 nucleotides, or about 1450 to about 1500 nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound may target a sequence more than 300 nucleotides upstream from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides downstream (or 3') from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence about 1 to about 20 nucleotides, about 20 to about 50 nucleotides, about 50 to about 100 nucleotides, about 100 to about 150 nucleotides, about 150 to about 200 nucleotides, about 200 to about 250 nucleotides, about 250 to about 300 nucleotides, about 350 to about 400 nucleotides, about 450 to about 500 nucleotides, about 550 to about 600 nucleotides, about 650 to about 700 nucleotides, about 750 to about 800 nucleotides, about 850 to about 900 nucleotides, about 950 to about 1000 nucleotides, about 1050 to about 1100 nucleotides, about 1150 to about 1200 nucleotides, about 1250 to about 1300 nucleotides, about 1350 to about 1400 nucleotides, or about 1450 to about 1500 nucleotides downstream from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from GRCh37/hg19: chr2: 166,863,740.

[0645] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence at least about 1 nucleotide, at least about 10 nucleotides, at least about 20 nucleotides, at least about 50 nucleotides, at least about 80 nucleotides, at least about 85 nucleotides, at least about 90 nucleotides, at least about 95 nucleotides, at least about 96 nucleotides, at least about 97 nucleotides, at least about 98 nucleotides, at least about 99 nucleotides, at least about 100 nucleotides, at least about 101 nucleotides, at least about 102 nucleotides, at least about 103 nucleotides, at least about 104 nucleotides, at least about 105 nucleotides, at least about 110 nucleotides, at least about 120 nucleotides, at least about 150 nucleotides, at least about 200 nucleotides, at least about 300 nucleotides, at least about 400 nucleotides, at least about 500 nucleotides, at least about 600 nucleotides, at least about 700 nucleotides, at least about 800 nucleotides, at least about 900 nucleotides, or at least about 1000

nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides downstream (or 3') from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence at least about 1 nucleotide, at least about 10 nucleotides, at least about 20 nucleotides, at least about 50 nucleotides, at least about 80 nucleotides, at least about 85 nucleotides, at least about 90 nucleotides, at least about 95 nucleotides, at least about 96 nucleotides, at least about 97 nucleotides, at least about 98 nucleotides, at least about 99 nucleotides, at least about 100 nucleotides, at least about 101 nucleotides, at least about 102 nucleotides, at least about 103 nucleotides, at least about 104 nucleotides, at least about 105 nucleotides, at least about 110 nucleotides, at least about 120 nucleotides, at least about 150 nucleotides, at least about 200 nucleotides, at least about 300 nucleotides, at least about 400 nucleotides, at least about 500 nucleotides, at least about 600 nucleotides, at least about 700 nucleotides, at least about 800 nucleotides, at least about 900 nucleotides, or at least about 1000 nucleotides downstream from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from GRCh37/hg19: chr2:166,863,740.

[0646] In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence at most about 10 nucleotides, at most about 20 nucleotides, at most about 50 nucleotides, at most about 80 nucleotides, at most about 85 nucleotides, at most about 90 nucleotides, at most about 95 nucleotides, at most about 96 nucleotides, at most about 97 nucleotides, at most about 98 nucleotides, at most about 99 nucleotides, at most about 100 nucleotides, at most about 101 nucleotides, at most about 102 nucleotides, at most about 103 nucleotides, at most about 104 nucleotides, at most about 105 nucleotides, at most about 110 nucleotides, at most about 120 nucleotides, at most about 150 nucleotides, at most about 200 nucleotides, at most about 300 nucleotides, at most about 400 nucleotides, at most about 500 nucleotides, at most about 600 nucleotides, at most about 700 nucleotides, at most about 800 nucleotides, at most about 900 nucleotides, at most about 1000 nucleotides, at most about 1100 nucleotides, at most about 1200 nucleotides, at most about 1300 nucleotides, at most about 1400 nucleotides, or at most about 1500 nucleotides upstream (or 5') from genomic site GRCh37/hg19: chr2:166,863,803. In some embodiments, the compound targets a sequence from about 4 to about 300 nucleotides downstream (or 3') from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence at most about 10 nucleotides, at most about 20 nucleotides, at most about 50 nucleotides, at most about 80 nucleotides, at most about 85 nucleotides, at most about 90 nucleotides, at most about 95 nucleotides, at most about 96 nucleotides, at most about 97 nucleotides, at most about 98 nucleotides, at most about 99 nucleotides, at most about 100 nucleotides, at most about 101 nucleotides, at most about 102 nucleotides, at most about 103 nucleotides, at most about 104 nucleotides, at most about 105 nucleotides, at most about 110 nucleotides, at most about 120 nucleotides, at most about 150 nucleotides, at most about 200 nucleotides, at most about 300 nucleotides, at most about 400 nucleotides, at most about 500 nucleotides, at most about 600 nucleotides, at most about 700 nucleotides, at most about 800 nucleotides, at most about 900 nucleotides, or at most about 1000 nucleotides, at most

about 1100 nucleotides, at most about 1200 nucleotides, at most about 1300 nucleotides, at most about 1400 nucleotides, or at most about 1500 nucleotides downstream from GRCh37/hg19: chr2:166,863,740. In some embodiments, the compound targets a sequence more than 300 nucleotides downstream from GRCh37/hg19: chr2:166,863,740.

[0647] The *SCN1A* gene (SEQ ID NO: 1) was analyzed for NIE and inclusion of a portion of intron 20 (SEQ ID NO: 4) (this portion is referred as exon 20x throughout the present disclosure) was observed. In some embodiments, the compounds (*e.g.,* ASOs) disclosed herein target a NIE containing pre-mRNA (SEQ ID NO: 2) transcribed from a SCN1A genomic sequence. In some embodiments, the compound targets a NIE containing pre-mRNA transcript from a SCN1A genomic sequence comprising a portion of intron 20. In some embodiments, the compound targets a NIE containing pre-mRNA transcript from a SCN1A genomic sequence comprising exon 20x (SEQ ID NO: 6). In some embodiments, the compound targets a NIE containing pre-mRNA transcript of SEQ ID NO: 2 or 12. In some embodiments, the compound targets a NIE containing pre-mRNA transcript of SEQ ID NO: 2 or 12 comprising an NIE. In some embodiments, the compound targets a NIE containing pre-mRNA transcript of SEQ ID NO: 2 comprising exon 20x (SEQ ID NO: 10). In some embodiments, the compounds disclosed herein target a *SCN1A* pre-mRNA sequence (SEQ ID NO: 2 or 12). In some embodiments, the compound targets a *SCN1A* pre-mRNA sequence comprising an NIE (SEQ ID NO: 10 or 20). In some embodiments, the compound targets a *SCN1A* pre-mRNA sequence according to any one of SEQ ID NOs: 7-10 or 17-20. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 21-67. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 68-114. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 115-209. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 210-256. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 257-303. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 304-341. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 342-379. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 380-1099. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 304-1099. In some embodiments, the ASO has a sequence according to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0648] In some embodiments, the SCN1A NIE containing pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO:: 1 or 11. In some embodiments, the SCN1A NIE pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS:: 2-10 and 12-20.

[0649] In some embodiments, the compound targets exon 20 of a SCN1A NIE containing pre-mRNA comprising NIE exon 20x. In some embodiments, the compound targets an exon 21 sequence downstream (or 3') of NIE exon 20x. In some embodiments, the compound targets a sequence about 4 to about 300 nucleotides upstream (or 5') from the 5' end of exon 20x. In some embodiments, the

compound targets a sequence about 4 to about 300 nucleotides downstream (or 3') from the 3' end of exon 20x. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 21-67. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 210-256. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 380-1099. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 304-1099. In some embodiments, the ASO has a sequence according to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0650] In some embodiments, the compound targets a sequence upstream from the 5' end of an NIE. For example, compounds (*e.g.,* ASOs) targeting a sequence upstream from the 5' end of an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 21-38. For another example, compounds (*e.g.,* ASOs) targeting a sequence upstream from the 5' end of an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 68-85. In some embodiments, the compounds target a sequence containing an exon-intron boundary (or junction). For example, compounds targeting a sequence containing an exon-intron boundary can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 39-41, 51, 52, 228-230, 240, or 241. For another example, compounds targeting a sequence containing an exon-intron boundary can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 86-88 and 98-99. In some embodiments, the compounds target a sequence downstream from the 3' end of an NIE. For example, compounds targeting a sequence down-stream from the 3' end of an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 53-67. For another example, compounds targeting a sequence downstream from the 3' end of an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 100-114. In some embodiments, compounds target a sequence within an NIE. For example, compounds targeting a sequence within an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 42-50, or 231-239. For another example, compounds targeting a sequence within an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A) can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 89-97.

[0651] In some embodiments, the compound (*e.g.,* compound (I) or a salt thereof, or compound (II)) targets exon 20x in a SCN1A NIE containing pre-mRNA comprising exon 20x. In some embodiments, the compound targets an exon 20x sequence downstream (or 3') from the 5' end of the exon 20x of a *SCN1A* pre-mRNA. In some embodiments, the compound targets an exon 20x sequence upstream (or 5') from the 3' end of the exon 20x of a *SCN1A* pre-mRNA.

[0652] In some embodiments, the *SCN1A* NIE containing pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 2, 7-10, 12, and 17-20. In some embodiments, SCN1A NIE containing pre-mRNA transcript is encoded by a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NOs: 1, 3-6, 11, and 13-16. In some embodiments, the targeted portion of the pre-mRNA containing an NMD exon and encoding $Na_V1.1$ comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of SEQ ID NOs: 2, 7-10, 12, and 17-20.

[0653] In some embodiments, the ASO targets a NIE containing pre-mRNA transcript. In some embodiments, the ASO targets a NIE containing pre-mRNA transcript comprising an NIE. In some embodiments, the ASO targets a NIE containing pre-mRNA transcript of comprising exon 20x. In some embodiments, the ASOs disclosed herein target a *SCN1A* pre-mRNA sequence. In some embodiments, the ASO targets a *SCN1A* pre-mRNA sequence comprising an NIE. In some embodiments, the ASO targets a *SCN1A* pre-mRNA sequence. In some embodiments, the ASO has a sequence according to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. For another example, the ASOs comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. For another example, the ASOs comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0654] In some embodiments, the ASO targets exon 20 of a SCN1A NIE containing pre-mRNA comprising NIE exon 20x. In some embodiments, the ASO targets an exon 21 sequence downstream (or 3') of NIE exon 20x. In some embodiments, the ASO targets a sequence about 4 to about 300 nucleotides upstream (or 5') from the 5' end of exon 20x. In some embodiments, the ASO targets a sequence about 4 to about 300 nucleotides downstream (or 3') from the 3' end of exon 20x.

[0655] In some embodiments, the ASO targets a sequence upstream from the 5' end of an NIE. In some embodiments, the ASOs target a sequence containing an exon-intron boundary (or junction). In some embodiments, the ASOs target a sequence downstream from the 3' end of an NIE (*e.g.,* exon 20x in human SCN1A, or exon 21x in mouse SCN1A). In some embodiments, ASOs target a sequence within an NIE.

[0656] In some embodiments, the ASO targets exon 20x in a SCN1A NIE containing pre-mRNA comprising exon 20x. In some embodiments, the ASO targets an exon 20x sequence downstream (or 3') from the 5' end of the exon 20x of a *SCN1A* pre-mRNA. In some embodiments, the ASO targets an exon 20x sequence upstream (or 5') from the 3' end of the exon 20x of a *SCN1A* pre-mRNA.

[0657] In some embodiments, the targeted portion of the SCN1A NIE containing pre-mRNA is in intron 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 (intron numbering corresponding to the mRNA sequence at NM_006920). In some embodiments, hybridization of an ASO to the targeted portion of the NIE pre-mRNA results in exon skipping of at least one of NIE within intron 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, and subsequently

increases $Na_V1.1$ protein production. In some embodiments, hybridization of an ASO to the targeted portion of the NIE pre-mRNA inhibits or blocks exon skipping of at least one of NIE within intron 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, and subsequently decreases $Na_V1.1$ protein production. In some embodiments, the targeted portion of the SCN1A NIE containing pre-mRNA is in intron 20. One of skill in the art can determine the corresponding intron number in any isoform based on an intron sequence provided herein or using the number provided in reference to the mRNA sequence at NM_006920, NM_001202435, NM_001165964, or NM_001165963. One of skill in the art also can determine the sequences of flanking exons in any SCN1A isoform for targeting using the methods of the invention, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_006920, NM_001202435, NM_001165964, or NM_001165963.

Therapeutic Agents

[0658] In various embodiments of the present disclosure, compositions and methods comprising a therapeutic agent are provided to modulate protein expression level of SCN1A. In some embodiments, provided herein are compositions and methods to modulate alternative splicing of SCNA1 pre-mRNA. In some embodiments, provided herein are compositions and methods to induce exon skipping in the splicing of *SCN1A* pre-mRNA, *e.g.,* to induce skipping of a pseudo-exon during splicing of *SCN1A* pre-mRNA. In other embodiments, therapeutic agents may be used to induce the inclusion of an exon in order to decrease the protein expression level.

[0659] In some embodiment, a therapeutic agent disclosed herein is a small molecule, a polypeptide, or a polynucleic acid polymer. In some instances, the therapeutic agent is a small molecule. In some instances, the therapeutic agent is a polypeptide. In some instances, the therapeutic agent is a polynucleic acid polymer. In some cases, the therapeutic agent is a repressor agent. In additional cases, the therapeutic agent is an enhancer agent.

[0660] A therapeutic agent disclosed herein can be a NIE repressor agent. A therapeutic agent may comprise a polynucleic acid polymer.

[0661] According to one aspect of the present disclosure, provided herein is a method of treatment or prevention of a condition associated with a functional-$Na_V1.1$ protein deficiency, comprising administering a NIE repressor agent to a subject to increase levels of functional $Na_V1.1$ protein, wherein the agent binds to a region of the pre-mRNA transcript to decrease inclusion of the NIE in the mature transcript. For example, provided herein is a method of treatment or prevention of a condition associated with a functional-$Na_V1.1$ protein deficiency, comprising administering a NIE repressor agent to a subject to increase levels of functional $Na_V1.1$ protein, wherein the agent binds to a region of an intron containing an NIE (*e.g.,* intron 20 in human *SCN1A* gene) of the pre-mRNA transcript or to a NIE-activating regulatory sequence in the same intron.

[0662] The sequence of the polynucleic acid polymer may be at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% complementary to a

target sequence of an mRNA transcript, *e.g.,* a partially processed mRNA transcript. The sequence of the polynucleic acid polymer may be 100% complementary to a target sequence of a pre-mRNA transcript.

[0663] The sequence of the polynucleic acid polymer may have 4 or fewer mismatches to a target sequence of the pre-mRNA transcript. The sequence of the polynucleic acid polymer may have 3 or fewer mismatches to a target sequence of the pre-mRNA transcript. The sequence of the polynucleic acid polymer may have 2 or fewer mismatches to a target sequence of the pre-mRNA transcript. The sequence of the polynucleic acid polymer may have 1 or fewer mismatches to a tar-get sequence of the pre-mRNA transcript. The sequence of the polynucleic acid polymer may have no mismatches to a target sequence of the pre-mRNA transcript.

[0664] The polynucleic acid polymer may specifically hybridize to a target sequence of the pre-mRNA transcript. For example, the polynucleic acid polymer may have 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 100% sequence complementarity to a target sequence of the pre-mRNA transcript. The hybridization may be under high stringent hybridization conditions.

[0665] The polynucleic acid polymer may have a sequence with at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 21-67. The polynucleic acid polymer may have a sequence with 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 21-67. In some instances, the polynucleic acid polymer may have a sequence with at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 68-114. In some cases, the polynucleic acid polymer may have a sequence with 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 68-114.

[0666] In some instances, the polynucleic acid polymer may have a sequence with at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some cases, the polynucleic acid polymer may have a sequence with 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some cases, the polynucleic acid polymer may have a sequence with 100% sequence identity to a sequence selected from the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0667] In some embodiments wherein the NIE repressor agent comprises a polynucleic acid polymer, the polynucleic acid polymer may be about 50 nucleotides in length. The polynucleic acid polymer may be about 45 nucleotides in length. The polynucleic acid polymer may be about 40 nucleotides in length. The polynucleic acid polymer may be about 35 nucleotides in length. The polynucleic acid polymer may be about 30 nucleotides in length. The polynucleic acid polymer may be about 24 nucleotides in length. The polynucleic acid polymer may be about 25 nucleotides in length. The polynucleic acid polymer may be about 20 nucleotides in length. The polynucleic acid polymer may be about 19 nucleotides in length. The polynucleic acid polymer may be about 18 nucleotides in length. The polynucleic acid polymer may be about 17 nucleotides in length. The polynucleic acid polymer may be about 16 nucleotides in length.

The polynucleic acid polymer may be about 15 nucleotides in length. The polynucleic acid polymer may be about 14 nucleotides in length. The polynucleic acid polymer may be about 13 nucleotides in length. The polynucleic acid polymer may be about 12 nucleotides in length. The polynucleic acid polymer may be about 11 nucleotides in length. The polynucleic acid polymer may be about 10 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 50 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 45 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 40 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 35 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 30 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 25 nucleotides in length. The polynucleic acid polymer may be between about 10 and about 20 nucleotides in length. The polynucleic acid polymer may be between about 15 and about 25 nucleotides in length. The polynucleic acid polymer may be between about 15 and about 30 nucleotides in length. The polynucleic acid polymer may be between about 12 and about 30 nucleotides in length.

[0668] The sequence of the polynucleic acid polymer may be at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% complementary to a target sequence of an mRNA transcript, *e.g.,* a partially processed mRNA transcript. The sequence of the polynucleic acid polymer may be 100% complementary to a target sequence of a pre-mRNA transcript.

[0669] As described herein in various examples, exon 20x in human *SCN1A* gene is equivalent to exon 21x in mouse *SCN1A* gene.

[0670] Also within the scope of the present disclosure is a method to identify or validate an NMD-inducing exon in the presence of an NMD inhibitor, for example, cycloheximide.

[0671] Where reference is made to a polynucleic acid polymer sequence, the skilled person will understand that one or more substitutions may be tolerated, optionally two substitutions may be tolerated in the sequence, such that it maintains the ability to hybridize to the target sequence; or where the substitution is in a target sequence, the ability to be recognized as the target sequence. References to sequence identity may be determined by BLAST sequence alignment using standard/default parameters. For example, the sequence may have 99% identity and still function according to the present disclosure. In other embodiments, the sequence may have 98% identity and still function according to the present disclosure. In another embodiment, the sequence may have 95% identity and still function according to the present disclosure. In another embodiment, the sequence may have 90% identity and still function according to the present disclosure.

Pharmaceutical compositions

[0672] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in an artificial cerebral spinal fluid (aCSF) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in an isotonic solution.

[0673] The term "artificial cerebrospinal fluid (aCSF)," as used herein, refers to a biological buffer solution that is commonly used as a vehicle solution for administration of agents to the central nervous

system (CNS). aCSF, for instance, closely matches the electrolyte concentrations and physiological compatibility of endogenous CSF to enable a vital environment for neuronal tissue by maintaining the homeostasis, osmolarity, and pH at physiological levels.

[0674] The term "isotonic solution," as used herein, refers to a solution that contains an electrolyte balance similar to plasma in the bloodstream. Administration of an isotonic solution to a subject or patient may increase the fluid volume of the subject or patient without a fluid shift. Exemplary isotonic solutions include, but are not limited to 0.9% normal saline, lactated Ringer's solution, Ringer's solution, plasmalyte, and 5% Dextrose in water (D_5W).

[0675] The term "hypotonic solution," as used herein, refers to a solution that has a lower concentration of electrolytes than plasma. Administration of a hypotonic solution, for example, via an intravenous route, may lead to shifting fluid out of the bloodstream to the area of higher concentration in the interstitial and intracellular spaces. Exemplary hypotonic solutions include, but are not limited to, 0.45% normal saline (half normal saline), 0.33% NaCl solution, 0.225% NaCl solution, and 2.5% Dextrose in water ($D_{2.5}W$).

[0676] The term "hypertonic solution," as used herein, refers to a solution that has a higher concentration of electrolytes than plasma. Administration of a hypertonic solution, for example, via an intravenous route, may shift fluid from the interstitial and intracellular spaces into the bloodstream to dilute the electrolytes. Exemplary hypertonic solutions include, but are not limited to, 3% NaCl solution, 5% Dextrose in 0.45% NaCl (D_5 ½ NS), 5% Dextrose in 0.9% normal saline (D_5NS), 5% Dextrose in lactated Ringer's solution (D_5LR), 10% Dextrose in water ($D_{10}W$), 20% Dextrose in water ($D_{20}W$), and 50% Dextrose in water ($D_{50}W$).

[0677] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.6-7.6) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 5.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.5, pH 4.6-8.5, pH 4.7-8.5, pH 4.8-8.5, pH 4.9-8.5, pH 5.0-8.5, pH 5.1-8.5, pH 5.2-8.5, pH 5.3-8.5, pH 5.4-8.5, pH 5.5-8.5, pH 5.6-8.5, pH 5.7-8.5, pH 5.8-8.5, pH 5.9-8.5, pH 6.0-8.5, pH 6.1-8.5, pH 6.2-8.5, pH 6.3-8.5, pH 6.4-8.5, pH 6.5-8.5, pH 6.6-8.5, pH 6.7-8.5, pH 6.8-8.5, pH 6.9-8.5, pH 7.0-8.5, pH 7.1-8.5, pH 7.2-8.5, pH 7.3-8.5, pH 7.4-8.5, pH 7.5-8.5, pH 7.6-8.5, pH 7.7-8.5, pH 7.8-8.5, pH 7.9-8.5, pH 8.0-8.5, pH 8.1-8.5, pH 8.2-8.5, pH 8.3-8.5, or pH 8.4-8.5. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.3, pH 4.5-8.2, pH 4.5-8.1, pH 4.5-8.0, pH 4.5-7.9, pH 4.5-7.8, pH 4.5-7.7, pH 4.5-7.6, pH 4.5-7.5, pH 4.5-7.4, pH 4.5-7.3, pH 4.5-7.2, pH 4.5-7.1, pH 4.5-7.0, pH 4.5-6.9, pH 4.5-6.8, pH 4.5-6.7, pH 4.5-6.6, pH 4.5-6.5, pH 4.5-6.4, pH 4.5-6.3, pH 4.5-6.2, pH 4.5-6.1, pH 4.5-6.0, pH 4.5-5.9, pH 4.5-5.8, pH 4.5-5.7, pH 4.5-5.6, pH 4.5-5.5, pH

4.5-5.4, pH 4.5-5.3, pH 4.5-5.2, pH 4.5-5.1, pH 4.5-5.0, pH 4.5-4.9, pH 4.5-4.8, pH 4.5-4.7, or pH 4.5-4.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.6, pH 6.1-7.6, pH 6.2-7.6, pH 6.3-7.6, pH 6.4-7.6, pH 6.5-7.6, pH 6.6-7.6, pH 6.7-7.6, pH 6.8-7.6, pH 6.9-7.6, pH 7.0-7.6, pH 7.1-7.6, pH 7.2-7.6, pH 7.3-7.6, pH 7.4-7.6, or pH 7.5-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.6-8.0, pH 6.6-7.9, pH 6.6-7.8, pH 6.6-7.7, pH 6.6-7.6, pH 6.6-7.5, pH 6.6-7.4, pH 6.6-7.3, pH 6.6-7.2, pH 6.6-7.1, pH 6.6-7.0, pH 6.6-6.9, pH 6.6-6.8, or pH 6.6-6.7. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-8.0, pH 6.1-8.0, pH 6.2-8.0, pH 6.3-8.0, pH 6.4-8.0, pH 6.5-8.0, pH 6.6-8.0, pH 6.7-8.0, pH 6.8-8.0, pH 6.9-8.0, pH 7.0-8.0, pH 7.1-8.0, pH 7.2-8.0, pH 7.3-8.0, pH 7.4-8.0, pH 7.5-8.0, pH 7.6-8.0, pH 7.7-8.0, pH 7.8-8.0, or pH 7.9-8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.9, pH 6.0-7.8, pH 6.0-7.7, pH 6.0-7.6, pH 6.0-7.5, pH 6.0-7.4, pH 6.0-7.3, pH 6.0-7.2, pH 6.0-7.1, pH 6.0-7.0, pH 6.0-6.9, pH 6.0-6.8, pH 6.0-6.7, pH 6.0-6.6, pH 6.0-6.5, pH 6.0-6.4, pH 6.0-6.3, pH 6.0-6.2, or pH 6.0-6.1. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.7-8.5, 5.8-8.4, 5.9-8.3, 6.0-8.2, 6.1-8.1, 6.2-8.0, 6.3-7.9, 6.4-7.8, 6.5-7.7, or 6.6-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with a pH of about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0.

[0678] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl.

[0679] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-245, 25-240, 25-235, 25-230, 25-225, 25-220, 25-215, 25-210, 25-205, 25-200, 25-195, 25-190, 25-185, 25-180, 25-175, 25-170, 25-165, 25-160, 25-155, 25-150, 25-145, 25-140, 25-135, 25-130, 25-125, 25-120, 25-115, 25-110, 25-105, 25-110, 25-105, 25-100, 25-95, 25-90, 25-85, 25-80, 25-75, 25-70, 25-65, 25-60, 25-55, 25-50, 25-45, 25-40, 25-35, or 25-30 mM NaCl. In some

embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 30-245, 35-240, 40-235, 45-230, 50-225, 55-220, 60-215, 65-210, 70-205, 75-200, 80-195, 85-190, 90-185, 95-180, 100-175, 105-170, 110-165, 115-160, 120-155, 125-150, 130-145, or 135-140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 100-140, 101-140, 102-140, 103-140, 104-140, 105-140, 106-140, 107-140, 108-140, 109-140, 110-140, 111-140, 112-140, 113-140, 114-140, 115-140, 116-140, 117-140, 118-140, 119-140, 120-140, 121-140, 122-140, 123-140, 124-140, 125-140, 126-140, 127-140, 128-140, 129-140, 130-140, 131-140, 132-140, 133-140, 134-140, 135-140, 136-140, 137-140, 138-140, or 139-140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 100-139, 100-138, 100-137, 100-136, 100-135, 100-134, 100-133, 100-132, 100-131, 100-130, 100-129, 100-128, 100-127, 100-126, 100-125, 100-124, 100-123, 100-122, 100-121, 100-120, 100-119, 100-118, 100-117, 100-116, 100-115, 100-114, 100-113, 100-112, 100-111, 100-110, 100-109, 100-108, 100-107, 100-106, 100-105, 100-104, 100-103, 100-102, or 100-101 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl.

[0680] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-20 mM KCl.

[0681] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-40, 0.1-39, 0.1-38, 0.1-37, 0.1-36, 0.1-35, 0.1-34, 0.1-33, 0.1-32, 0.1-31, 0.1-30, 0.1-29, 0.1-28, 0.1-27, 0.1-26, 0.1-25, 0.1-24, 0.1-23, 0.1-22, 0.1-21, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, or 0.1-1 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.2-40, 0.3-40, 0.4-40, 0.5-40, 0.6-40, 0.7-40, 0.8-40, 0.9-40, 1-40, 2-40, 3-40, 4-40, 5-40, 6-40, 7-40, 8-40, 9-40, 10-40, 11-40, 12-40, 13-40, 14-40, 15-40, 16-40, 17-40, 18-40, 19-40, 20-40, 21-40, 22-40, 23-40, 24-40, 25-40, 26-40, 27-40, 28-40, 29-40, 30-40, 31-40, 32-40, 33-40, 34-40, 35-40, 36-40,

37-40, 38-40, or 39-40 mM KCl. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.5, 0.2-3.5, 0.3-3.5, 0.4-3.5, 0.5-3.5, 0.6-3.5, 0.7-3.5, 0.8-3.5, 0.9-3.5, 1.0-3.5, 1.1-3.5, 1.2-3.5, 1.3-3.5, 1.4-3.5, 1.5-3.5, 1.6-3.5, 1.7-3.5, 1.8-3.5, 1.9-3.5, 2.0-3.5, 2.1-3.5, 2.2-3.5, 2.3-3.5, 2.4-3.5, 2.5-3.5, 2.6-3.5, 2.7-3.5, 2.8-3.5, 2.9-3.5, 3.0-3.5, 3.1-3.5, 3.2-3.5, 3.3-3.5, or 3.4-3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM KCl. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl.

[0682] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM Na_2HPO_4.

[0683] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.2-3.0, 0.3-

3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or 2.9-3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4.

[0684] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM NaH_2PO_4.

[0685] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.2-3.0, 0.3-3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or 2.9-3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3,

0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4.

[0686] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM $CaCl_2$.

[0687] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$.

[0688] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM $MgCl_2$.

[0689] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a

buffer comprising 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$.

[0690] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof.

[0691] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM $NaHCO_3$.

[0692] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0,

26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$.

[0693] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM $KHCO_3$.

[0694] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0, 26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9,

27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$.

[0695] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50 mM KH_2PO_4.

[0696] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-100, 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-95, 0-90, 0-85, 0-80, 0-75, 0-70, 0-65, 0-60, 0-55, 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-15, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, 0-0.2, 0-0.1, 0-0.09, 0-0.08, 0-0.07, 0-0.06, 0-0.05, 0-0.04, 0-0.03, or 0-0.02 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-3.0, 0-2.9, 0-2.8, 0-2.7, 0-2.6, 0-2.5, 0-2.4, 0-2.3, 0-2.2, 0-2.1, 0-2.0, 0-1.9, 0-1.8, 0-1.7, 0-1.6, 0-1.5, 0-1.4, 0-1.3, 0-1.2, 0-1.1, 0-1.0, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-3.0, 0.1-3.0, 0.2-3.0, 0.3-3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or

2.9-3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4.

[0697] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50 mM NaH_2PO_4.

[0698] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-11, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50, 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1-50, 2-50, 3-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 1-50, 11-50, 12-50, 13-50, 14-50, 15-50, 16-50, 17-50, 18-50, 19-50, 20-50, 25-50, 30-50, 35-50, 40-50, or 45-50 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-20, 0.1-20, 0.2-20, 0.3-20, 0.4-20, 0.5-20, 0.6-20, 0.7-20, 0.8-20, 0.9-20, 1-20, 2-20, 3-20, 4-20, 5-20, 6-20, 7-20, 8-20, 9-20, 10-20, 11-20, 12-20, 13-20, 14-20, 15-20, 16-20, 17-20, 18-20, or 19-20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4.

[0699] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising carbohydrates. In some

embodiments, the carbohydrates comprise D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising 1-100 mM D-glucose.

[0700] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM D-glucose.

[0701] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 11-100, 12-100, 13-100, 14-100, 15-100, 16-100, 17-100, 18-100, 19-100, 20-100, 21-100, 22-100, 23-100, 24-100, 25-100, 26-100, 29-100, 28-100, 29-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-30, 3-30, 4-30, 5-30, 6-30, 7-30, 8-30, 9-30, 10-30, 11-30, 12-30, 13-30, 14-30, 15-30, 16-30, 17-30, 18-30, 19-30, 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 26-30, 27-30, 28-30, or 29-30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose.

[0702] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 11-100, 12-100, 13-100, 14-100, 15-100, 16-100, 17-100, 18-100, 19-100, 20-100, 21-100, 22-100, 23-100, 24-100, 25-100, 26-100, 29-100, 28-100, 29-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-30, 3-30, 4-30, 5-30, 6-30, 7-30, 8-30, 9-30, 10-30, 11-30, 12-30, 13-30, 14-30, 15-30, 16-30, 17-30, 18-30, 19-30, 20-30, 21-30, 22-30, 23-30,

24-30, 25-30, 26-30, 27-30, 28-30, or 29-30 mM glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose.

[0703] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na_2HPO_4, 0.1-50 mM NaH_2PO_4, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0704] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$.

[0705] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising an antioxidant. In some embodiments, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising an antioxidant, wherein the antioxidant is ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, α-tocopherol (vitamin E), ubiquinol (coenzyme Q), or any combination thereof.

[0706] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0-50 mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, 0.1-50 mM $MgCl_2$, or any combination thereof.

[0707] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0-50 mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0708] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 127 mM NaCl, 1.0 mM KCl, 1.2 mM KH_2PO_4, 26 mM $NaHCO_3$, 10 mM D-glucose, 2.4 mM $CaCl_2$, and 1.3 mM $MgCl_2$.

[0709] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 119 mM NaCl, 26.2 mM $NaHCO_3$, 2.5 mM KCl, 1 mM NaH_2PO_4, 1.3 mM $MgCl_2$, 10 mM glucose, and 2.5 mM $CaCl_2$.

[0710] In some embodiments, the pharmaceutical composition does not comprise a preservative. In some embodiments, the pharmaceutical composition comprises a preservative.

[0711] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 5-250 mg/mL.

[0712] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 5-250, 5-247.5, 5-245, 5-242.5, 5-240, 5-237.5, 5-235, 5-232.5, 5-230, 5-227.5, 5-225, 5-225.5, 5-220, 5-217.5, 5-215, 5-212.5, 5-210, 5-205.5, 5-205, 5-202.5, 5-200, 5-197.5, 5-195, 5-192.5, 5-190, 5-187.5, 5-185, 5-182.5, 5-180, 5-177.5, 5-175, 5-172.5, 5-170, 5-167.5, 5-165, 5-162.5, 5-160, 5-157.5, 5-155, 5-152.5, 5-150, 5-147.5, 5-145, 5-142.5, 5-140, 5-137.5, 5-135, 5-132.5, 5-130, 5-127.5, 5-125, 5-122.5, 5-120, 5-117.5, 5-115, 5-112.5, 5-110, 5-107.5, 5-105, 5-102.5, 5-100, 5-97.5, 5-95, 5-92.5, 5-90, 5-87.5, 5-85, 5-82.5, 5-80, 5-77.5, 5-75, 5-72.5, 5-70, 5-67.5, 5-65, 5-62.5, 5-60, 5-57.5, 5-55, 5-52.5, 5-50, 5-47.5, 5-45, 5-42.5, 5-40, 5-37.5, 5-35, 5-32.5, 5-30, 5-27.5, 5-25, 5-22.5, 5-20, 5-17.5, 5-15, 5-12.5, or 5-10 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 10-250, 15-250, 20-250, 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, or 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130,

131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL.

[0713] I In some embodiments, the method comprises administering the pharmaceutical composition as a bolus injection. In some embodiments, the method comprises administering the pharmaceutical composition as a bolus injection over 1 to 180 minutes, 175 minutes, 1 to 170 minutes, 1 to 165 minutes, 1 to 160 minutes, 1 to 155 minutes, 1 to 150 minutes, 1 to 145 minutes, 1 to 140 minutes, 1 to 135 minutes, 1 to 130 minutes, 1 to 125 minutes, 1 to 120 minutes, 1 to 115 minutes, 1 to 110 minutes, 1 to 105 minutes, 1 to 100 minutes, 1 to 95 minutes, 1 to 90 minutes, 1 to 85 minutes, 1 to 80 minutes, 1 to 75 minutes, 1 to 70 minutes, 1 to 65 minutes, 1 to 60 minutes, 1 to 55 minutes, 1 to 50 minutes, 1 to 45 minutes, 1 to 40 minutes, 1 to 35 minutes, 1 to 30 minutes, 1 to 25 minutes, 1 to 20 minutes, 1 to 15 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes. In some embodiments, the method comprises administering the pharmaceutical composition as a bolus injection using a spinal anesthesia needle.

[0714] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, or 20 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160

mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, or 200 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL in the solution or diluent.

[0715] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.2 mg/mL to 250 mg/mL, from 0.3 mg/mL to 250 mg/mL, from 0.4 mg/mL to 250 mg/mL, from 0.5 mg/mL to 250 mg/mL, from 0.6 mg/mL to 250 mg/mL, from 0.7 mg/mL to 250 mg/mL, from 0.8 mg/mL to 250 mg/mL, from 0.9 mg/mL to 250 mg/mL, from 1.0 mg/mL to 250 mg/mL, from 1.1 mg/mL to 250 mg/mL, from 1.2 mg/mL to 250 mg/mL, from 1.3 mg/mL to 250 mg/mL, from 1.4 mg/mL to 250 mg/mL, from 1.5 mg/mL to 250 mg/mL, from 1.6 mg/mL to 250 mg/mL, from 1.7 mg/mL to 250 mg/mL, from 1.8 mg/mL to 250 mg/mL, from 1.9 mg/mL to 250 mg/mL, from 2.0 mg/mL to 250 mg/mL, from 2.1 mg/mL to 250 mg/mL, from 2.2 mg/mL to 250 mg/mL, from 2.3 mg/mL to 250 mg/mL, from 2.4 mg/mL to 250 mg/mL, from 2.5 mg/mL to 250 mg/mL, from 2.6 mg/mL to 250 mg/mL, from 2.7 mg/mL to 250 mg/mL, from 2.8 mg/mL to 250 mg/mL, from 2.9 mg/mL to 250 mg/mL, from 3.0 mg/mL to 250 mg/mL, from 3.1 mg/mL to 250 mg/mL, from 3.2 mg/mL to 250 mg/mL, from 3.3 mg/mL to 250 mg/mL, from 3.4 mg/mL to 250 mg/mL, from 3.5 mg/mL to 250 mg/mL, from 3.6 mg/mL to 250 mg/mL, from 3.7 mg/mL to 250 mg/mL, from 3.8 mg/mL to 250 mg/mL, from 3.9 mg/mL to 250 mg/mL, from 4.0 mg/mL to 250 mg/mL, from 5.0 mg/mL to 250 mg/mL, from 6.0 mg/mL to 250 mg/mL, from 7.0 mg/mL to 250 mg/mL, from 8.0 mg/mL to 250 mg/mL, from 9.0 mg/mL to 250 mg/mL, from 10 mg/mL to 250 mg/mL, from 15 mg/mL to 250 mg/mL, from 20 mg/mL to 250 mg/mL, from 25 mg/mL to 250 mg/mL, from 30 mg/mL to 250 mg/mL, from 35 mg/mL to 250 mg/mL, from 40 mg/mL to 250 mg/mL, from 45 mg/mL to 250 mg/mL, from 50 mg/mL to 250 mg/mL, from 55 mg/mL to 250 mg/mL, from 60 mg/mL to 250 mg/mL, from 65 mg/mL to 250 mg/mL, from 70 mg/mL to 250 mg/mL, from 75 mg/mL to 250 mg/mL, from 80 mg/mL to 250 mg/mL, from 85 mg/mL to 250 mg/mL, from 90 mg/mL to 250 mg/mL, from 95 mg/mL to 250 mg/mL, from 100 mg/mL to 250 mg/mL, from 105 mg/mL to 250 mg/mL, from 110 mg/mL to 250 mg/mL, from 115 mg/mL to 250 mg/mL, from 120 mg/mL to 250 mg/mL, from 125 mg/mL to 250 mg/mL, from 130 mg/mL to 250 mg/mL, from 135 mg/mL to 250 mg/mL, from 140 mg/mL to 250 mg/mL, from 145 mg/mL to 250 mg/mL, from 150 mg/mL to 250 mg/mL, from 155 mg/mL to 250 mg/mL, from 160 mg/mL to 250 mg/mL, from 165 mg/mL to 250 mg/mL, from 170 mg/mL to 250 mg/mL, from 175 mg/mL to 250 mg/mL, from 180 mg/mL to 250 mg/mL, from 185 mg/mL to 250 mg/mL, from 190 mg/mL to 250 mg/mL, from 195 mg/mL to 250 mg/mL, from 200 mg/mL to 250 mg/mL, from 205 mg/mL to 250 mg/mL, from 210 mg/mL to 250 mg/mL, from 215 mg/mL to 250 mg/mL, from 220 mg/mL to 250 mg/mL, from 225 mg/mL to 250 mg/mL, from 230 mg/mL to 250 mg/mL, from 235 mg/mL to 250 mg/mL, from 240 mg/mL to 250 mg/mL, or from 245 mg/mL to 250 mg/mL.

[0716] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.1 mg/mL to 245 mg/mL, from 0.1 mg/mL to 240 mg/mL, from 0.1 mg/mL to 235 mg/mL, from 0.1 mg/mL to 230 mg/mL, from 0.1 mg/mL to 225 mg/mL, from 0.1 mg/mL to 220 mg/mL, from 0.1 mg/mL to 215 mg/mL, from 0.1 mg/mL to 210 mg/mL, from 0.1 mg/mL to 205 mg/mL, from 0.1 mg/mL to 200 mg/mL, from 0.1 mg/mL to 195 mg/mL, from 0.1 mg/mL to 190 mg/mL, from 0.1 mg/mL to 185 mg/mL, from 0.1 mg/mL to 180 mg/mL, from 0.1 mg/mL to 175 mg/mL, from 0.1 mg/mL to 170 mg/mL, from 0.1 mg/mL to 165 mg/mL, from 0.1 mg/mL to 160 mg/mL, from 0.1 mg/mL to 155 mg/mL, from 0.1 mg/mL to 150 mg/mL, from 0.1 mg/mL to 145 mg/mL, from 0.1 mg/mL to 140 mg/mL, from 0.1 mg/mL to 135 mg/mL, from 0.1 mg/mL to 130 mg/mL, from 0.1 mg/mL to 125 mg/mL, from 0.1 mg/mL to 120 mg/mL, from 0.1 mg/mL to 115 mg/mL, from 0.1 mg/mL to 110 mg/mL, from 0.1 mg/mL to 100 mg/mL, from 0.1 mg/mL to 95 mg/mL, from 0.1 mg/mL to 90 mg/mL, from 0.1 mg/mL to 85 mg/mL, from 0.1 mg/mL to 80 mg/mL, from 0.1 mg/mL to 75 mg/mL, from 0.1 mg/mL to 70 mg/mL, from 0.1 mg/mL to 65 mg/mL, from 0.1 mg/mL to 60 mg/mL, from 0.1 mg/mL to 55 mg/mL, from 0.1 mg/mL to 50 mg/mL, from 0.1 mg/mL to 45 mg/mL, from 0.1 mg/mL to 40 mg/mL, from 0.1 mg/mL to 35 mg/mL, from 0.1 mg/mL to 30 mg/mL, from 0.1 mg/mL to 25 mg/mL, from 0.1 mg/mL to 20 mg/mL, from 0.1 mg/mL to 15 mg/mL, from 0.1 mg/mL to 10 mg/mL, from 0.1 mg/mL to 9 mg/mL, from 0.1 mg/mL to 8 mg/mL, from 0.1 mg/mL to 7 mg/mL, from 0.1 mg/mL to 6 mg/mL, from 0.1 mg/mL to 5 mg/mL, from 0.1 mg/mL to 4 mg/mL, from 0.1 mg/mL to 3.9 mg/mL, from 0.1 mg/mL to 3.8 mg/mL, from 0.1 mg/mL to 3.7 mg/mL, from 0.1 mg/mL to 3.6 mg/mL, from 0.1 mg/mL to 3.5 mg/mL, from 0.1 mg/mL to 3.4 mg/mL, from 0.1 mg/mL to 3.3 mg/mL, from 0.1 mg/mL to 3.2 mg/mL, from 0.1 mg/mL to 3.1 mg/mL, from 0.1 mg/mL to 3.0 mg/mL, from 0.1 mg/mL to 2.9 mg/mL, from 0.1 mg/mL to 2.8 mg/mL, from 0.1 mg/mL to 2.7 mg/mL, from 0.1 mg/mL to 2.6 mg/mL, from 0.1 mg/mL to 2.5 mg/mL, from 0.1 mg/mL to 2.4 mg/mL, from 0.1 mg/mL to 2.3 mg/mL, from 0.1 mg/mL to 2.2 mg/mL, from 0.1 mg/mL to 2.1 mg/mL, from 0.1 mg/mL to 2.0 mg/mL, from 0.1 mg/mL to 1.9 mg/mL, from 0.1 mg/mL to 1.8 mg/mL, from 0.1 mg/mL to 1.7 mg/mL, from 0.1 mg/mL to 1.6 mg/mL, from 0.1 mg/mL to 1.5 mg/mL, from 0.1 mg/mL to 1.4 mg/mL, from 0.1 mg/mL to 1.3 mg/mL, from 0.1 mg/mL to 1.2 mg/mL, from 0.1 mg/mL to 1.1 mg/mL, from 0.1 mg/mL to 1.0 mg/mL, from 0.1 mg/mL to 0.9 mg/mL, from 0.1 mg/mL to 0.8 mg/mL, from 0.1 mg/mL to 0.7 mg/mL, from 0.1 mg/mL to 0.6 mg/mL, from 0.1 mg/mL to 0.5 mg/mL, from 0.1 mg/mL to 0.4 mg/mL, from 0.1 mg/mL to 0.3 mg/mL, or from 0.1 mg/mL to 0.2 mg/mL.

[0717] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93,

94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution.

[0718] Pharmaceutical compositions comprising the compound, *e.g.*, antisense oligomer, of the described compositions and for use in any of the described methods can be prepared according to

conventional techniques well known in the pharmaceutical industry and described in the published literature. In some embodiments, a pharmaceutical composition for treating a subject comprises an effective amount of any compound as described herein, or a pharmaceutically acceptable salt, solvate, hydrate or ester thereof. In some embodiments, the pharmaceutical composition described herein further comprises a pharmaceutically acceptable excipient, carrier, or diluent.

[0719] Pharmaceutical compositions can be formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. A proper formulation is dependent upon the route of administration chosen and a summary of pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference. In some embodiments, the pharmaceutical composition facilitates administration of the compound to an organism.

[0720] Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (*e.g.,* aluminum hydroxide); and preservatives.

[0721] The terms "pharmaceutical composition" and "pharmaceutical formulation" (or "formulation") are used interchangeably and denote a mixture or solution comprising an active pharmaceutical ingredient together with one or more pharmaceutically acceptable excipients to be administered to a subject, *e.g.,* a human in need thereof.

[0722] The term "pharmaceutically acceptable" denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use. "Pharmaceutically acceptable" can refer a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, *i.e.,* the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0723] The terms "pharmaceutically acceptable excipient," "pharmaceutically acceptable carrier," and "therapeutically inert excipient" can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents, excipients, preservatives or lubricants used in formulating pharmaceutical products.

[0724] In some embodiments, the compositions are prepared with carriers that will protect the components of the composition against rapid elimination from the body, such as a controlled release

formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral anti-gens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811, of which entire content is incorporated herein by reference.

[0725] Pharmaceutical compositions or formulations comprising the compound, *e.g.,* antisense oligomer, of the described compositions and for use in any of the described methods can be prepared according to conventional techniques well known in the pharmaceutical industry and described in the published literature. In some embodiments, a pharmaceutical composition or formulation for treating a subject comprises an effective amount of any compound as described herein, or a pharmaceutically acceptable salt, solvate, hydrate or ester thereof. The pharmaceutical formulation comprising the compound may further comprise a pharmaceutically acceptable excipient, diluent, or carrier.

[0726] Pharmaceutically acceptable salts are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, *etc.*, and are commensurate with a reasonable benefit/risk ratio. (See, *e.g.,* S. M. Berge, *et al.*, J. Pharmaceutical Sciences, 66: 1-19 (1977), incorporated herein by reference for this purpose. The salts can be prepared in situ during the final isolation and purification of the compounds, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other documented methodologies such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0727] In some embodiments, provided herein is a method of producing the pharmaceutical composition as described herein.

Pharmaceutical Formulation

[0728] In some aspects, provided herein is a pharmaceutical formulation comprising: a compound (*e.g.*, an ASO) as described herein, wherein the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099; and a pharmaceutically acceptable diluent; wherein about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 102.5, 105, 107.5, 110, 112.5, 115, 117.5, 120, 122.5, 125, 127.5, 130, 132.5, 135, 137.5, 140, 142.5, 145, 147.5, 150, 152.5, 155, 157.5, 160, 162.5, 165, 167.5, 170, 172.5, 175, 177.5, 180, 182.5, 185, 187.5, 190, 192.5, 195, 197.5, 200, 202.5, 205, 207.5, 210, 212.5, 215, 217.5, 220, 222.5, 225, 227.5, 230, 232.5, 235, 237.5, 240, 242.5, 245, 247.5, or 250 mg of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 0.1-250 mg/mL. In some embodiments, the ASO as described herein comprises a sequence with at least 80% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0729] In some embodiments, the ASO as described herein comprises a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO as described herein consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO as described herein consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0730] In some embodiments, about 1-500, 2-500, 3-500, 4-500, 5-500, 6-500, 7-500, 8-500, 9-500, 10-500, 15-500, 20-500, 25-500, 30-500, 35-500, 40-500, 45-500, 50-500, 55-500, 60-500, 65-500, 70-500, 75-500, 80-500, 85-500, 90-500, 95-500, 100-500, 105-500, 110-500, 115-500, 120-500, 125-500, 130-500, 135-500, 140-500, 145-500, 150-500, 155-500, 160-500, 165-500, 170-500, 175-500, 180-500, 185-500, 190-500, 195-500, 205-500, 210-500, 215-500, 220-500, 225-500, 230-500, 235-500, 240-500, 245-500, 250-500, 255-500, 260-500, 265-500, 270-500, 275-500, 280-500, 285-500, 290-500, 295-500, 300-500, 305-500, 310-500, 315-500, 320-500, 325-500, 330-500, 335-500, 340-500, 345-500, 350-500, 355-500, 360-500, 365-500, 370-500, 375-500, 380-500, 385-500, 390-500, 395-500, 400-500, 405-500, 410-500, 415-500, 420-500, 425-500, 430-500, 435-500, 440-500, 445-500, 450-500, 455-500, 460-500, 465-500, 470-500, 475-500, 480-500, 485-500, 490-500, or 495-500 mg of the compound as described herein

(*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 5-200 mg/mL. In some embodiments, about 1-495, 1-490, 1-485, 1-480, 1-475, 1-470, 1-465, 1-460, 1-455, 1-450, 1-445, 1-440, 1-435, 1-430, 1-425, 1-420, 1-415, 1-410, 1-405, 1-400, 1-395, 1-390, 1-385, 1-380, 1-375, 1-370, 1-365, 1-360, 1-355, 1-350, 1-345, 1-340, 1-335, 1-330, 1-325, 1-320, 1-315, 1-310, 1-305, 1-300, 1-295, 1-290, 1-285, 1-280, 1-275, 1-270, 1-265, 1-260, 1-255, 1-250, 1-245, 1-240, 1-235, 1-230, 1-225, 1-220, 1-215, 1-210, 1-205, 1-200, 1-195, 1-190, 1-185, 1-180, 1-175, 1-170, 1-165, 1-160, 1-155, 1-150, 1-145, 1-140, 1-135, 1-130, 1-125, 1-120, 1-115, 1-110, 1-105, 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-0, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mg of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 5-200 mg/mL.

[0731] In some embodiments, at least about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 102.5, 105, 107.5, 110, 112.5, 115, 117.5, 120, 122.5, 125, 127.5, 130, 132.5, 135, 137.5, 140, 142.5, 145, 147.5, 150, 152.5, 155, 157.5, 160, 162.5, 165, 167.5, 170, 172.5, 175, 177.5, 180, 182.5, 185, 187.5, 190, 192.5, 195, 197.5, 200, 202.5, 205, 207.5, 210, 212.5, 215, 217.5, 220, 222.5, 225, 227.5, 230, 232.5, 235, 237.5, 240, 242.5, 245, 247.5, or 250 mg of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 0.1-250 mg/mL. In some embodiments, at most about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 102.5, 105, 107.5, 110, 112.5, 115, 117.5, 120, 122.5, 125, 127.5, 130, 132.5, 135, 137.5, 140, 142.5, 145, 147.5, 150, 152.5, 155, 157.5, 160, 162.5, 165, 167.5, 170, 172.5, 175, 177.5, 180, 182.5, 185, 187.5, 190, 192.5, 195, 197.5, 200, 202.5, 205, 207.5, 210, 212.5, 215, 217.5, 220, 222.5, 225, 227.5, 230, 232.5, 235, 237.5, 240, 242.5, 245, 247.5, or 250 mg of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 0.1-250 mg/mL. In some embodiments, about 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 102.5, 105, 107.5, 110, 112.5, 115, 117.5, 120, 122.5, 125, 127.5, 130, 132.5, 135, 137.5, 140, 142.5, 145, 147.5, 150, 152.5, 155, 157.5, 160, 162.5, 165, 167.5, 170, 172.5, 175, 177.5, 180, 182.5, 185, 187.5, 190, 192.5, 195, 197.5, 200, 202.5, 205, 207.5, 210, 212.5, 215, 217.5, 220, 222.5, 225, 227.5, 230, 232.5, 235, 237.5, 240, 242.5, 245, 247.5, or 250 mg of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 0.1-250 mg/mL.

[0732] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 5-250, 5-247.5, 5-245, 5-242.5, 5-240, 5-237.5, 5-235, 5-232.5, 5-230, 5-227.5, 5-225, 5-225.5, 5-220, 5-217.5, 5-215, 5-212.5,

5-210, 5-205.5, 5-205, 5-202.5, 5-200, 5-197.5, 5-195, 5-192.5, 5-190, 5-187.5, 5-185, 5-182.5, 5-180, 5-177.5, 5-175, 5-172.5, 5-170, 5-167.5, 5-165, 5-162.5, 5-160, 5-157.5, 5-155, 5-152.5, 5-150, 5-147.5, 5-145, 5-142.5, 5-140, 5-137.5, 5-135, 5-132.5, 5-130, 5-127.5, 5-125, 5-122.5, 5-120, 5-117.5, 5-115, 5-112.5, 5-110, 5-107.5, 5-105, 5-102.5, 5-100, 5-97.5, 5-95, 5-92.5, 5-90, 5-87.5, 5-85, 5-82.5, 5-80, 5-77.5, 5-75, 5-72.5, 5-70, 5-67.5, 5-65, 5-62.5, 5-60, 5-57.5, 5-55, 5-52.5, 5-50, 5-47.5, 5-45, 5-42.5, 5-40, 5-37.5, 5-35, 5-32.5, 5-30, 5-27.5, 5-25, 5-22.5, 5-20, 5-17.5, 5-15, 5-12.5, or 5-10 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 10-250, 15-250, 20-250, 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, or 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is dissolved or suspended in a solution at a concentration of from 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL.

[0733] In some embodiments, the pharmaceutically acceptable diluent comprises an artificial cerebral spinal fluid (aCSF) solution. In some embodiments, the solution comprises a cerebral spinal fluid (CSF) sample from the subject. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in an iso-tonic solution.

[0734] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.6-7.6) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 5.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.5, pH 4.6-8.5, pH 4.7-8.5, pH 4.8-8.5, pH 4.9-8.5, pH 5.0-8.5, pH 5.1-8.5, pH 5.2-8.5, pH 5.3-8.5, pH5.4-8.5, pH 5.5-8.5, pH 5.6-8.5, pH 5.7-8.5, pH 5.8-8.5, pH 5.9-8.5, pH 6.0-8.5, pH 6.1-8.5, pH 6.2-8.5, pH 6.3-8.5, pH 6.4-8.5, pH 6.5-8.5, pH 6.6-8.5, pH 6.7-8.5, pH 6.8-8.5, pH 6.9-8.5, pH 7.0-8.5, pH 7.1-8.5, pH 7.2-8.5, pH 7.3-8.5, pH 7.4-8.5, pH 7.5-8.5, pH 7.6-8.5, pH 7.7-8.5, pH 7.8-8.5, pH 7.9-8.5, pH 8.0-8.5, pH 8.1-8.5, pH 8.2-8.5, pH 8.3-8.5, or pH 8.4-8.5. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.3, pH 4.5-8.2, pH 4.5-8.1, pH 4.5-8.0, pH 4.5-7.9, pH 4.5-7.8, pH 4.5-7.7, pH 4.5-7.6, pH 4.5-7.5, pH 4.5-7.4, pH 4.5-7.3, pH 4.5-7.2, pH 4.5-7.1, pH 4.5-7.0, pH 4.5-6.9, pH 4.5-6.8, pH 4.5-6.7, pH 4.5-6.6, pH 4.5-6.5, pH 4.5-6.4, pH 4.5-6.3, pH 4.5-6.2, pH 4.5-6.1, pH 4.5-6.0, pH 4.5-5.9, pH 4.5-5.8, pH 4.5-5.7, pH 4.5-5.6, pH 4.5-5.5, pH 4.5-5.4, pH 4.5-5.3, pH 4.5-5.2, pH 4.5-5.1, pH 4.5-5.0, pH 4.5-4.9, pH 4.5-4.8, pH 4.5-4.7, or pH 4.5-4.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.6, pH 6.1-7.6, pH 6.2-7.6, pH 6.3-7.6, pH 6.4-7.6, pH 6.5-7.6, pH 6.6-7.6, pH 6.7-7.6, pH 6.8-7.6, pH 6.9-7.6, pH 7.0-7.6, pH 7.1-7.6, pH 7.2-7.6, pH 7.3-7.6, pH 7.4-7.6, or pH 7.5-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a

phosphate-buffered solution with pH 6.6-8.0, pH 6.6-7.9, pH 6.6-7.8, pH 6.6-7.7, pH 6.6-7.6, pH 6.6-7.5, pH 6.6-7.4, pH 6.6-7.3, pH 6.6-7.2, pH 6.6-7.1, pH 6.6-7.0, pH 6.6-6.9, pH 6.6-6.8, or pH 6.6-6.7. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-8.0, pH 6.1-8.0, pH 6.2-8.0, pH 6.3-8.0, pH 6.4-8.0, pH 6.5-8.0, pH 6.6-8.0, pH 6.7-8.0, pH 6.8-8.0, pH 6.9-8.0, pH 7.0-8.0, pH 7.1-8.0, pH 7.2-8.0, pH 7.3-8.0, pH 7.4-8.0, pH 7.5-8.0, pH 7.6-8.0, pH 7.7-8.0, pH 7.8-8.0, or pH 7.9-8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.9, pH 6.0-7.8, pH 6.0-7.7, pH 6.0-7.6, pH 6.0-7.5, pH 6.0-7.4, pH 6.0-7.3, pH 6.0-7.2, pH 6.0-7.1, pH 6.0-7.0, pH 6.0-6.9, pH 6.0-6.8, pH 6.0-6.7, pH 6.0-6.6, pH 6.0-6.5, pH 6.0-6.4, pH 6.0-6.3, pH 6.0-6.2, or pH 6.0-6.1. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.7-8.5, 5.8-8.4, 5.9-8.3, 6.0-8.2, 6.1-8.1, 6.2-8.0, 6.3-7.9, 6.4-7.8, 6.5-7.7, or 6.6-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0.

[0735] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl.

[0736] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-245, 25-240, 25-235, 25-230, 25-225, 25-220, 25-215, 25-210, 25-205, 25-200, 25-195, 25-190, 25-185, 25-180, 25-175, 25-170, 25-165, 25-160, 25-155, 25-150, 25-145, 25-140, 25-135, 25-130, 25-125, 25-120, 25-115, 25-110, 25-105, 25-110, 25-105, 25-100, 25-95, 25-90, 25-85, 25-80, 25-75, 25-70, 25-65, 25-60, 25-55, 25-50, 25-45, 25-40, 25-35, or 25-30 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 30-245, 35-240, 40-235, 45-230, 50-225, 55-220, 60-215, 65-210, 70-205, 75-200, 80-195, 85-190, 90-185, 95-180, 100-175, 105-170, 110-165, 115-160, 120-155, 125-150, 130-145, or 135-140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 100-140, 101-140, 102-140, 103-140, 104-140, 105-140, 106-140, 107-140, 108-140, 109-140, 110-140, 111-

140, 112-140, 113-140, 114-140, 115-140, 116-140, 117-140, 118-140, 119-140, 120-140, 121-140, 122-140, 123-140, 124-140, 125-140, 126-140, 127-140, 128-140, 129-140, 130-140, 131-140, 132-140, 133-140, 134-140, 135-140, 136-140, 137-140, 138-140, or 139-140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 100-139, 100-138, 100-137, 100-136, 100-135, 100-134, 100-133, 100-132, 100-131, 100-130, 100-129, 100-128, 100-127, 100-126, 100-125, 100-124, 100-123, 100-122, 100-121, 100-120, 100-119, 100-118, 100-117, 100-116, 100-115, 100-114, 100-113, 100-112, 100-111, 100-110, 100-109, 100-108, 100-107, 100-106, 100-105, 100-104, 100-103, 100-102, or 100-101 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl.

[0737] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-20 mM KCl.

[0738] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-40, 0.1-39, 0.1-38, 0.1-37, 0.1-36, 0.1-35, 0.1-34, 0.1-33, 0.1-32, 0.1-31, 0.1-30, 0.1-29, 0.1-28, 0.1-27, 0.1-26, 0.1-25, 0.1-24, 0.1-23, 0.1-22, 0.1-21, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, or 0.1-1 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.2-40, 0.3-40, 0.4-40, 0.5-40, 0.6-40, 0.7-40, 0.8-40, 0.9-40, 1-40, 2-40, 3-40, 4-40, 5-40, 6-40, 7-40, 8-40, 9-40, 10-40, 11-40, 12-40, 13-40, 14-40, 15-40, 16-40, 17-40, 18-40, 19-40, 20-40, 21-40, 22-40, 23-40, 24-40, 25-40, 26-40, 27-40, 28-40, 29-40, 30-40, 31-40, 32-40, 33-40, 34-40, 35-40, 36-40, 37-40, 38-40, or 39-40 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.5, 0.2-3.5, 0.3-3.5, 0.4-3.5, 0.5-3.5, 0.6-3.5, 0.7-3.5, 0.8-3.5, 0.9-3.5, 1.0-3.5, 1.1-3.5, 1.2-3.5, 1.3-3.5, 1.4-3.5, 1.5-3.5, 1.6-3.5, 1.7-3.5, 1.8-3.5, 1.9-3.5, 2.0-3.5, 2.1-3.5, 2.2-3.5, 2.3-3.5, 2.4-3.5, 2.5-3.5, 2.6-3.5, 2.7-3.5, 2.8-3.5, 2.9-3.5, 3.0-3.5, 3.1-3.5, 3.2-3.5, 3.3-3.5, or 3.4-3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or

diluted in a buffer comprising 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl.

[0739] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM Na_2HPO_4.

[0740] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.2-3.0, 0.3-3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or 2.9-3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I)

or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM Na_2HPO_4.

[0741] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM NaH_2PO_4.

[0742] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.2-3.0, 0.3-3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or 2.9-3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM NaH_2PO_4.

[0743] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM $CaCl_2$.

[0744] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$.

[0745] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50 mM $MgCl_2$.

[0746] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $MgCl_2$. In some

embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$.

[0747] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof.

[0748] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM $NaHCO_3$.

[0749] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0, 26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9,

27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$.

[0750] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM $KHCO_3$.

[0751] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0, 26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the

compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$.

[0752] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50 mM KH_2PO_4.

[0753] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-100, 0.01-100, 0.02-100, 0.03-100, 0.04-100, 0.05-100, 0.06-100, 0.07-100, 0.08-100, 0.09-100, 0.1-100, 0.2-100, 0.3-100, 0.4-100, 0.5-100, 0.6-100, 0.7-100, 0.8-100, 0.9-100, 1-100, 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-95, 0-90, 0-85, 0-80, 0-75, 0-70, 0-65, 0-60, 0-55, 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-15, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, 0-0.2, 0-0.1, 0-0.09, 0-0.08, 0-0.07, 0-0.06, 0-0.05, 0-0.04, 0-0.03, or 0-0.02 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.01-95, 0.01-90, 0.01-85, 0.01-80, 0.01-75, 0.01-70, 0.01-65, 0.01-60, 0.01-55, 0.01-50, 0.01-45, 0.01-40, 0.01-35, 0.01-30, 0.01-25, 0.01-20, 0.01-15, 0.01-10, 0.01-9, 0.01-8, 0.01-7, 0.01-6, 0.01-5, 0.01-4, 0.01-3, 0.01-2, 0.01-1, 0.01-0.9, 0.01-0.8, 0.01-0.7, 0.01-0.6, 0.01-0.5, 0.01-0.4, 0.01-0.3, 0.01-0.2, 0.01-0.1, 0.01-0.09, 0.01-0.08, 0.01-0.07, 0.01-0.06, 0.01-0.05, 0.01-0.04, 0.01-0.03, or 0.01-0.02 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-3.0, 0-2.9, 0-2.8, 0-2.7, 0-2.6, 0-2.5, 0-2.4, 0-2.3, 0-2.2, 0-2.1, 0-2.0, 0-1.9, 0-1.8, 0-1.7, 0-1.6, 0-1.5, 0-1.4, 0-1.3, 0-1.2, 0-1.1, 0-1.0, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-3.0, 0.1-3.0, 0.2-3.0, 0.3-3.0, 0.4-3.0, 0.5-3.0, 0.6-3.0, 0.7-3.0, 0.8-3.0, 0.9-3.0, 1.0-3.0, 1.2-3.0, 1.3-3.0, 1.4-3.0, 1.5-3.0, 1.6-3.0, 1.7-3.0, 1.8-3.0, 1.9-3.0, 2.0-3.0, 2.1-3.0, 2.2-3.0, 2.3-3.0, 2.4-3.0, 2.5-3.0, 2.6-3.0, 2.7-3.0, 2.8-3.0, or 2.9-3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0, 0.1, 0.2, 0.3,

0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0 mM KH_2PO_4.

[0754] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50 mM NaH_2PO_4.

[0755] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0.1-50, 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-11, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-50, 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1-50, 2-50, 3-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 1-50, 11-50, 12-50, 13-50, 14-50, 15-50, 16-50, 17-50, 18-50, 19-50, 20-50, 25-50, 30-50, 35-50, 40-50, or 45-50 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0-20, 0.1-20, 0.2-20, 0.3-20, 0.4-20, 0.5-20, 0.6-20, 0.7-20, 0.8-20, 0.9-20, 1-20, 2-20, 3-20, 4-20, 5-20, 6-20, 7-20, 8-20, 9-20, 10-20, 11-20, 12-20, 13-20, 14-20, 15-20, 16-20, 17-20, 18-20, or 19-20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4.

[0756] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising carbohydrates. In some embodiments, the carbohydrates comprise D-glucose. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising 1-100 mM D-glucose.

[0757] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100 mM D-glucose.

[0758] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM D-glucose. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 11-100, 12-100, 13-100, 14-100, 15-100, 16-100, 17-100, 18-100, 19-100, 20-100, 21-100, 22-100, 23-100, 24-100, 25-100, 26-100, 29-100, 28-100, 29-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM D-glucose. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 2-30, 3-30, 4-30, 5-30, 6-30, 7-30, 8-30, 9-30, 10-30, 11-30, 12-30, 13-30, 14-30, 15-30, 16-30, 17-30, 18-30, 19-30, 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 26-30, 27-30, 28-30, or 29-30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose.

[0759] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na_2HPO_4, 0.1-50 mM NaH_2PO_4, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0760] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$.

[0761] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising an antioxidant. In some embodiments, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising an antioxidant, wherein the antioxidant is ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, α-tocopherol (vitamin E), ubiquinol (coenzyme Q), or any combination thereof.

[0762] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0-50

mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, 0.1-50 mM $MgCl_2$, or any combination thereof.

[0763] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0-50 mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0764] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 127 mM NaCl, 1.0 mM KCl, 1.2 mM KH_2PO_4, 26 mM $NaHCO_3$, 10 mM D-glucose, 2.4 mM $CaCl_2$, and 1.3 mM $MgCl_2$.

[0765] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer comprising 119 mM NaCl, 26.2 mM $NaHCO_3$, 2.5 mM KCl, 1 mM NaH_2PO_4, 1.3 mM $MgCl_2$, 10 mM glucose, and 2.5 mM $CaCl_2$.

[0766] In some embodiments, the pharmaceutical composition lacks phosphate ion. In some embodiments, the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4. In some of these embodiments, the pharmaceutical composition comprises 5-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM $CaCl_2$ or $CaCl_2{\cdot}2H_2O$, and 0.1-50 mM $MgCl_2$ or $MgCl_2{\cdot}6H_2O$. In some cases, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium chloride or magnesium chloride hexahydrate ($MgCl_2{\cdot}6H_2O$) at a concentration of about 0.1 mM to about 50 mM; (c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM; (d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and (e) water. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$) is 0.2 mM to 25 mM, 0.5 mM to 10 mM, 0.75 mM to 5 mM, or 1 mM to 2 mM. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$) is from about 1 mM to about 2 mM. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$) is about 1.4 mM. In some cases, the concentration of magnesium chloride or magnesium chloride hexahydrate is 0.2 mM to 25 mM, 0.3 mM to 15 mM, 0.4 mM to 5 mM, 0.5 mM to 1.5 mM, or 0.6 mM to 1 mM. In some cases, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2{\cdot}6H_2O$) is from about 0.6 mM to about 1 mM. In some cases, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2{\cdot}6H_2O$) is about 0.79 mM. In some cases, the concentration of potassium chloride is 0.5 mM to 10 mM, 1 mM to 7.5 mM, or 2 mM to 5 mM. In some cases, the concentration of potassium chloride is from about 2 mM to about 5 mM. In some cases, the concentration of potassium chloride is about 3 mM. In some cases, the concentration of sodium chloride is 25 mM to 250 mM, 100 mM to 160 mM, 110 mM to 140 mM, or 130 mM to 160 mM. In some cases, the concentration of sodium chloride is from about 125 mM to 145 mM. In some cases, the concentration of sodium chloride is about 130 mM. In some cases, the concentration of sodium chloride is from about 140 mM to 160 mM. In some cases, the concentration of sodium chloride is about 150 mM. In some cases, the concentration of the compound

in the pharmaceutical composition provided herein is about 3 mg/mL, about 4.5 mg/mL, about 7 mg/mL, or about 33 mg/mL; the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM; the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM; the concentration of potassium chloride is about 3 mM; and the concentration of sodium chloride is about 150 mM. In some cases, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium ion (Ca^{2+}) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.1 mM to about 50 mM; (c) potassium ion (K^+) at a concentration of about 0.1 mM to about 20 mM; (d) sodium ion (Na^+) at a concentration of about 25 mM to about 250 mM; (e) chloride ion (Cl^-) at a concentration of about 25 mM to about 250 mM; and (f) water. In some cases, the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL, (a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM; (c) potassium ion (K^+) at a concentration of about 3 mM; (d) sodium ion (Na^+) at a concentration of about 160 mM; (e) chloride ion (Cl^-) at a concentration of about 160 mM; and (f) water.

[0767] In some embodiments, the pharmaceutical formulation does not comprise a preservative. In some embodiments, the pharmaceutical formulation comprises a preservative.

[0768] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from 5-250 mg/mL in the solution.

[0769] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from 5-250, 5-247.5, 5-245, 5-242.5, 5-240, 5-237.5, 5-235, 5-232.5, 5-230, 5-227.5, 5-225, 5-225.5, 5-220, 5-217.5, 5-215, 5-212.5, 5-210, 5-205.5, 5-205, 5-202.5, 5-200, 5-197.5, 5-195, 5-192.5, 5-190, 5-187.5, 5-185, 5-182.5, 5-180, 5-177.5, 5-175, 5-172.5, 5-170, 5-167.5, 5-165, 5-162.5, 5-160, 5-157.5, 5-155, 5-152.5, 5-150, 5-147.5, 5-145, 5-142.5, 5-140, 5-137.5, 5-135, 5-132.5, 5-130, 5-127.5, 5-125, 5-122.5, 5-120, 5-117.5, 5-115, 5-112.5, 5-110, 5-107.5, 5-105, 5-102.5, 5-100, 5-97.5, 5-95, 5-92.5, 5-90, 5-87.5, 5-85, 5-82.5, 5-80, 5-77.5, 5-75, 5-72.5, 5-70, 5-67.5, 5-65, 5-62.5, 5-60, 5-57.5, 5-55, 5-52.5, 5-50, 5-47.5, 5-45, 5-42.5, 5-40, 5-37.5, 5-35, 5-32.5, 5-30, 5-27.5, 5-25, 5-22.5, 5-20, 5-17.5, 5-15, 5-12.5, or 5-10 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from 10-250, 15-250, 20-250, 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, or 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71,

72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution.

[0770] In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is present in the

pharmaceutical composition at a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, or 20 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160 mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, or 200 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 22.5 mg/mL, 25 mg/mL, 27.5 mg/mL, 30 mg/mL, 32.5 mg/mL, 35 mg/mL, 37.5 mg/mL, 40 mg/mL, 42.5 mg/mL, 45 mg/mL, 47.5 mg/mL, 50 mg/mL, 52.5 mg/mL, 55 mg/mL, 57.5 mg/mL, 60 mg/mL, 62.5 mg/mL, 65 mg/mL, 67.5 mg/mL, 70 mg/mL, 72.5 mg/mL, 75 mg/mL, 77.5 mg/mL, 80 mg/mL, 82.5 mg/mL, 85 mg/mL, 87.5 mg/mL, 90 mg/mL, 92.5 mg/mL, 95 mg/mL, 97.5 mg/mL, 100 mg/mL, 102.5 mg/mL, 105 mg/mL, 107.5 mg/mL, 110 mg/mL, 112.5 mg/mL, 115 mg/mL, 117.5 mg/mL, 120 mg/mL, 122.5 mg/mL, 125 mg/mL, 127.5 mg/mL, 130 mg/mL, 132.5 mg/mL, 135 mg/mL, 137.5 mg/mL, 140 mg/mL, 142.5 mg/mL, 145 mg/mL, 147.5 mg/mL, 150 mg/mL, 152.5 mg/mL, 155 mg/mL, 157.5 mg/mL, 160 mg/mL, 162.5 mg/mL, 165 mg/mL, 167.5 mg/mL, 170 mg/mL, 172.5 mg/mL, 175 mg/mL, 177.5 mg/mL, 180 mg/mL, 182.5 mg/mL, 185 mg/mL, 187.5 mg/mL, 190 mg/mL, 192.5 mg/mL, 195 mg/mL, 197.5 mg/mL, 200 mg/mL, 202.5 mg/mL, 205 mg/mL, 207.5 mg/mL, 210 mg/mL, 212.5 mg/mL, 215 mg/mL, 217.5 mg/mL, 220 mg/mL, 222.5 mg/mL, 225 mg/mL, 227.5 mg/mL, 230 mg/mL, 232.5 mg/mL, 235 mg/mL, 237.5 mg/mL, 240 mg/mL, 242.5 mg/mL, 245 mg/mL, 247.5 mg/mL, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL in the solution.

[0771] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.2 mg/mL to 250 mg/mL, from 0.3 mg/mL to 250 mg/mL, from 0.4 mg/mL to 250 mg/mL, from 0.5 mg/mL to 250 mg/mL, from 0.6 mg/mL to 250 mg/mL, from 0.7 mg/mL to 250 mg/mL, from 0.8 mg/mL to 250 mg/mL, from 0.9 mg/mL to 250 mg/mL, from 1.0 mg/mL to 250 mg/mL, from 1.1 mg/mL to 250 mg/mL, from 1.2 mg/mL to 250 mg/mL, from 1.3 mg/mL to 250 mg/mL, from 1.4 mg/mL to 250 mg/mL, from 1.5 mg/mL to 250 mg/mL, from 1.6 mg/mL to 250 mg/mL, from 1.7 mg/mL to 250 mg/mL, from 1.8 mg/mL to 250 mg/mL, from 1.9 mg/mL to 250 mg/mL, from 2.0 mg/mL to 250 mg/mL, from 2.1 mg/mL to 250 mg/mL, from 2.2 mg/mL to 250 mg/mL, from 2.3 mg/mL to 250 mg/mL, from 2.4 mg/mL to 250 mg/mL, from 2.5 mg/mL to 250 mg/mL, from 2.6 mg/mL to 250 mg/mL, from 2.7 mg/mL to 250 mg/mL, from 2.8 mg/mL to 250 mg/mL, from 2.9 mg/mL to 250 mg/mL, from 3.0 mg/mL to 250 mg/mL, from 3.1 mg/mL to 250 mg/mL, from 3.2 mg/mL to 250 mg/mL, from 3.3 mg/mL to 250 mg/mL, from 3.4 mg/mL to 250 mg/mL, from 3.5 mg/mL to 250 mg/mL, from 3.6 mg/mL to 250 mg/mL, from 3.7 mg/mL to 250

mg/mL, from 3.8 mg/mL to 250 mg/mL, from 3.9 mg/mL to 250 mg/mL, from 4.0 mg/mL to 250 mg/mL, from 5.0 mg/mL to 250 mg/mL, from 6.0 mg/mL to 250 mg/mL, from 7.0 mg/mL to 250 mg/mL, from 8.0 mg/mL to 250 mg/mL, from 9.0 mg/mL to 250 mg/mL, from 10 mg/mL to 250 mg/mL, from 15 mg/mL to 250 mg/mL, from 20 mg/mL to 250 mg/mL, from 25 mg/mL to 250 mg/mL, from 30 mg/mL to 250 mg/mL, from 35 mg/mL to 250 mg/mL, from 40 mg/mL to 250 mg/mL, from 45 mg/mL to 250 mg/mL, from 50 mg/mL to 250 mg/mL, from 55 mg/mL to 250 mg/mL, from 60 mg/mL to 250 mg/mL, from 65 mg/mL to 250 mg/mL, from 70 mg/mL to 250 mg/mL, from 75 mg/mL to 250 mg/mL, from 80 mg/mL to 250 mg/mL, from 85 mg/mL to 250 mg/mL, from 90 mg/mL to 250 mg/mL, from 95 mg/mL to 250 mg/mL, from 100 mg/mL to 250 mg/mL, from 105 mg/mL to 250 mg/mL, from 110 mg/mL to 250 mg/mL, from 115 mg/mL to 250 mg/mL, from 120 mg/mL to 250 mg/mL, from 125 mg/mL to 250 mg/mL, from 130 mg/mL to 250 mg/mL, from 135 mg/mL to 250 mg/mL, from 140 mg/mL to 250 mg/mL, from 145 mg/mL to 250 mg/mL, from 150 mg/mL to 250 mg/mL, from 155 mg/mL to 250 mg/mL, from 160 mg/mL to 250 mg/mL, from 165 mg/mL to 250 mg/mL, from 170 mg/mL to 250 mg/mL, from 175 mg/mL to 250 mg/mL, from 180 mg/mL to 250 mg/mL, from 185 mg/mL to 250 mg/mL, from 190 mg/mL to 250 mg/mL, from 195 mg/mL to 250 mg/mL, 200 mg/mL to 250 mg/mL, from 205 mg/mL to 250 mg/mL, from 210 mg/mL to 250 mg/mL, from 215 mg/mL to 250 mg/mL, from 220 mg/mL to 250 mg/mL, from 225 mg/mL to 250 mg/mL, from 230 mg/mL to 250 mg/mL, from 235 mg/mL to 250 mg/mL, from 240 mg/mL to 250 mg/mL, or from 245 mg/mL to 250 mg/mL.

[0772] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.1 mg/mL to 245 mg/mL, from 0.1 mg/mL to 240 mg/mL, from 0.1 mg/mL to 235 mg/mL, from 0.1 mg/mL to 230 mg/mL, from 0.1 mg/mL to 225 mg/mL, from 0.1 mg/mL to 220 mg/mL, from 0.1 mg/mL to 215 mg/mL, from 0.1 mg/mL to 210 mg/mL, from 0.1 mg/mL to 205 mg/mL, from 0.1 mg/mL to 200 mg/mL, from 0.1 mg/mL to 195 mg/mL, from 0.1 mg/mL to 190 mg/mL, from 0.1 mg/mL to 185 mg/mL, from 0.1 mg/mL to 180 mg/mL, from 0.1 mg/mL to 175 mg/mL, from 0.1 mg/mL to 170 mg/mL, from 0.1 mg/mL to 165 mg/mL, from 0.1 mg/mL to 160 mg/mL, from 0.1 mg/mL to 155 mg/mL, from 0.1 mg/mL to 150 mg/mL, from 0.1 mg/mL to 145 mg/mL, from 0.1 mg/mL to 140 mg/mL, from 0.1 mg/mL to 135 mg/mL, from 0.1 mg/mL to 130 mg/mL, from 0.1 mg/mL to 125 mg/mL, from 0.1 mg/mL to 120 mg/mL, from 0.1 mg/mL to 115 mg/mL, from 0.1 mg/mL to 110 mg/mL, from 0.1 mg/mL to 100 mg/mL, from 0.1 mg/mL to 95 mg/mL, from 0.1 mg/mL to 90 mg/mL, from 0.1 mg/mL to 85 mg/mL, from 0.1 mg/mL to 80 mg/mL, from 0.1 mg/mL to 75 mg/mL, from 0.1 mg/mL to 70 mg/mL, from 0.1 mg/mL to 65 mg/mL, from 0.1 mg/mL to 60 mg/mL, from 0.1 mg/mL to 55 mg/mL, from 0.1 mg/mL to 50 mg/mL, from 0.1 mg/mL to 45 mg/mL, from 0.1 mg/mL to 40 mg/mL, from 0.1 mg/mL to 35 mg/mL, from 0.1 mg/mL to 30 mg/mL, from 0.1 mg/mL to 25 mg/mL, from 0.1 mg/mL to 20 mg/mL, from 0.1 mg/mL to 15 mg/mL, from 0.1 mg/mL to 10 mg/mL, from 0.1 mg/mL to 9 mg/mL, from 0.1 mg/mL to 8 mg/mL, from 0.1 mg/mL to 7 mg/mL, from 0.1 mg/mL to 6 mg/mL, from 0.1 mg/mL to 5 mg/mL, from 0.1 mg/mL to 4 mg/mL, from 0.1

mg/mL to 3.9 mg/mL, from 0.1 mg/mL to 3.8 mg/mL, from 0.1 mg/mL to 3.7 mg/mL, from 0.1 mg/mL to 3.6 mg/mL, from 0.1 mg/mL to 3.5 mg/mL, from 0.1 mg/mL to 3.4 mg/mL, from 0.1 mg/mL to 3.3 mg/mL, from 0.1 mg/mL to 3.2 mg/mL, from 0.1 mg/mL to 3.1 mg/mL, from 0.1 mg/mL to 3.0 mg/mL, from 0.1 mg/mL to 2.9 mg/mL, from 0.1 mg/mL to 2.8 mg/mL, from 0.1 mg/mL to 2.7 mg/mL, from 0.1 mg/mL to 2.6 mg/mL, from 0.1 mg/mL to 2.5 mg/mL, from 0.1 mg/mL to 2.4 mg/mL, from 0.1 mg/mL to 2.3 mg/mL, from 0.1 mg/mL to 2.2 mg/mL, from 0.1 mg/mL to 2.1 mg/mL, from 0.1 mg/mL to 2.0 mg/mL, from 0.1 mg/mL to 1.9 mg/mL, from 0.1 mg/mL to 1.8 mg/mL, from 0.1 mg/mL to 1.7 mg/mL, from 0.1 mg/mL to 1.6 mg/mL, from 0.1 mg/mL to 1.5 mg/mL, from 0.1 mg/mL to 1.4 mg/mL, from 0.1 mg/mL to 1.3 mg/mL, from 0.1 mg/mL to 1.2 mg/mL, from 0.1 mg/mL to 1.1 mg/mL, from 0.1 mg/mL to 1.0 mg/mL, from 0.1 mg/mL to 0.9 mg/mL, from 0.1 mg/mL to 0.8 mg/mL, from 0.1 mg/mL to 0.7 mg/mL, from 0.1 mg/mL to 0.6 mg/mL, from 0.1 mg/mL to 0.5 mg/mL, from 0.1 mg/mL to 0.4 mg/mL, from 0.1 mg/mL to 0.3 mg/mL, or from 0.1 mg/mL to 0.2 mg/mL.

[0773] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211,

212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution.

[0774] In some embodiments, the pharmaceutical formulation does not comprise a preservative. In some embodiments, the pharmaceutical formulation comprises a preservative.

[0775] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration.

[0776] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be delivered to the brain/CNS through the intended route of administration. Routes of delivery to the CNS/brain include, but are not limited to intrathecal administration (*e.g.,* via the cisterna magna or via lumbar puncture), intracranial administration, *e.g.,* intracerebroventricular administration, or lateral cerebroventricular administration, endovascular administration, and intraparenchymal administration.

[0777] In some embodiments, the pharmaceutical formulation is suitable for an intracerebroventricular or intrathecal (IT) injection. Intrathecal administration: As used herein, the term "intrathecal administration" or "intrathecal injection" refers to an injection into the spinal canal (intrathecal space surrounding the spinal cord). Various techniques can be used, including, without limitation, lateral cerebroventricular injection through a lumen or lumen puncture or puncture hole or the like. In some embodiments, "intrathecal administration" or "intrathecal administration" in accordance with the present invention refers to administration or administration of IT through the lumbar area or region, *i.e.,* administration or administration of lumbar IT. As used herein, the term "lumbar region" or "lumbar area" refers to the area between the third and fourth lumbar vertebrae (lower back) and, more inclusive, the L2-S1 region of the spine vertebral.

[0778] In some embodiments, the pharmaceutical formulation is suitable for oral, rectal, intranasal, intradermal, subcutaneous, intrathecal, intracerebroventricular, intraperitoneal, intramuscular, intravitreal, intravenous, intracranial, intrabuccal, or sublingual administration. In some embodiments,

the pharmaceutical formulation is suitable for intradermal, subcutaneous, intrathecal, intranasal, intracranial, intracerebroventricular, intraperitoneal, intramuscular, intravitreal, or intravenous injection.

[0779] In some embodiments, the pharmaceutical formulation is packaged in a single use vial. In some embodiments, the pharmaceutical formulation is packaged in a multiple use vial.

[0780] Pharmaceutical formulations comprising the compound, *e.g.,* antisense oligomer, of the described compositions and for use in any of the described methods can be prepared according to conventional techniques well known in the pharmaceutical industry and described in the published literature. In some embodiments, a pharmaceutical formulation for treating a subject comprises an effective amount of any compound as described herein, or a pharmaceutically acceptable salt, solvate, hydrate or ester thereof. In some embodiments, the pharmaceutical composition described herein further comprises a pharmaceutically acceptable excipient, carrier, or diluent.

[0781] Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (*e.g.,* aluminum hydroxide); and preservatives.

[0782] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration.

[0783] In some embodiments, the compositions are formulated into any of many possible dosage forms such as, but not limited to, solutions, liquids, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. In some embodiments, the compositions are formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers. In some embodiments, a pharmaceutical formulation or composition of the present invention includes, but is not limited to, a solution, emulsion, microemulsion, foam or liposome-containing formulation (*e.g.,* cationic or noncationic liposomes).

[0784] The pharmaceutical composition or formulation described herein may comprise one or more penetration enhancers, carriers, excipients or other active or inactive ingredients as appropriate and well known to those of skill in the art or described in the published literature. In some embodiments, liposomes also include sterically stabilized liposomes, *e.g.,* liposomes comprising one or more specialized lipids. These specialized lipids result in liposomes with enhanced circulation lifetimes. In some embodiments, a sterically stabilized liposome comprises one or more glycolipids or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. In some embodiments, a surfactant is included in the pharmaceutical formulation or compositions. The use of surfactants in drug products, formulations and emulsions is well known in the art. In some embodiments, the present invention employs a penetration enhancer to effect the efficient delivery of the compound, *e.g.,* oligomer, *e.g.,* to aid diffusion across cell membranes and/or enhance the permeability of a lipophilic drug. In some embodiments, the penetration enhancers are a surfactant, fatty acid, bile salt, chelating agent, or non-chelating nonsurfactant.

[0785] In some embodiments, the pharmaceutical formulation comprises multiple compounds, *e.g.*, multiple antisense oligomers. In some embodiments, the compound (*e.g.*, antisense oligomer) is administered in combination with another drug or therapeutic agent.

[0786] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. Solutions or suspensions used for parenteral, intranasal, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. For example, depending on the injection site, the vehicle may contain water, synthetic or vegetable oil, and/or organic co-solvents. In certain instances, such as with lyophilized product or a concentrate, the parenteral formulation would be reconstituted or diluted prior to administration. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. Depot formulations, providing controlled or sustained release of an invention composition, may include injectable suspensions of nano/micro particles or nano/micro or non-micronized crystals.

[0787] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, poly(ol) (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the particle size in the case of dispersion and by the use of surfactants.

[0788] Sterile injectable solutions can be prepared by incorporating the composition in an appropriate solvent with one or a combination of ingredients enumerated above, followed by filtered sterilization. Prevention of the action of micro-organisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

[0789] Generally, dispersions are prepared by incorporating the active composition into a sterile vehicle which contains a basic dispersion medium and the other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0790] For oral administration, the compositions can be formulated in liquid or solid dosage forms and as instant or controlled/sustained release formulations. Suitable dosage forms for oral ingestion by a subject include powders, tablets, pills, granules, dragees, hard- and soft-shell capsules, liquids, gels, syrups, slurries, suspensions, emulsions and the like. Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active agent can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the agent in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, granules, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; dissolution retardant; anti-adherents; cationic exchange resin; wetting agents; antioxidants; preservatives; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a preservative; a colorant; a sweetening agent such as sugars such as dextrose, sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring, each of these being synthetic and/or natural.

[0791] For administration by inhalation, *e.g.,* intranasal administration, the compositions are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer. Systemic administration can also be by transmucosal or trans-dermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active agents are formulated into ointments, salves, gels, or creams, emulsion, a solution, a suspension, or a foam, as generally known in the art. The penetration of the drug into the skin and underlying tissues can be regulated, for example, using penetration enhancers; the appropriate choice and combination of lipophilic, hydrophilic, and amphiphilic excipients, including water, organic solvents, waxes, oils, synthetic and natural polymers, surfactants, emulsifiers; by pH adjustments; use of complexing agents and other techniques, such as iontophoresis, may be used to regulate skin penetration of the active ingredient.

[0792] The compositions may also be formulated in rectal compositions, such as suppositories (*e.g.,* with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas.

[0793] Examples of pharmaceutically or physiologically acceptable carriers, diluents or excipients include, but are not limited to, antifoaming agents, antioxidants, binders, carriers or carrier materials, dispersing agents, viscosity modulating agents, diluents, filling agents, lubricants, glidants, plasticizers, solubilizers, stabilizers, suspending agents, surfactants, viscosity enhancing agents, and wetting agents.

[0794] The separate components of the compositions of the invention may be preblended or each component may be added separately to the same environment according to a predetermined dosage for the purpose of achieving the desired concentration level of the treatment components and so long as the components eventually come into intimate admixture with each other. Further, the invention may be administered or delivered on a continuous or intermittent basis.

[0795] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier. The specification for the dosage unit forms of the invention is dictated by and directly dependent on the unique characteristics of the compositions and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

[0796] In some embodiments, provided herein is a method of producing the pharmaceutical formulation as described herein.

Combination Therapies

[0797] In some embodiments, the compounds disclosed in the present disclosure can be used in combination with one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents can comprise a small molecule. For example, the one or more additional therapeutic agents can comprise a small molecule described in WO2016128343A1, WO2017053982A1, WO2016196386A1, WO201428459A1, WO201524876A2, WO2013119916A2, and WO2014209841A2, which are incorporated by reference herein in their entirety. In some embodiments, the one or more additional therapeutic agents comprise an ASO that can be used to correct intron retention. In some embodiments, the one or more other agents are selected from the ASOs listed in **Table 7A** or **Table 7B**.

[0798] In some embodiments, the compounds disclosed in the present disclosure can be administered concomitantly with one or more anti-seizure medications to a human subject in need thereof. In some embodiments, the compounds disclosed herein can be administered concomitantly with at least one anti-seizure medication to a human subject in need thereof. In some embodiments, the compounds disclosed herein can be administered concomitantly with at least two anti-seizure medications to a human subject in need thereof. In some embodiments, the compounds disclosed herein can be administered concomitantly with at least three or four anti-seizure medications to a human subject in need thereof. In one nonlimiting embodiment, the at least one anti-seizure medication comprises fenfluramine.

Treatment of Subjects

[0799] Any of the compositions provided herein may be administered to an individual. “Individual” may be used interchangeably with “subject” or “patient.” An individual may be a mammal, for example a human or animal such as a non-human primate, a rodent, a rabbit, a rat, a mouse, a horse, a donkey, a goat, a cat, a dog, a cow, a pig, or a sheep. In some embodiments, the individual is a human. In some

embodiments, the individual is a fetus, an embryo, or a child. In other embodiments, the individual may be another eukaryotic organism, such as a plant. In some embodiments, the compositions provided herein are administered to a cell *ex vivo*.

[0800] In some embodiments, the compositions provided herein are administered to an individual as a method of treating a disease or disorder. In some embodiments, the individual has a genetic disease, such as any of the diseases described herein. In some embodiments, the individual is at risk of having a disease, such as any of the diseases described herein. In some embodiments, the individual is at increased risk of having a disease or disorder characterized by an insufficient amount of a protein or insufficient activity of a protein. If an individual is "at an increased risk" of having a disease or disorder caused insufficient amount of a protein or insufficient activity of a protein, the method involves preventative or prophylactic treatment. For example, an individual may be at an increased risk of having such a disease or disorder because of family history of the disease. Typically, individuals at an increased risk of having such a disease or disorder benefit from prophylactic treatment (*e.g.,* by preventing or delaying the onset or progression of the disease or disorder). In some embodiments, a fetus is treated in utero, *e.g.,* by administering the composition to the fetus directly or indirectly (*e.g.,* via the mother).

[0801] Suitable routes for administration of compounds of the present disclosure may vary depending on cell type to which delivery of the compounds is desired. Multiple tissues and organs are affected by Dravet syndrome; Epilepsy, generalized, with febrile seizures plus, type 2; Febrile seizures, familial, 3A; Migraine, familial hemiplegic, 3; Autism; Epileptic encephalopathy, early infantile, 13; Sick sinus syndrome 1; Alzheimer's disease or SUDEP, with the brain being the most significantly affected tissue. The compounds of the present disclosure may be administered to patients parenterally, for example, by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, intravitreal injection, or intravenous injection.

Mode of Action

[0802] In some embodiments, the reduced expression or function of $Na_V1.1$ protein is associated with an altered splicing of a nonsense-mediated RNA decay-inducing exon (NMD exon) from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein. For example, the reduced expression or function of $Na_V1.1$ protein can be associated with a reduced splicing of a nonsense-mediated RNA decay-inducing exon (NMD exon) from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein.

[0803] In some embodiments, the compound as described herein promotes exclusion of the NMD exon from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein.

[0804] In some embodiments, the compound as described herein promotes exclusion of the NMD exon from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 2000%, at least 3000%, at least 4000%, at least 5000%, at least 6000%, at least 7000%, at least 8000%, at least 9000%, at least 10000%, at least

20000%, at least 30000%, at least 40000%, at least 50000%, at least 60000%, at least 70000%, at least 80000%, at least 90000%, or at least 100000% as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique. In some embodiments, the compound as described herein promotes exclusion of the NMD exon a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 200 fold, at least 300 fold, at least 400 fold, at least 500 fold, at least 600 fold, at least 700 fold, at least 800 fold, at least 900 fold, at least 1000 fold, at least 2000 fold, at least 3000 fold, at least 4000 fold, at least 5000 fold, at least 6000 fold, at least 7000 fold, at least 8000 fold, at least 9000 fold, or at least 10000 fold as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique.

[0805] In some embodiments, the compound as described herein binds to a targeted portion of a pre-mRNA that contains a nonsense-mediated RNA decay-inducing exon and that encodes $Na_V1.1$ protein.

[0806] In some embodiments, the compound as described herein promotes exclusion of a nonsense-mediated mRNA decay-inducing exon (NMD exon) from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein.

[0807] In some embodiments, the compound as described herein promotes exclusion of an NMD exon from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 2000%, at least 3000%, at least 4000%, at least 5000%, at least 6000%, at least 7000%, at least 8000%, at least 9000%, at least 10000%, at least 20000%, at least 30000%, at least 40000%, at least 50000%, at least 60000%, at least 70000%, at least 80000%, at least 90000%, or at least 100000% as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique. In some embodiments, the compound as described herein promotes exclusion of an NMD exon from a pre-mRNA that contains the NMD exon and that encodes $Na_V1.1$ protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 200 fold, at least 300 fold, at least 400 fold, at least 500 fold, at least 600 fold, at least 700 fold, at least 800 fold, at least 900 fold, at least 1000 fold, at least 2000 fold, at least 3000 fold, at least 4000 fold, at least 5000 fold, at least 6000 fold, at least 7000 fold, at least 8000 fold, at least 9000 fold, or at least 10000 fold as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the

same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique.

[0808] In some embodiments, the compound as described herein increases a level of processed mRNA encoding the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell.

[0809] In some embodiments, when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell, the compound as described herein increases a level of processed mRNA encoding the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 2000%, at least 3000%, at least 4000%, at least 5000%, at least 6000%, at least 7000%, at least 8000%, at least 9000%, at least 10000%, at least 20000%, at least 30000%, at least 40000%, at least 50000%, at least 60000%, at least 70000%, at least 80000%, at least 90000%, or at least 100000% as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique. In some embodiments, when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell, the compound as described herein increases a level of processed mRNA encoding the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 200 fold, at least 300 fold, at least 400 fold, at least 500 fold, at least 600 fold, at least 700 fold, at least 800 fold, at least 900 fold, at least 1000 fold, at least 2000 fold, at least 3000 fold, at least 4000 fold, at least 5000 fold, at least 6000 fold, at least 7000 fold, at least 8000 fold, at least 9000 fold, or at least 10000 fold as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique.

[0810] In some embodiments, the compound as described herein increases a level of the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell.

[0811] In some embodiments, when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell, the compound as described herein increases a level of the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, at least

500%, at least 600%, at least 700%, at least 800%, at least 900%, at least 1000%, at least 2000%, at least 3000%, at least 4000%, at least 5000%, at least 6000%, at least 7000%, at least 8000%, at least 9000%, at least 10000%, at least 20000%, at least 30000%, at least 40000%, at least 50000%, at least 60000%, at least 70000%, at least 80000%, at least 90000%, or at least 100000% as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique. In some embodiments, when the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is introduced into the cell, the compound as described herein increases a level of the $Na_V1.1$ protein in a cell having a pre-mRNA that contains an NMD exon and that encodes $Na_V1.1$ protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 25 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, at least 200 fold, at least 300 fold, at least 400 fold, at least 500 fold, at least 600 fold, at least 700 fold, at least 800 fold, at least 900 fold, at least 1000 fold, at least 2000 fold, at least 3000 fold, at least 4000 fold, at least 5000 fold, at least 6000 fold, at least 7000 fold, at least 8000 fold, at least 9000 fold, or at least 10000 fold as compared to an untreated control cell, tissue or subject, or compared to the corresponding activity in the same type of cell, tissue or subject before treatment with the compound as described herein as measured by any standard technique.

[0812] In some embodiments, the targeted portion is within an intron sequence flanking the NMD exon.

[0813] In some embodiments, the targeted portion comprises at least one nucleotide of the NMD exon.

[0814] In some embodiments, the targeted portion comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 nucleotide(s) of the NMD exon. In some embodiments, the targeted portion comprises at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 nucleotide(s) of the NMD exon.

[0815] In some embodiments, the targeted portion is within the NMD exon.

[0816] In some embodiments, the NMD exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the NMD exon comprises a sequence selected from the group consisting of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in **Table 1** or **Table 2**.

Splicing and Nonsense-Mediated mRNA Decay

[0817] Intervening sequences or introns are removed by a large and highly dynamic RNA-protein complex termed the spliceosome, which orchestrates complex interactions between primary transcripts,

small nuclear RNAs (snRNAs) and a large number of proteins. Spliceosomes assemble ad hoc on each intron in an ordered manner, starting with recognition of the 5' splice site (5'ss) by U1 snRNA or the 3' splice site (3'ss) by the U2 pathway, which involves binding of the U2 auxiliary factor (U2AF) to the 3'ss region to facilitate U2 binding to the branch point sequence (BPS). U2AF is a stable heterodimer composed of a U2AF2-encoded 65-kD subunit (U2AF65), which binds the polypyrimidine tract (PPT), and a U2AF1-encoded 35-kD subunit (U2AF35), which interacts with highly conserved AG dinucleotides at 3'ss and stabilizes U2AF65 binding. In addition to the BPS/PPT unit and 3'ss/5'ss, auxiliary sequences or structures that activate or repress splice site recognition, known as intronic or exonic splicing enhancers or silencers, facilitate accurate splicing. These elements allow genuine splice sites to be recognized among a vast excess of cryptic or pseudo-sites in the genome of higher eukaryotes, which have the same sequences but outnumber authentic sites by an order of magnitude. Although they often have a regulatory function, the exact mechanisms of their activation or repression are poorly understood.

[0818] The decision of whether to splice or not to splice can be typically modeled as a stochastic rather than deterministic process, such that even the most defined splicing signals can sometimes splice incorrectly. However, under normal conditions, pre-mRNA splicing proceeds at surprisingly high fidelity. This is attributed in part to the activity of adjacent cis-acting auxiliary exonic and intronic splicing regulatory elements (ESRs or ISRs). Typically, these functional elements are classified as either exonic or intronic splicing enhancers (ESEs or ISEs) or silencers (ESSs or ISSs) based on their ability to stimulate or inhibit splicing, respectively. Although there is now evidence that some auxiliary cis-acting elements may act by influencing the kinetics of spliceosome assembly, such as the arrangement of the complex between U1 snRNP and the 5'ss, it seems very likely that many elements function in concert with trans-acting RNA-binding proteins (RBPs). For example, the serine- and arginine-rich family of RBPs (SR proteins) is a conserved family of proteins that have a key role in defining exons. SR proteins promote exon recognition by recruiting components of the pre-spliceosome to adjacent splice sites or by antagonizing the effects of ESSs in the vicinity. The repressive effects of ESSs can be mediated by members of the heterogeneous nuclear ribonucleoprotein (hnRNP) family and can alter recruitment of core splicing factors to adjacent splice sites. In addition to their roles in splicing regulation, silencer elements are suggested to have a role in repression of pseudo-exons, sets of decoy intronic splice sites with the typical spacing of an exon but without a functional open reading frame. ESEs and ESSs, in cooperation with their cognate trans-acting RBPs, represent important components in a set of splicing controls that specify how, where and when mRNAs are assembled from their precursors.

[0819] The sequences marking the exon-intron boundaries are degenerate signals of varying strengths that can occur at high frequency within human genes. In multi-exon genes, different pairs of splice sites can be linked together in many different combinations, creating a diverse array of transcripts from a single gene. This is commonly referred to as alternative pre-mRNA splicing. Although most mRNA isoforms produced by alternative splicing can be exported from the nucleus and translated into functional polypeptides, different mRNA isoforms from a single gene can vary greatly in their translation

efficiency. Those mRNA isoforms with premature termination codons (PTCs) at least 50 bp upstream of an exon junction complex are likely to be targeted for degradation by the nonsense-mediated mRNA decay (NMD) pathway. Mutations in traditional (BPS/PPT/3'ss/5'ss) and auxiliary splicing motifs can cause aberrant splicing, such as exon skipping or cryptic (or pseudo-) exon inclusion or splice-site activation, and contribute significantly to human morbidity and mortality. Both aberrant and alternative splicing patterns can be influenced by natural DNA variants in exons and introns.

[0820] Given that exon-intron boundaries can occur at any of the three positions of a codon, it is clear that only a subset of alternative splicing events can maintain the canonical open reading frame. For example, only exons that are evenly divisible by 3 can be skipped or included in the mRNA without any alteration of reading frame. Splicing events that do not have compatible phases will induce a frameshift. Unless reversed by downstream events, frameshifts can certainly lead to one or more PTCs, probably resulting in subsequent degradation by NMD. NMD is a translation-coupled mechanism that eliminates mRNAs containing PTCs. NMD can function as a surveillance pathway that exists in all eukaryotes. NMD can reduce errors in gene expression by eliminating mRNA transcripts that contain premature stop codons. Translation of these aberrant mRNAs could, in some cases, lead to deleterious gain-of-function or dominant-negative activity of the resulting proteins. NMD targets not only transcripts with PTCs but also a broad array of mRNA isoforms expressed from many endogenous genes, suggesting that NMD is a master regulator that drives both fine and coarse adjustments in steady-state RNA levels in the cell.

[0821] An NMD-inducing exon (NIE) is an exon or a pseudo-exon that is a region within an intron and can activate the NMD pathway if included in a mature RNA transcript. In the constitutive splicing events, the intron containing an NIE is usually spliced out, but the intron or a portion thereof (*e.g.,* NIE) can be retained during alternative or aberrant splicing events. Mature mRNA transcripts containing such an NIE can be non-productive due to frame shift which induce NMD pathway. Inclusion of a NIE in mature RNA transcripts can downregulate gene expression. mRNA transcripts, such as a pre-mRNA transcript, containing an NIE can be referred as "NIE containing mRNA" or "NMD exon mRNA" in the current disclosure.

[0822] Cryptic (or pseudo-splice sites) have the same splicing recognition sequences as genuine splice sites but are not used in the splicing reactions. They outnumber genuine splice sites in the human genome by an order of a magnitude and are normally repressed by thus far poorly understood molecular mechanisms. Cryptic 5' splice sites have the consensus NNN/GUNNNN or NNN/GCNNNN where N is any nucleotide and/is the exon-intron boundary. Cryptic 3' splice sites have the consensus NAG/N. Their activation is positively influenced by surrounding nucleotides that make them more similar to the optimal consensus of authentic splice sites, namely MAG/GURAGU and YAG/G, respectively, where M is C or A, R is G or A, and Y is C or U.

[0823] Splice sites and their regulatory sequences can be readily identified by a skilled person using suitable algorithms publicly available, listed for example in Kralovicova, J. and Vorechovsky, I. (2007) Global control of aberrant splice site activation by auxiliary splicing sequences: evidence for a gradient

in exon and intron definition. Nucleic Acids Res., 35, 6399-6413, (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095810/pdf/gkm680.pdf)

[0824] The cryptic splice sites or splicing regulatory sequences may compete for RNA-binding proteins such as U2AF with a splice site of the NIE. In one embodiment, an agent may bind to the cryptic splice site or splicing regulatory sequences to prevent the binding of RNA-binding proteins and thereby favoring utilization of the NIE splice sites.

[0825] In one embodiment, the cryptic splice site may not comprise the 5' or 3' splice site of the NIE. The cryptic splice site may be at least 10 nucleotides upstream of the NIE 5' splice site. The cryptic splice site may be at least 20 nucleotides upstream of the NIE 5' splice site. The cryptic splice site may be at least 50 nucleotides upstream of the NIE 5' splice site. The cryptic splice site may be at least 100 nucleotides upstream of the NIE 5' splice site. The cryptic splice site may be at least 200 nucleotides upstream of the NIE 5' splice site.

[0826] The cryptic splice site may be at least 10 nucleotides downstream of the NIE 3' splice site. The cryptic splice site may be at least 20 nucleotides downstream of the NIE 3' splice site. The cryptic splice site may be at least 50 nucleotides downstream of the NIE 3' splice site. The cryptic splice site may be at least 100 nucleotides downstream of the NIE 3' splice site. The cryptic splice site may be at least 200 nucleotides downstream of the NIE 3' splice site.

[0827] In some embodiments, the methods of the present disclosure exploit the presence of NIE in the pre-mRNA transcribed from the *SCN1A* gene. Splicing of the identified SCN1A NIE pre-mRNA species to produce functional mature *Scn1a* mRNA can be induced using a therapeutic agent such as an ASO that stimulates exon skipping of an NIE. Induction of exon skipping can result in inhibition of an NMD pathway. The resulting mature *Scn1a* mRNA can be translated normally without activating NMD pathway, thereby increasing the amount of $Na_V1.1$ (also termed "$Na_V1.1$ protein" herein) in the patient's cells and alleviating symptoms of a condition associated with SCN1A deficiency, such as Dravet Syndrome (DS); Epilepsy, generalized, with febrile seizures plus, type 2; Febrile seizures, familial, 3A; Autism; Epileptic encephalopathy, early infantile, 13; Sick sinus syndrome 1; Alzheimer's disease; or SUDEP.

[0828] Where reference is made to reducing NIE inclusion in the mature mRNA, the reduction may be complete, *e.g.,* 100%, or may be partial. The reduction may be clinically significant. The reduction/correction may be relative to the level of NIE inclusion in the subject without treatment, or relative to the amount of NIE inclusion in a population of similar subjects. The reduction/correction may be at least 10% less NIE inclusion relative to the average subject, or the subject prior to treatment. The reduction may be at least 20% less NIE inclusion relative to an average subject, or the subject prior to treatment. The reduction may be at least 40% less NIE inclusion relative to an average subject, or the subject prior to treatment. The reduction may be at least 50% less NIE inclusion relative to an average subject, or the subject prior to treatment. The reduction may be at least 60% less NIE inclusion relative to an average subject, or the subject prior to treatment. The reduction may be at least 80% less NIE

inclusion relative to an average subject, or the subject prior to treatment. The reduction may be at least 90% less NIE inclusion relative to an average subject, or the subject prior to treatment.

[0829] Where reference is made to increasing active-$Na_V1.1$ protein levels, the increase may be clinically significant. The increase may be relative to the level of active-$Na_V1.1$ protein in the subject without treatment, or relative to the amount of active-$Na_V1.1$ protein in a population of similar subjects. The increase may be at least 10% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 20% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 40% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 50% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 80% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 100% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 200% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment. The increase may be at least 500% more active-$Na_V1.1$ protein relative to the average subject, or the subject prior to treatment.

Exon Inclusion

[0830] As used herein, a "NIE containing pre-mRNA" is a pre-mRNA transcript that contains at least one pseudo-exon. Alternative or aberrant splicing can result in inclusion of the at least one pseudo-exon in the mature mRNA transcripts. The terms "mature mRNA," and "fully spliced mRNA," are used interchangeably herein to describe a fully processed mRNA. Inclusion of the at least one pseudo-exon can be non-productive mRNA and lead to NMD of the mature mRNA. NIE containing mature mRNA may sometimes lead to aberrant protein expression.

[0831] One of skill in the art also can determine the sequences of flanking exons in any SCN1A isoform for targeting using the methods of the disclosure, based on an intron sequence provided herein or using the intron number provided in reference to the mRNA sequence at NM_006920, NM_001202435, NM_001165964, or NM_001165963.

[0832] In some embodiments, the methods and compositions of the present disclosure are used to modulate, *e.g.,* increase or decrease, the expression of SCN1A by inducing or inhibiting exon skipping of a pseudo-exon of an SCN1A NIE containing pre-mRNA. In some embodiments, the pseudo-exon is a sequence within any of introns 1-25. In some embodiments, the pseudo-exon is a sequence within any of introns 2, 4, 6, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, and 25. In some embodiments, the pseudo-exon is a sequence within any of introns 15, 18, and 19. In some embodiments, the pseudo-exon can be any SCN1A intron or a portion thereof. In some embodiments, the pseudo-exon is within intron 20. The SCN1A intron numbering used herein corresponds to the mRNA sequence at NM_006920. It is understood that the intron numbering may change in reference to a different SCN1A isoform sequence.

[0833] In some embodiments, the included pseudo-exon is the most abundant pseudo-exon in a population of NIE containing pre-mRNAs transcribed from the gene encoding the target protein in a cell. In some embodiments, the included pseudo-exon is the most abundant pseudo-exon in a population of

NIE containing pre-mRNAs transcribed from the gene encoding the target protein in a cell, where-in the population of NIE containing pre-mRNAs comprises two or more included pseudo-exons. In some embodiments, an antisense oligomer targeted to the most abundant pseudo-exon in the population of NIE containing pre-mRNAs encoding the target protein induces exon skipping of one or two or more pseudo-exons in the population, including the pseudo-exon to which the antisense oligomer is targeted or binds. In some embodiments, the targeted region is in a pseudo-exon that is the most abundant pseudo-exon in a NIE containing pre-mRNA encoding the $Na_V1.1$ protein.

[0834] The degree of exon inclusion can be expressed as percent exon inclusion, *e.g.,* the percentage of transcripts in which a given pseudo-exon is included. In brief, percent exon inclusion can be calculated as the percentage of the amount of RNA transcripts with the exon inclusion, over the sum of the average of the amount of RNA transcripts with exon inclusion plus the average of the amount of RNA transcripts with exon exclusion.

[0835] In some embodiments, an included pseudo-exon is an exon that is identified as an included pseudo-exon based on a determination of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50%, inclusion. In some embodiments, a included pseudo-exon is an exon that is identified as a included pseudo-exon based on a determination of about 5% to about 100%, about 5% to about 95%, about 5% to about 90%, about 5% to about 85%, about 5% to about 80%, about 5% to about 75%, about 5% to about 70%, about 5% to about 65%, about 5% to about 60%, about 5% to about 55%, about 5% to about 50%, about 5% to about 45%, about 5% to about 40%, about 5% to about 35%, about 5% to about 30%, about 5% to about 25%, about 5% to about 20%, about 5% to about 15%, about 10% to about 100%, about 10% to about 95%, about 10% to about 90%, about 10% to about 85%, about 10% to about 80%, about 10% to about 75%, about 10% to about 70%, about 10% to about 65%, about 10% to about 60%, about 10% to about 55%, about 10% to about 50%, about 10% to about 45%, about 10% to about 40%, about 10% to about 35%, about 10% to about 30%, about 10% to about 25%, about 10% to about 20%, about 15% to about 100%, about 15% to about 95%, about 15% to about 90%, about 15% to about 85%, about 15% to about 80%, about 15% to about 75%, about 15% to about 70%, about 15% to about 65%, about 15% to about 60%, about 15% to about 55%, about 15% to about 50%, about 15% to about 45%, about 15% to about 40%, about 15% to about 35%, about 15% to about 30%, about 15% to about 25%, about 20% to about 100%, about 20% to about 95%, about 20% to about 90%, about 20% to about 85%, about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 25% to about 100%, about 25% to about 95%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, or about 25% to about 35%, inclusion. ENCODE data (described by, *e.g.,* Tilgner, *et al.*, 2012, "Deep sequencing of subcellular RNA fractions shows splicing to be predominantly co-

transcriptional in the human genome but inefficient for lncRNAs," Genome Research 22(9):1616-25, of which entire content is incorporated herein by reference) can be used to aid in identifying exon inclusion.

[0836] In some embodiments, contacting cells with an ASO that is complementary to a targeted portion of a *SCN1A* pre-mRNA transcript results in an increase in the amount of $Na_V1.1$ protein produced by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In some embodiments, the total amount of $Na_V1.1$ protein produced by the cell to which the antisense oligomer is contacted is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the amount of target protein produced by a control compound. A control compound can be, for example, an oligonucleotide that is not complementary to a targeted portion of the pre-mRNA.

[0837] In some embodiments, contacting cells with an ASO that is complementary to a targeted portion of a *SCN1A* pre-mRNA transcript results in a decrease in the amount of $Na_V1.1$ protein produced by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In some embodiments, the total amount of $Na_V1.1$ protein produced by the cell to which the antisense oligomer is contacted is decreased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the amount of target protein produced by a control compound. A control compound can be, for example, an oligonucleotide that is not complementary to a targeted portion of the pre-mRNA.

[0838] In some embodiments, contacting cells with an ASO that is complementary to a targeted portion of a *SCN1A* pre-mRNA transcript results in an increase in the amount of mRNA encoding SCN1A, including the mature mRNA encoding the target protein. In some embodiments, the amount of mRNA encoding $Na_V1.1$ protein, or the mature mRNA encoding the $Na_V1.1$ protein, is increased by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In some embodiments, the

total amount of the mRNA encoding $Na_V1.1$ protein, or the mature mRNA encoding $Na_V1.1$ protein produced in the cell to which the antisense oligomer is contacted is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold compared to the amount of mature RNA produced in an untreated cell, *e.g.,* an untreated cell or a cell treated with a control compound. A control compound can be, for example, an oligonucleotide that is not complementary to a targeted portion of the SCN1A NIE containing pre-mRNA.

[0839] In some embodiments, contacting cells with an ASO that is complementary to a targeted portion of a *SCN1A* pre-mRNA transcript results in a decrease in the amount of mRNA encoding SCN1A, including the mature mRNA encoding the target protein. In some embodiments, the amount of mRNA encoding $Na_V1.1$ protein, or the mature mRNA encoding the $Na_V1.1$ protein, is decreased by at least 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1000%, compared to the amount of the protein produced by a cell in the absence of the ASO/absence of treatment. In some embodiments, the total amount of the mRNA encoding $Na_V1.1$ protein, or the mature mRNA encoding $Na_V1.1$ protein produced in the cell to which the antisense oligomer is contacted is decreased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold compared to the amount of mature RNA produced in an untreated cell, *e.g.,* an untreated cell or a cell treated with a control compound. A control compound can be, for example, an oligonucleotide that is not complementary to a targeted portion of the SCN1A NIE containing pre-mRNA.

[0840] The NIE can be in any length. In some embodiments, the NIE can be a portion of the intron. In some embodiments, the NIE can be a 5' end portion of an intron including a 5'ss sequence. In some embodiments, the NIE can be a 3' end portion of an intron including a 3'ss sequence. In some embodiments, the NIE can be a portion within an intron without inclusion of a 5'ss sequence. In some embodiments, the NIE can be a portion within an intron without inclusion of a 3'ss sequence. In some embodiments, the NIE can be a portion within an intron without inclusion of either a 5'ss or a 3'ss sequence. In some embodiments, the NIE can be from 5 nucleotides to 10 nucleotides in length, from 10 nucleotides to 15 nucleotides in length, from 15 nucleotides to 20 nucleotides in length, from 20

nucleotides to 25 nucleotides in length, from 25 nucleotides to 30 nucleotides in length, from 30 nucleotides to 35 nucleotides in length, from 35 nucleotides to 40 nucleotides in length, from 40 nucleotides to 45 nucleotides in length, from 45 nucleotides to 50 nucleotides in length, from 50 nucleotides to 55 nucleotides in length, from 55 nucleotides to 60 nucleotides in length, from 60 nucleotides to 65 nucleotides in length, from 65 nucleotides to 70 nucleotides in length, from 70 nucleotides to 75 nucleotides in length, from 75 nucleotides to 80 nucleotides in length, from 80 nucleotides to 85 nucleotides in length, from 85 nucleotides to 90 nucleotides in length, from 90 nucleotides to 95 nucleotides in length, or from 95 nucleotides to 100 nucleotides in length. In some embodiments, the NIE can be at least 10 nucleotides, at least 20 nucleotides, at least 30 nucleotides, at least 40 nucleotides, at least 50 nucleotides, at least 60 nucleoids, at least 70 nucleotides, at least 80 nucleotides in length, at least 90 nucleotides, or at least 100 nucleotides in length. In some embodiments, the NIE can be from 100 to 200 nucleotides in length, from 200 to 300 nucleotides in length, from 300 to 400 nucleotides in length, from 400 to 500 nucleotides in length, from 500 to 600 nucleotides in length, from 600 to 700 nucleotides in length, from 700 to 800 nucleotides in length, from 800 to 900 nucleotides in length, or from 900 to 1,000 nucleotides in length. In some embodiments, the NIE may be longer than 1,000 nucleotides in length.

[0841] Inclusion of a pseudo-exon can lead to a frameshift and the introduction of a premature termination codon (PIC) in the mature mRNA transcript rendering the transcript a target of NMD. Mature mRNA transcript containing NIE can be non-productive mRNA transcript which does not lead to protein expression. The PIC can be present in any position downstream of an NIE. In some embodiments, the PIC can be present in any exon downstream of an NIE. In some embodiments, the PIC can be present within the NIE. For example, inclusion of exon 20x in an mRNA transcript encoded by the *SCN1A* gene can induce a PIC in the mRNA transcript, *e.g.,* a PIC in exon 21 of the mRNA transcript.

[0842] ASOs that when hybridized to a region of a pre-mRNA result in exon skipping (or enhanced splicing of the intron containing a NIE) and increased protein production may be tested *in vivo* using animal models, for example transgenic mouse models in which the full-length human gene has been knocked-in or in humanized mouse models of disease. Suitable routes for administration of ASOs may vary depending on the disease and/or the cell types to which delivery of the ASOs is desired. ASOs may be administered, for example, by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, intravitreal injection, or intravenous injection. Following administration, the cells, tissues, and/or organs of the model animals may be assessed to determine the effect of the treatment by for example evaluating splicing (efficiency, rate, extent) and protein production by methods known in the art and described herein. The animal models may also be any phenotypic or behavioral indication of the disease or disease severity.

[0843] In some embodiments, the compound (*e.g.,* ASO) is administered with one or more agents capable of promoting penetration of the subject compound across the blood-brain barrier by any method known in the art. For example, delivery of agents by administration of an adenovirus vector to motor neurons in muscle tissue is described in U.S. Pat. No. 6,632,427, "Adenoviral-vector-mediated gene

transfer into medullary motor neurons," incorporated herein by reference. Delivery of vectors directly to the brain, *e.g.,* the striatum, the thalamus, the hippocampus, or the substantia nigra, is described, *e.g.,* in U.S. Pat. No. 6,756,523, "Adenovirus vectors for the transfer of foreign genes into cells of the central nervous system particularly in brain," incorporated herein by reference.

[0844] In some embodiments, the compounds (*e.g.,* ASOs) are linked or conjugated with agents that provide desirable pharmaceutical or pharmacodynamic properties. In some embodiments, the compound is coupled to a substance, known in the art to promote penetration or transport across the blood-brain barrier, *e.g.,* an antibody to the transferrin receptor. In some embodiments, the compound is linked with a viral vector, *e.g.,* to render the antisense compound more effective or increase transport across the blood-brain barrier. In some embodiments, osmotic blood brain barrier disruption is assisted by infusion of sugars, *e.g.,* meso erythritol, xylitol, D(+) galactose, D(+) lactose, D(+) xylose, dulcitol, myo-inositol, L(-) fructose, D(-) mannitol, D(+) glucose, D(+) arabinose, D(-) arabinose, cellobiose, D(+) maltose, D(+) raffinose, L(+) rhamnose, D(+) melibiose, D(-) ribose, adonitol, D(+) arabitol, L(-) arabitol, D(+) fucose, L(-) fucose, D(-) lyxose, L(+) lyxose, and L(-) lyxose, or amino acids, *e.g.,* glutamine, lysine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine, and taurine. Methods and materials for enhancing blood brain barrier penetration are described, *e.g.,* in U.S. Pat. No. 9,193,969, "Compositions and methods for selective delivery of oligonucleotide molecules to specific neuron types," U.S. Pat. No. 4,866,042, "Method for the delivery of genetic material across the blood brain barrier," U.S. Pat. No. 6,294,520, "Material for passage through the blood-brain barrier," and U.S. Pat. No. 6,936,589, "Parenteral delivery systems," each incorporated herein by reference.

[0845] In some embodiments, a compound of the disclosure is coupled to a dopamine reuptake inhibitor (DRI), a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), and a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI), using methods described in, *e.g.,* U.S. Pat. No. 9,193,969, incorporated herein by reference.

[0846] In some embodiments, subjects treated using the methods and compositions are evaluated for improvement in condition using any methods known and described in the art.

[0847] In some embodiments, the SCN1A NIE containing pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the SCN1A NIE pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**.

[0848] In some embodiments, the SCN1A NIE containing pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, SCN1A NIE containing pre-mRNA transcript is encoded by a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the targeted portion of the pre-

mRNA containing an NMD exon and encoding $Na_V1.1$ comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of any one of the sequences listed in **Table 1** or **Table 2**.

[0849] In some embodiments, the pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a pre-mRNA transcript of *SCN1A* pre-mRNA transcripts or a complement thereof described herein. In some embodiments, the targeted portion of the pre-mRNA selected from the group consisting of *SCN1A* pre-mRNAs comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of a sequence of the pre-mRNA transcripts of **Table 1** or **Table 2** or complements thereof. In some embodiments, the targeted portion of the pre-mRNA of *SCN1A* pre-mRNA comprises a sequence that is complementary to at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides of a sequence of **Table 1** or **Table 2** or a complement thereof.

[0850] In some embodiments, the pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a pre-mRNA transcript of *SCN1A* pre-mRNA transcripts or a complement thereof described herein. In some embodiments, the targeted portion of the pre-mRNA selected from the group consisting of *SCN1A* pre-mRNAs comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of a sequence of the pre-mRNA transcripts of **Table 1** or **Table 2** or complements thereof. In some embodiments, the targeted portion of the pre-mRNA of *SCN1A* pre-mRNA comprises a sequence that is complementary to at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleotides of a sequence of **Table 1** or **Table 2** or a complement thereof.

[0851] In some embodiments, the targeted portion of the *SCN1A* pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of a sequence of sequence of **Table 3** or complements thereof. In some embodiments, the targeted portion of the *SCN1A* pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleotides of a sequence selected from the group consisting of sequences listed in **Table 2** or **Table 3** or complements thereof.

[0852] In some embodiments, the ASO has a sequence complementary to the targeted portion of the pre-mRNA containing an NMD exon according to any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the ASO targets a sequence upstream from the 5' end of an NIE. For example, ASOs targeting a sequence upstream from the 5' end of an NIE comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complementary to at least 8 contiguous nucleotides of any one of the sequences listed in **Table 1** or **Table 2**. For example, ASOs targeting a sequence upstream from the 5' end of an NIE can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**.

[0853] In some embodiments, the ASOs target a sequence containing an exon-intron boundary (or junction). For example, ASOs targeting a sequence containing an exon-intron boundary can comprise a

sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complementary to at least 8 contiguous nucleotides of any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, the ASOs target a sequence downstream from the 3' end of an NIE. For example, ASOs targeting a sequence downstream from the 3' end of an NIE can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**. For example, ASOs targeting a sequence downstream from the 3' end of an NIE can comprise a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of the sequences listed in **Table 1** or **Table 2**. In some embodiments, ASOs target a sequence within an NIE.

Methods of Identifying Additional ASOs that Induce Exon Skipping

[0854] Also within the scope of the present disclosure are methods for identifying or determining ASOs that induce exon skipping of a SCN1A NIE containing pre-mRNA. For example, a method can comprise identifying or determining ASOs that induce pseudo-exon skipping of a SCN1A NIE containing pre-mRNA. ASOs that specifically hybridize to different nucleotides within the target region of the pre-mRNA may be screened to identify or determine ASOs that improve the rate and/or extent of splicing of the target intron. In some embodiments, the ASO may block or interfere with the binding site(s) of a splicing repressor(s)/silencer. Any method known in the art may be used to identify (determine) an ASO that when hybridized to the target region of the exon results in the desired effect (*e.g.*, pseudo-exon skipping, protein or functional RNA production). These methods also can be used for identifying ASOs that induce exon skipping of the included exon by binding to a targeted region in an intron flanking the included exon, or in a non-included exon. An example of a method that may be used is provided below.

[0855] A round of screening, referred to as an ASO "walk" may be performed using ASOs that have been designed to hybridize to a target region of a pre-mRNA. For example, the ASOs used in the ASO walk can be tiled every 5 nucleotides from approximately 100 nucleotides upstream of the 3' splice site of the included exon (*e.g.*, a portion of sequence of the exon located upstream of the target/included exon) to approximately 100 nucleotides downstream of the 3' splice site of the target/included exon and/or from approximately 100 nucleotides upstream of the 5' splice site of the included exon to approximately 100 nucleotides downstream of the 5' splice site of the target/included exon (*e.g.*, a portion of sequence of the exon located downstream of the target/included exon). For example, a first ASO of 15 nucleotides in length may be designed to specifically hybridize to nucleotides +6 to +20 relative to the 3' splice site of the target/included exon. A second ASO may be designed to specifically hybridize to nucleotides +11 to +25 relative to the 3' splice site of the target/included exon. ASOs are designed as such spanning the target region of the pre-mRNA. In some embodiments, the ASOs can be tiled more closely, *e.g.*, every 1, 2, 3, or 4 nucleotides. Further, the ASOs can be tiled from 100 nucleotides downstream of the 5' splice site, to 100 nucleotides upstream of the 3' splice site. In some embodiments, the ASOs can be tiled from about 1,160 nucleotides upstream of the 3' splice site, to about 500 nucleotides downstream of the 5' splice site. In some embodiments, the ASOs can be tiled from about 500 nucleotides upstream of the 3' splice site, to about 1,920 nucleotides downstream of the 3' splice site.

[0856] One or more ASOs, or a control ASO (an ASO with a scrambled sequence, sequence that is not expected to hybridize to the target region) are delivered, for example by transfection, into a disease-relevant cell line that expresses the target pre-mRNA (*e.g.,* a NIE containing pre-mRNA described herein). The exon skipping effects of each of the ASOs may be assessed by any method known in the art, for example by reverse transcriptase (RT)-PCR using primers that span the splice junction. A reduction or absence of a longer RT-PCR product produced using the primers spanning the region containing the included exon (*e.g.,* including the flanking exons of the NIE) in ASO-treated cells as compared to in control ASO-treated cells indicates that splicing of the target NIE has been enhanced. In some embodiments, the exon skipping efficiency (or the splicing efficiency to splice the intron containing the NIE), the ratio of spliced to unspliced pre-mRNA, the rate of splicing, or the extent of splicing may be improved using the ASOs described herein. The amount of protein or functional RNA that is encoded by the target pre-mRNA can also be assessed to determine whether each ASO achieved the desired effect (*e.g.,* enhanced functional protein production). Any method known in the art for assessing and/or quantifying protein production, such as Western blotting, flow cytometry, immunofluorescence microscopy, and ELISA, can be used.

[0857] A second round of screening, referred to as an ASO "micro-walk" may be performed using ASOs that have been designed to hybridize to a target region of a pre-mRNA. The ASOs used in the ASO micro-walk are tiled every 1 nucleotide to further refine the nucleotide acid sequence of the pre-mRNA that when hybridized with an ASO results in exon skipping (or enhanced splicing of NIE).

[0858] Regions defined by ASOs that promote splicing of the target intron are explored in greater detail by means of an ASO "micro-walk", involving ASOs spaced in 1-nt steps, as well as longer ASOs, typically 18-25 nt.

[0859] As described for the ASO walk above, the ASO micro-walk is performed by delivering one or more ASOs, or a control ASO (an ASO with a scrambled sequence, sequence that is not expected to hybridize to the target region), for example by transfection, into a disease-relevant cell line that expresses the target pre-mRNA. The splicing-inducing effects of each of the ASOs may be assessed by any method known in the art, for example by reverse transcriptase (RT)-PCR using primers that span the NIE, as described herein. A reduction or absence of a longer RT-PCR product produced using the primers spanning the NIE in ASO-treated cells as compared to in control ASO-treated cells indicates that exon skipping (or splicing of the target intron containing an NIE) has been enhanced. In some embodiments, the exon skipping efficiency (or the splicing efficiency to splice the intron containing the NIE), the ratio of spliced to unspliced pre-mRNA, the rate of splicing, or the extent of splicing may be improved using the ASOs described herein. The amount of protein or functional RNA that is encoded by the target pre-mRNA can also be assessed to determine whether each ASO achieved the desired effect (*e.g.,* enhanced functional protein production). Any method known in the art for assessing and/or quantifying protein production, such as Western blotting, flow cytometry, immunofluorescence microscopy, and ELISA, can be used.

Kits and Compositions

[0860] In some aspects, provided herein is a kit comprising: a concentrate comprising a compound disclosed herein and a diluent, wherein the concentrate is miscible with the diluent; and instructions for diluting or solubilizing the compound in the diluent. In some aspects, provided herein is a kit comprising: a concentrate comprising an antisense oligomer (ASO), wherein the ASO comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099; and a diluent, wherein the concentrate is miscible with the diluent; and instructions for diluting or solubilizing the ASO in the diluent. In some embodiments, the ASO comprises a sequence with at least 80% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0861] In some embodiments, the ASO comprises a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099. In some embodiments, the ASO comprises a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**. In some embodiments, the ASO consists of a sequence with at least 60%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 884%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.8%, 99.9%, or 100% sequence identity to any one of the sequences listed in listed in **Tables 4A, 4B, 5A, 5B, 6, 7A,** and **7B**.

[0862] In some embodiments, the diluent is an artificial cerebral spinal fluid (aCSF) solution. In some embodiments, the solution comprises a cerebral spinal fluid (CSF) sample from the subject. In some embodiments, the diluent comprises an isotonic solution. In some embodiments, the diluent comprises a phosphate-buffered (pH 6.6 – 7.6) solution.

[0863] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.6-7.6) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 6.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered (pH 5.0-8.0) solution. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.5, pH 4.6-8.5, pH 4.7-8.5, pH 4.8-8.5, pH 4.9-8.5, pH5.0-8.5, pH 5.1-8.5, pH 5.2-8.5, pH 5.3-8.5, pH 5.4-8.5, pH 5.5-8.5, pH 5.6-8.5, pH 5.7-8.5, pH 5.8-8.5, pH 5.9-8.5, pH 6.0-

8.5, pH 6.1-8.5, pH 6.2-8.5, pH 6.3-8.5, pH 6.4-8.5, pH 6.5-8.5, pH 6.6-8.5, pH 6.7-8.5, pH 6.8-8.5, pH 6.9-8.5, pH 7.0-8.5, pH 7.1-8.5, pH 7.2-8.5, pH 7.3-8.5, pH 7.4-8.5, pH 7.5-8.5, pH 7.6-8.5, pH 7.7-8.5, pH 7.8-8.5, pH 7.9-8.5, pH 8.0-8.5, pH 8.1-8.5, pH 8.2-8.5, pH 8.3-8.5, or pH 8.4-8.5. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 4.5-8.3, pH 4.5-8.2, pH 4.5-8.1, pH 4.5-8.0, pH 4.5-7.9, pH 4.5-7.8, pH 4.5-7.7, pH 4.5-7.6, pH 4.5-7.5, pH 4.5-7.4, pH 4.5-7.3, pH 4.5-7.2, pH 4.5-7.1, pH 4.5-7.0, pH 4.5-6.9, pH 4.5-6.8, pH 4.5-6.7, pH 4.5-6.6, pH 4.5-6.5, pH 4.5-6.4, pH 4.5-6.3, pH 4.5-6.2, pH 4.5-6.1, pH 4.5-6.0, pH 4.5-5.9, pH 4.5-5.8, pH 4.5-5.7, pH 4.5-5.6, pH 4.5-5.5, pH 4.5-5.4, pH 4.5-5.3, pH 4.5-5.2, pH 4.5-5.1, pH 4.5-5.0, pH 4.5-4.9, pH 4.5-4.8, pH 4.5-4.7, or pH 4.5-4.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.6, pH 6.1-7.6, pH 6.2-7.6, pH 6.3-7.6, pH 6.4-7.6, pH 6.5-7.6, pH 6.6-7.6, pH 6.7-7.6, pH 6.8-7.6, pH 6.9-7.6, pH 7.0-7.6, pH 7.1-7.6, pH 7.2-7.6, pH 7.3-7.6, pH 7.4-7.6, or pH 7.5-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.6-8.0, pH 6.6-7.9, pH 6.6-7.8, pH 6.6-7.7, pH 6.6-7.6, pH 6.6-7.5, pH 6.6-7.4, pH 6.6-7.3, pH 6.6-7.2, pH 6.6-7.1, pH 6.6-7.0, pH 6.6-6.9, pH 6.6-6.8, or pH 6.6-6.7. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-8.0, pH 6.1-8.0, pH 6.2-8.0, pH 6.3-8.0, pH 6.4-8.0, pH 6.5-8.0, pH 6.6-8.0, pH 6.7-8.0, pH 6.8-8.0, pH 6.9-8.0, pH 7.0-8.0, pH 7.1-8.0, pH 7.2-8.0, pH 7.3-8.0, pH 7.4-8.0, pH 7.5-8.0, pH 7.6-8.0, pH 7.7-8.0, pH 7.8-8.0, or pH 7.9-8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 6.0-7.9, pH 6.0-7.8, pH 6.0-7.7, pH 6.0-7.6, pH 6.0-7.5, pH 6.0-7.4, pH 6.0-7.3, pH 6.0-7.2, pH 6.0-7.1, pH 6.0-7.0, pH 6.0-6.9, pH 6.0-6.8, pH 6.0-6.7, pH 6.0-6.6, pH 6.0-6.5, pH 6.0-6.4, pH 6.0-6.3, pH 6.0-6.2, or pH 6.0-6.1. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.7-8.5, 5.8-8.4, 5.9-8.3, 6.0-8.2, 6.1-8.1, 6.2-8.0, 6.3-7.9, 6.4-7.8, 6.5-7.7, or 6.6-7.6. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a phosphate-buffered solution with pH 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, or 8.0.

[0864] In some embodiments, the diluent comprises 25-250 mM NaCl.

[0865] In some embodiments, the diluent comprises 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, 195-250, 200-250, 205-250, 210-250, 215-250, 220-250,

225-250, 230-250, 235-250, 240-250, or 245-250 mM NaCl. In some embodiments, the diluent comprises 25-245, 25-240, 25-235, 25-230, 25-225, 25-220, 25-215, 25-210, 25-205, 25-200, 25-195, 25-190, 25-185, 25-180, 25-175, 25-170, 25-165, 25-160, 25-155, 25-150, 25-145, 25-140, 25-135, 25-130, 25-125, 25-120, 25-115, 25-110, 25-105, 25-110, 25-105, 25-100, 25-95, 25-90, 25-85, 25-80, 25-75, 25-70, 25-65, 25-60, 25-55, 25-50, 25-45, 25-40, 25-35, or 25-30 mM NaCl. In some embodiments, the diluent comprises 30-245, 35-240, 40-235, 45-230, 50-225, 55-220, 60-215, 65-210, 70-205, 75-200, 80-195, 85-190, 90-185, 95-180, 100-175, 105-170, 110-165, 115-160, 120-155, 125-150, 130-145 or 135-140 mM NaCl. In some embodiments, the diluent comprises 100-140, 101-140, 102-140, 103-140, 104-140, 105-140, 106-140, 107-140, 108-140, 109-140, 110-140, 111-140, 112-140, 113-140, 114-140, 115-140, 116-140, 117-140, 118-140, 119-140, 120-140, 121-140, 122-140, 123-140, 124-140, 125-140, 126-140, 127-140, 128-140, 129-140, 130-140, 131-140, 132-140, 133-140, 134-140, 135-140, 136-140, 137-140, 138-140, or 139-140 mM NaCl. In some embodiments, the diluent comprises 100-139, 100-138, 100-137, 100-136, 100-135, 100-134, 100-133, 100-132, 100-131, 100-130, 100-129, 100-128, 100-127, 100-126, 100-125, 100-124, 100-123, 100-122, 100-121, 100-120, 100-119, 100-118, 100-117, 100-116, 100-115, 100-114, 100-113, 100-112, 100-111, 100-110, 100-109, 100-108, 100-107, 100-106, 100-105, 100-104, 100-103, 100-102, or 100-101 mM NaCl. In some embodiments, the diluent comprises at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the diluent comprises at most 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl. In some embodiments, the diluent comprises 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140 mM NaCl.

[0866] In some embodiments, the diluent comprises 0.1-20 mM KCl.

[0867] In some embodiments, the diluent comprises 0.1-40, 0.1-39, 0.1-38, 0.1-37, 0.1-36, 0.1-35, 0.1-34, 0.1-33, 0.1-32, 0.1-31, 0.1-30, 0.1-29, 0.1-28, 0.1-27, 0.1-26, 0.1-25, 0.1-24, 0.1-23, 0.1-22, 0.1-21, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, or 0.1-1 mM KCl. In some embodiments, the diluent comprises 0.2-40, 0.3-40, 0.4-40, 0.5-40, 0.6-40, 0.7-40, 0.8-40, 0.9-40, 1-40, 2-40, 3-40, 4-40, 5-40, 6-40, 7-40, 8-40, 9-40, 10-40, 11-40, 12-40, 13-40, 14-40, 15-40, 16-40, 17-40, 18-40, 19-40, 20-40, 21-40, 22-40, 23-40, 24-40, 25-40, 26-40, 27-40, 28-40, 29-40, 30-40, 31-40, 32-40, 33-40, 34-40, 35-40, 36-40, 37-40, 38-40, or 39-40 mM KCl. In some embodiments, the diluent comprises 0.1-3.5, 0.2-3.5, 0.3-3.5, 0.4-3.5, 0.5-3.5, 0.6-3.5, 0.7-3.5, 0.8-3.5, 0.9-3.5, 1.0-3.5, 1.1-3.5, 1.2-3.5, 1.3-3.5, 1.4-3.5, 1.5-3.5, 1.6-3.5, 1.7-3.5, 1.8-3.5, 1.9-3.5, 2.0-3.5, 2.1-3.5, 2.2-3.5, 2.3-3.5, 2.4-3.5, 2.5-3.5, 2.6-3.5, 2.7-3.5, 2.8-3.5, 2.9-3.5, 3.0-3.5, 3.1-3.5, 3.2-3.5, 3.3-3.5, or 3.4-3.5 mM KCl. In some embodiments, the diluent comprises 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-

1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM KCl. In some embodiments, the diluent comprises at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the diluent comprises at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl. In some embodiments, the diluent comprises 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 mM KCl.

[0868] In some embodiments, the diluent comprises 0.1-50 mM $CaCl_2$.

[0869] In some embodiments, the diluent comprises 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $CaCl_2$. In some embodiments, the diluent comprises 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $CaCl_2$. In some embodiments, the diluent comprises at least 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the diluent comprises at most 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$. In some embodiments, the diluent comprises 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $CaCl_2$.

[0870] In some embodiments, the diluent comprises 0.1-50 mM $MgCl_2$.

[0871] In some embodiments, the diluent comprises 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1.0-50, -50, 1.1-50, 1.2-50, 1.3-50, 1.4-50, 1.5-50, 1.6-50, 1.7-50, 1.8-50, 1.9-50, 2.0-50, 2.1-50, 2.2-50, 2.3-50, 2.4-50, 2.5-50, 2.6-50, 2.7-50, 2.8-50, 2.9-50, 3.0-50, 3.1-50, 3.2-50, 3.3-50, 3.4-50, 3.5-50, 3.6-50, 3.7-50, 3.8-50, 3.9-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 10-50, 15-50, 20-50, 25-50, 1 30-50, 35-50, 40-50, or 45-50 mM $MgCl_2$. In some embodiments, the diluent comprises 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-15, 0.1-10, 0.1-5, 0.1-4, 0.1-4.9, 0.1-4.8, 0.1-4.7, 0.1-4.6, 0.1-4.5, 0.1-4.4, 0.1-4.3, 0.1-4.2, 0.1-4.1, 0.1-4.0, 0.1-3.9, 0.1-3.8, 0.1-3.7, 0.1-3.6, 0.1-3.5, 0.1-3.4, 0.1-3.3, 0.1-3.2, 0.1-3.1, 0.1-3.0, 0.1-2.9, 0.1-2.8, 0.1-2.7, 0.1-2.6, 0.1-2.5, 0.1-2.4, 0.1-2.3, 0.1-2.2, 0.1-2.1, 0.1-2.0, 0.1-1.9, 0.1-1.8, 0.1-1.7, 0.1-1.6, 0.1-1.5, 0.1-1.4, 0.1-1.3, 0.1-1.2, 0.1-1.1, 0.1-1.0, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM $MgCl_2$. In some embodiments the diluent comprises at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some

embodiments, the diluent comprises at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$. In some embodiments, the diluent comprises 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM $MgCl_2$.

[0872] In some embodiments, the diluent lacks sodium phosphate. In some cases, the diluent lacks phosphate ion. In some cases, the diluent lacks Na_2HPO_4 and/or NaH_2PO_4. In some of these cases, the diluent comprises In some embodiments, calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM; magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM; potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM; sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and water. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is 0.2 mM to 25 mM, 0.5 mM to 10 mM, 0.75 mM to 5 mM, or 1 mM to 2 mM. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is from about 1 mM to about 2 mM. In some cases, the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM. In some cases, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is 0.2 mM to 25 mM, 0.3 mM to 15 mM, 0.4 mM to 5 mM, 0.5 mM to 1.5 mM, or 0.6 mM to 1 mM. In some cases, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) in the diluent is from about 0.6 mM to about 1 mM. In some cases, the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) in the diluent is about 0.79 mM. In some cases, the concentration of potassium chloride in the diluent is 0.5 mM to 10 mM, 1 mM to 7.5 mM, or 2 mM to 5 mM. In some cases, the concentration of potassium chloride in the diluent is from about 2 mM to about 5 mM. In some cases, the concentration of potassium chloride in the diluent is about 3 mM. In some cases, the concentration of sodium chloride in the diluent is 25 mM to 250 mM, 100 mM to 160 mM, 110 mM to 140 mM, or 130 mM to 160 mM. In some cases, the concentration of sodium chloride in the diluent is from about 125 mM to 145 mM. In some cases, the concentration of sodium chloride in the diluent is about 130 mM. In some cases, the concentration of sodium chloride in the diluent is from about 140 mM to 160 mM. In some cases, the concentration of sodium chloride in the diluent is about 150 mM. In some cases, the concentration of the compound in the diluent provided herein is about 3 mg/mL, about 4.5 mg/mL, about 7 mg/mL, or about 33 mg/mL; the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM; the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM; the concentration of potassium chloride is about 3 mM; and the concentration of sodium chloride is about 150 mM. In some cases, the diluent comprises (a) calcium ion (Ca^{2+}) at a concentration of about 0.1 mM to about 50 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.1 mM to about 50 mM; (c) potassium ion (K^+) at a concentration of about 0.1 mM to about 20 mM; (d) sodium ion (Na^+) at a concentration of about 25 mM to about 250 mM; (e) chloride ion (Cl^-) at a

concentration of about 25 mM to about 250 mM; and (f) water. In some cases, the diluent comprises (a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM; (b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM; (c) potassium ion (K^{+}) at a concentration of about 3 mM; (d) sodium ion (Na^{+}) at a concentration of about 160 mM; (e) chloride ion (Cl^{-}) at a concentration of about 160 mM; and (f) water.

[0873] In some embodiments, the diluent comprises 0-50 mM Na_2HPO_4.

[0874] In some embodiments, the diluent comprises 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM Na_2HPO_4. In some embodiments, the diluent comprises 0.1-50, 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-11, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM Na_2HPO_4. In some embodiments, the diluent comprises 0-50, 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1-50, 2-50, 3-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 1-50, 11-50, 12-50, 13-50, 14-50, 15-50, 16-50, 17-50, 18-50, 19-50, 20-50, 25-50, 30-50, 35-50, 40-50, or 45-50 mM Na_2HPO_4. In some embodiments, the diluent comprises 0-20, 0.1-20, 0.2-20, 0.3-20, 0.4-20, 0.5-20, 0.6-20, 0.7-20, 0.8-20, 0.9-20, 1-20, 2-20, 3-20, 4-20, 5-20, 6-20, 7-20, 8-20, 9-20, 10-20, 11-20, 12-20, 13-20, 14-20, 15-20, 16-20, 17-20, 18-20, or 19-20 mM Na_2HPO_4. In some embodiments, the diluent comprises at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM Na_2HPO_4. In some embodiments, the diluent comprises at most 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM Na_2HPO_4. In some embodiments, the diluent comprises 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM Na_2HPO_4.

[0875] In some embodiments, the diluent comprises 0-50 mM NaH_2PO_4.

[0876] In some embodiments, the diluent comprises 0-50, 0-45, 0-40, 0-35, 0-30, 0-25, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.9, 0-0.8, 0-0.7, 0-0.6, 0-0.5, 0-0.4, 0-0.3, or 0-0.2 mM NaH_2PO_4. In some embodiments, the diluent comprises 0.1-50, 0.1-45, 0.1-40, 0.1-35, 0.1-30, 0.1-25, 0.1-20, 0.1-19, 0.1-18, 0.1-17, 0.1-16, 0.1-15, 0.1-14, 0.1-13, 0.1-12, 0.1-11, 0.1-10, 0.1-9, 0.1-8, 0.1-7, 0.1-6, 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1, 0.1-0.9, 0.1-0.8, 0.1-0.7, 0.1-0.6, 0.1-0.5, 0.1-0.4, 0.1-0.3, or 0.1-0.2 mM NaH_2PO_4. In some embodiments, the diluent comprises 0-50, 0.1-50, 0.2-50, 0.3-50, 0.4-50, 0.5-50, 0.6-50, 0.7-50, 0.8-50, 0.9-50, 1-50, 2-50, 3-50, 4-50, 5-50, 6-50, 7-50, 8-50, 9-50, 1-50, 11-50, 12-50, 13-50, 14-50, 15-50, 16-50, 17-50, 18-50, 19-50, 20-50, 25-50, 30-50, 35-50, 40-50, or 45-50 mM NaH_2PO_4. In some embodiments, the diluent comprises 0-20, 0.1-20, 0.2-20, 0.3-20, 0.4-20, 0.5-20, 0.6-20, 0.7-20, 0.8-20, 0.9-20, 1-20, 2-20, 3-20, 4-20, 5-20, 6-20, 7-20, 8-20, 9-20, 10-20, 11-20, 12-20, 13-20, 14-20, 15-20, 16-20, 17-20, 18-20, or 19-20 mM NaH_2PO_4. In some embodiments, the diluent comprises at least 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the diluent comprises at most 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4. In some embodiments, the diluent comprises 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mM NaH_2PO_4.

[0877] In some embodiments, the diluent comprises 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof.

[0878] In some embodiments, the diluent comprises 1-100 mM $NaHCO_3$.

[0879] In some embodiments, the diluent comprises 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $NaHCO_3$. In some embodiments, the diluent comprises 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $NaHCO_3$. In some embodiments, the diluent comprises 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $NaHCO_3$. In some embodiments, the diluent comprises 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0, 26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $NaHCO_3$. In some embodiments, the diluent comprises at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the diluent comprises at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$. In some embodiments, the diluent comprises 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $NaHCO_3$.

[0880] In some embodiments, the diluent comprises 1-100 mM $KHCO_3$.

[0881] In some embodiments, the diluent comprises 1-99, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-25, 1-20, 1-15, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM $KHCO_3$. In some embodiments, the diluent comprises 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 15-100, 20-100, 25-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM $KHCO_3$. In some embodiments, the diluent comprises 24.0-28.0, 24.0-27.9, 24.0-27.8, 24.0-27.7, 24.0-27.6, 24.0-27.5, 24.0-27.4, 24.0-27.3, 24.0-27.2, 24.0-27.1, 24.0-27.0, 24.0-26.9, 24.0-26.8, 24.0-26.7, 24.0-26.6, 24.0-26.5, 24.0-26.4, 24.0-26.3, 24.0-26.2, 24.0-26.1, 24.0-26.0, 24.0-25.9, 4.0-25.8, 24.0-25.7, 24.0-25.6, 24.0-25.5, 24.0-25.4, 24.0-25.3, 24.0-25.2, 24.0-25.1, 24.0-25.0, 24.0-24.9, 24.0-24.8, 24.0-24.7, 24.0-24.6, 24.0-24.5, 24.0-24.4, 24.0-24.3, 24.0-24.2, or 24.0-24.1 mM $KHCO_3$. In some embodiments, the diluent comprises 24.1-28.0, 24.2-28.0, 24.3-28.0, 24.4-28.0, 24.5-28.0, 24.6-28.0, 24.7-28.0, 24.8-28.0, 24.9-28.0, 25.0-28.0, 25.1-

28.0, 25.2-28.0, 25.3-28.0, 25.4-28.0, 25.5-28.0, 25.6-28.0, 25.7-28.0, 25.8-28.0, 25.9-28.0, 26.0-28.0, 26.1-28.0, 26.2-28.0, 26.3-28.0, 26.4-28.0, 26.5-28.0, 26.6-28.0, 26.7-28.0, 26.8-28.0, 26.9-28.0, 27.0-28.0, 27.1-28.0, 27.2-28.0, 27.3-28.0, 27.4-28.0, 27.5-28.0, 27.6-28.0, 27.7-28.0, 27.8-28.0, or 27.9-28.0 mM $KHCO_3$. In some embodiments, the diluent comprises at least 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the diluent comprises at most 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$. In some embodiments, the diluent comprises 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, or 28.0 mM $KHCO_3$.

[0882] In some embodiments, the diluent comprises 1-100 mM D-glucose.

[0883] In some embodiments, the diluent comprises 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM D-glucose. In some embodiments, the diluent comprises 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 11-100, 12-100, 13-100, 14-100, 15-100, 16-100, 17-100, 18-100, 19-100, 20-100, 21-100, 22-100, 23-100, 24-100, 25-100, 26-100, 29-100, 28-100, 29-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM D-glucose. In some embodiments, the diluent comprises 2-30, 3-30, 4-30, 5-30, 6-30, 7-30, 8-30, 9-30, 10-30, 11-30, 12-30, 13-30, 14-30, 15-30, 16-30, 17-30, 18-30, 19-30, 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 26-30, 27-30, 28-30, or 29-30 mM D-glucose. In some embodiments, the diluent comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the diluent comprises at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose. In some embodiments, the diluent comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM D-glucose.

[0884] In some embodiments, the diluent comprises 1-100, 1-95, 1-90, 1-85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 mM glucose. In some embodiments, the diluent comprises 2-100, 3-100, 4-100, 5-100, 6-100, 7-100, 8-100, 9-100, 10-100, 11-100, 12-100, 13-100, 14-100, 15-100, 16-100, 17-100, 18-100, 19-100, 20-100, 21-100, 22-100, 23-100, 24-100, 25-100, 26-100, 29-100, 28-100, 29-100, 30-100, 35-100, 40-100, 45-100, 50-100, 55-100, 60-100, 65-100, 70-100, 75-100, 80-100, 85-100, 90-100, or 95-100 mM glucose. In some embodiments, the diluent comprises 2-30, 3-30, 4-30, 5-30, 6-30, 7-30, 8-30, 9-30, 10-30, 11-30, 12-30, 13-30, 14-30, 15-30, 16-30, 17-30, 18-30, 19-30, 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 26-30, 27-30, 28-30, or 29-30 mM glucose. In some embodiments, the diluent comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose. In some embodiments, the diluent comprises at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose. In some embodiments, the diluent comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mM glucose.

[0885] In some embodiments, the diluent comprises 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na_2HPO_4, 0.1-50 mM NaH_2PO_4, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0886] In some embodiments, the diluent comprises 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$.

[0887] In some embodiments, the diluent further comprises an antioxidant. In some embodiments, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted in a buffer further comprising an antioxidant, wherein the antioxidant is ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, α-tocopherol (vitamin E), ubiquinol (coenzyme Q), or any combination thereof.

[0888] In some embodiments, the diluent comprises 25-250 mM NaCl, 0.1-20 mM KCl, 0-50 mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, 0.1-50 mM $MgCl_2$, or any combinations thereof.

[0889] In some embodiments, the diluent comprises 25-250 mM NaCl, 0.1-20 mM KCl, 0-50 mM KH_2PO_4, 1-100 mM $NaHCO_3$, 0-50 mM NaH_2PO_4, 1-100 mM D-glucose, 0.1-50 mM $CaCl_2$, and 0.1-50 mM $MgCl_2$.

[0890] In some embodiments, the diluent comprises 127 mM NaCl, 1.0 mM KCl, 1.2 mM KH_2PO_4, 26 mM $NaHCO_3$, 10 mM D-glucose, 2.4 mM $CaCl_2$, and 1.3 mM $MgCl_2$.

[0891] In some embodiments, the diluent comprises 119 mM NaCl, 26.2 mM $NaHCO_3$, 2.5 mM KCl, 1 mM NaH_2PO_4, 1.3 mM $MgCl_2$, 10 mM glucose, and 2.5 mM $CaCl_2$.

[0892] In some embodiments, the diluent does not comprise a preservative. In some embodiments, the diluent comprises a preservative.

[0893] In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 5-200 mg/mL in the diluent.

[0894] In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 5-250, 5-247.5, 5-245, 5-242.5, 5-240, 5-237.5, 5-235, 5-232.5, 5-230, 5-227.5, 5-225, 5-225.5, 5-220, 5-217.5, 5-215, 5-212.5, 5-210, 5-205.5, 5-205, 5-202.5, 5-200, 5-197.5, 5-195, 5-192.5, 5-190, 5-187.5, 5-185, 5-182.5, 5-180, 5-177.5, 5-175, 5-172.5, 5-170, 5-167.5, 5-165, 5-162.5, 5-160, 5-157.5, 5-155, 5-152.5, 5-150, 5-147.5, 5-145, 5-142.5, 5-140, 5-137.5, 5-135, 5-132.5, 5-130, 5-127.5, 5-125, 5-122.5, 5-120, 5-117.5, 5-115, 5-112.5, 5-110, 5-107.5, 5-105, 5-102.5, 5-100, 5-97.5, 5-

95, 5-92.5, 5-90, 5-87.5, 5-85, 5-82.5, 5-80, 5-77.5, 5-75, 5-72.5, 5-70, 5-67.5, 5-65, 5-62.5, 5-60, 5-57.5, 5-55, 5-52.5, 5-50, 5-47.5, 5-45, 5-42.5, 5-40, 5-37.5, 5-35, 5-32.5, 5-30, 5-27.5, 5-25, 5-22.5, 5-20, 5-17.5, 5-15, 5-12.5, or 5-10 mg/mL in the diluent. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 10-250, 15-250, 20-250, 25-250, 30-250, 35-250, 40-250, 45-250, 50-250, 55-250, 60-250, 65-250, 70-250, 75-250, 80-250, 85-250, 90-250, 95-250, 100-250, 105-250, 110-250, 115-250, 120-250, 125-250, 130-250, 135-250, 140-250, 145-250, 150-250, 155-250, 160-250, 165-250, 170-250, 175-250, 180-250, 185-250, 190-250, or 195-250, 200-250, 205-250, 210-250, 215-250, 220-250, 225-250, 230-250, 235-250, 240-250, or 245-250 mg/mL in the diluent. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the diluent. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the diluent. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39,

40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the diluent.

[0895] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, or 20 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160 mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, or 200 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of about 22.5 mg/mL, 25 mg/mL, 27.5 mg/mL, 30 mg/mL, 32.5 mg/mL, 35 mg/mL, 37.5 mg/mL, 40 mg/mL, 42.5 mg/mL, 45 mg/mL, 47.5 mg/mL, 50 mg/mL, 52.5 mg/mL, 55 mg/mL, 57.5 mg/mL, 60 mg/mL, 62.5 mg/mL, 65 mg/mL, 67.5 mg/mL, 70 mg/mL, 72.5 mg/mL, 75 mg/mL, 77.5 mg/mL, 80 mg/mL, 82.5 mg/mL, 85 mg/mL, 87.5 mg/mL, 90 mg/mL, 92.5 mg/mL, 95 mg/mL, 97.5 mg/mL, 100 mg/mL, 102.5 mg/mL, 105 mg/mL, 107.5 mg/mL, 110 mg/mL, 112.5 mg/mL, 115 mg/mL, 117.5 mg/mL, 120 mg/mL, 122.5 mg/mL, 125 mg/mL, 127.5 mg/mL, 130 mg/mL, 132.5 mg/mL, 135 mg/mL, 137.5 mg/mL, 140 mg/mL, 142.5 mg/mL, 145 mg/mL, 147.5 mg/mL, 150 mg/mL, 152.5 mg/mL, 155 mg/mL, 157.5 mg/mL, 160 mg/mL, 162.5 mg/mL, 165 mg/mL, 167.5 mg/mL, 170 mg/mL, 172.5 mg/mL, 175 mg/mL, 177.5 mg/mL, 180 mg/mL, 182.5 mg/mL, 185 mg/mL, 187.5 mg/mL, 190 mg/mL, 192.5 mg/mL, 195 mg/mL, 197.5 mg/mL, 200 mg/mL, 202.5 mg/mL, 205 mg/mL, 207.5 mg/mL, 210 mg/mL, 212.5 mg/mL, 215 mg/mL, 217.5 mg/mL, 220 mg/mL, 222.5 mg/mL, 225 mg/mL, 227.5 mg/mL, 230 mg/mL, 232.5 mg/mL, 235 mg/mL, 237.5 mg/mL, 240 mg/mL, 242.5 mg/mL, 245 mg/mL, 247.5 mg/mL, or 250 mg/mL. In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or

compound (II)) is solubilized or diluted to a concentration of 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL in the diluent.

[0896] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.2 mg/mL to 250 mg/mL, from 0.3 mg/mL to 250 mg/mL, from 0.4 mg/mL to 250 mg/mL, from 0.5 mg/mL to 250 mg/mL, from 0.6 mg/mL to 250 mg/mL, from 0.7 mg/mL to 250 mg/mL, from 0.8 mg/mL to 250 mg/mL, from 0.9 mg/mL to 250 mg/mL, from 1.0 mg/mL to 250 mg/mL, from 1.1 mg/mL to 250 mg/mL, from 1.2 mg/mL to 250 mg/mL, from 1.3 mg/mL to 250 mg/mL, from 1.4 mg/mL to 250 mg/mL, from 1.5 mg/mL to 250 mg/mL, from 1.6 mg/mL to 250 mg/mL, from 1.7 mg/mL to 250 mg/mL, from 1.8 mg/mL to 250 mg/mL, from 1.9 mg/mL to 250 mg/mL, from 2.0 mg/mL to 250 mg/mL, from 2.1 mg/mL to 250 mg/mL, from 2.2 mg/mL to 250 mg/mL, from 2.3 mg/mL to 250 mg/mL, from 2.4 mg/mL to 250 mg/mL, from 2.5 mg/mL to 250 mg/mL, from 2.6 mg/mL to 250 mg/mL, from 2.7 mg/mL to 250 mg/mL, from 2.8 mg/mL to 250 mg/mL, from 2.9 mg/mL to 250 mg/mL, from 3.0 mg/mL to 250 mg/mL, from 3.1 mg/mL to 250 mg/mL, from 3.2 mg/mL to 250 mg/mL, from 3.3 mg/mL to 250 mg/mL, from 3.4 mg/mL to 250 mg/mL, from 3.5 mg/mL to 250 mg/mL, from 3.6 mg/mL to 250 mg/mL, from 3.7 mg/mL to 250 mg/mL, from 3.8 mg/mL to 250 mg/mL, from 3.9 mg/mL to 250 mg/mL, from 4.0 mg/mL to 250 mg/mL, from 5.0 mg/mL to 250 mg/mL, from 6.0 mg/mL to 250 mg/mL, from 7.0 mg/mL to 250 mg/mL, from 8.0 mg/mL to 250 mg/mL, from 9.0 mg/mL to 250 mg/mL, from 10 mg/mL to 250 mg/mL, from 15 mg/mL to 250 mg/mL, from 20 mg/mL to 250 mg/mL, from 25 mg/mL to 250 mg/mL, from 30 mg/mL to 250 mg/mL, from 35 mg/mL to 250 mg/mL, from 40 mg/mL to 250 mg/mL, from 45 mg/mL to 250 mg/mL, from 50 mg/mL to 250 mg/mL, from 55 mg/mL to 250 mg/mL, from 60 mg/mL to 250 mg/mL, from 65 mg/mL to 250 mg/mL, from 70 mg/mL to 250 mg/mL, from 75 mg/mL to 250 mg/mL, from 80 mg/mL to 250 mg/mL, from 85 mg/mL to 250 mg/mL, from 90 mg/mL to 250 mg/mL, from 95 mg/mL to 250 mg/mL, from 100 mg/mL to 250 mg/mL, from 105 mg/mL to 250 mg/mL, from 110 mg/mL to 250 mg/mL, from 115 mg/mL to 250 mg/mL, from 120 mg/mL to 250 mg/mL, from 125 mg/mL to 250 mg/mL, from 130 mg/mL to 250 mg/mL, from 135 mg/mL to 250 mg/mL, from 140 mg/mL to 250 mg/mL, from 145 mg/mL to 250 mg/mL, from 150 mg/mL to 250 mg/mL, from 155 mg/mL to 250 mg/mL, from 160 mg/mL to 250 mg/mL, from 165 mg/mL to 250 mg/mL, from 170 mg/mL to 250 mg/mL, from 175 mg/mL to 250 mg/mL, from 180 mg/mL to 250 mg/mL, from 185 mg/mL to 250 mg/mL, from 190 mg/mL to 250 mg/mL, from 195 mg/mL to 250 mg/mL, 200 mg/mL to 250 mg/mL, from 205 mg/mL to 250 mg/mL, from 210 mg/mL to 250 mg/mL, from 215 mg/mL to 250 mg/mL, from 220 mg/mL to 250 mg/mL, from 225 mg/mL to 250 mg/mL, from 230 mg/mL to 250 mg/mL, from 235 mg/mL to 250 mg/mL, from 240 mg/mL to 250 mg/mL, or from 245 mg/mL to 250 mg/mL.

[0897] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL, from 0.1 mg/mL to 245 mg/mL, from 0.1 mg/mL to 240 mg/mL, from 0.1 mg/mL to 235

mg/mL, from 0.1 mg/mL to 230 mg/mL, from 0.1 mg/mL to 225 mg/mL, from 0.1 mg/mL to 220 mg/mL, from 0.1 mg/mL to 215 mg/mL, from 0.1 mg/mL to 210 mg/mL, from 0.1 mg/mL to 205 mg/mL, from 0.1 mg/mL to 200 mg/mL, from 0.1 mg/mL to 195 mg/mL, from 0.1 mg/mL to 190 mg/mL, from 0.1 mg/mL to 185 mg/mL, from 0.1 mg/mL to 180 mg/mL, from 0.1 mg/mL to 175 mg/mL, from 0.1 mg/mL to 170 mg/mL, from 0.1 mg/mL to 165 mg/mL, from 0.1 mg/mL to 160 mg/mL, from 0.1 mg/mL to 155 mg/mL, from 0.1 mg/mL to 150 mg/mL, from 0.1 mg/mL to 145 mg/mL, from 0.1 mg/mL to 140 mg/mL, from 0.1 mg/mL to 135 mg/mL, from 0.1 mg/mL to 130 mg/mL, from 0.1 mg/mL to 125 mg/mL, from 0.1 mg/mL to 120 mg/mL, from 0.1 mg/mL to 115 mg/mL, from 0.1 mg/mL to 110 mg/mL, from 0.1 mg/mL to 100 mg/mL, from 0.1 mg/mL to 95 mg/mL, from 0.1 mg/mL to 90 mg/mL, from 0.1 mg/mL to 85 mg/mL, from 0.1 mg/mL to 80 mg/mL, from 0.1 mg/mL to 75 mg/mL, from 0.1 mg/mL to 70 mg/mL, from 0.1 mg/mL to 65 mg/mL, from 0.1 mg/mL to 60 mg/mL, from 0.1 mg/mL to 55 mg/mL, from 0.1 mg/mL to 50 mg/mL, from 0.1 mg/mL to 45 mg/mL, from 0.1 mg/mL to 40 mg/mL, from 0.1 mg/mL to 35 mg/mL, from 0.1 mg/mL to 30 mg/mL, from 0.1 mg/mL to 25 mg/mL, from 0.1 mg/mL to 20 mg/mL, from 0.1 mg/mL to 15 mg/mL, from 0.1 mg/mL to 10 mg/mL, from 0.1 mg/mL to 9 mg/mL, from 0.1 mg/mL to 8 mg/mL, from 0.1 mg/mL to 7 mg/mL, from 0.1 mg/mL to 6 mg/mL, from 0.1 mg/mL to 5 mg/mL, from 0.1 mg/mL to 4 mg/mL, from 0.1 mg/mL to 3.9 mg/mL, from 0.1 mg/mL to 3.8 mg/mL, from 0.1 mg/mL to 3.7 mg/mL, from 0.1 mg/mL to 3.6 mg/mL, from 0.1 mg/mL to 3.5 mg/mL, from 0.1 mg/mL to 3.4 mg/mL, from 0.1 mg/mL to 3.3 mg/mL, from 0.1 mg/mL to 3.2 mg/mL, from 0.1 mg/mL to 3.1 mg/mL, from 0.1 mg/mL to 3.0 mg/mL, from 0.1 mg/mL to 2.9 mg/mL, from 0.1 mg/mL to 2.8 mg/mL, from 0.1 mg/mL to 2.7 mg/mL, from 0.1 mg/mL to 2.6 mg/mL, from 0.1 mg/mL to 2.5 mg/mL, from 0.1 mg/mL to 2.4 mg/mL, from 0.1 mg/mL to 2.3 mg/mL, from 0.1 mg/mL to 2.2 mg/mL, from 0.1 mg/mL to 2.1 mg/mL, from 0.1 mg/mL to 2.0 mg/mL, from 0.1 mg/mL to 1.9 mg/mL, from 0.1 mg/mL to 1.8 mg/mL, from 0.1 mg/mL to 1.7 mg/mL, from 0.1 mg/mL to 1.6 mg/mL, from 0.1 mg/mL to 1.5 mg/mL, from 0.1 mg/mL to 1.4 mg/mL, from 0.1 mg/mL to 1.3 mg/mL, from 0.1 mg/mL to 1.2 mg/mL, from 0.1 mg/mL to 1.1 mg/mL, from 0.1 mg/mL to 1.0 mg/mL, from 0.1 mg/mL to 0.9 mg/mL, from 0.1 mg/mL to 0.8 mg/mL, from 0.1 mg/mL to 0.7 mg/mL, from 0.1 mg/mL to 0.6 mg/mL, from 0.1 mg/mL to 0.5 mg/mL, from 0.1 mg/mL to 0.4 mg/mL, from 0.1 mg/mL to 0.3 mg/mL, or from 0.1 mg/mL to 0.2 mg/mL.

[0898] In some embodiments, the compound as described herein (*e.g.,* compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161,

162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of at most 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution. In some embodiments, the compound as described herein (*e.g.*, compound (I) or a salt thereof, or compound (II)) is solubilized or diluted to a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, or 250 mg/mL in the solution.

[0899] In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 0.1 mg/mL to 200 mg/mL. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL,

10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, or 20 mg/mL. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of about 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160 mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, or 200 mg/mL. In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL in the diluent.

[0900] In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 0.1 mg/mL to 200 mg/mL, from 0.2 mg/mL to 200 mg/mL, from 0.3 mg/mL to 200 mg/mL, from 0.4 mg/mL to 200 mg/mL, from 0.5 mg/mL to 200 mg/mL, from 0.6 mg/mL to 200 mg/mL, from 0.7 mg/mL to 200 mg/mL, from 0.8 mg/mL to 200 mg/mL, from 0.9 mg/mL to 200 mg/mL, from 1.0 mg/mL to 200 mg/mL, from 1.1 mg/mL to 200 mg/mL, from 1.2 mg/mL to 200 mg/mL, from 1.3 mg/mL to 200 mg/mL, from 1.4 mg/mL to 200 mg/mL, from 1.5 mg/mL to 200 mg/mL, from 1.6 mg/mL to 200 mg/mL, from 1.7 mg/mL to 200 mg/mL, from 1.8 mg/mL to 200 mg/mL, from 1.9 mg/mL to 200 mg/mL, from 2.0 mg/mL to 200 mg/mL, from 2.1 mg/mL to 200 mg/mL, from 2.2 mg/mL to 200 mg/mL, from 2.3 mg/mL to 200 mg/mL, from 2.4 mg/mL to 200 mg/mL, from 2.5 mg/mL to 200 mg/mL, from 2.6 mg/mL to 200 mg/mL, from 2.7 mg/mL to 200 mg/mL, from 2.8 mg/mL to 200 mg/mL, from 2.9 mg/mL to 200 mg/mL, from 3.0 mg/mL to 200 mg/mL, from 3.1 mg/mL to 200 mg/mL, from 3.2 mg/mL to 200 mg/mL, from 3.3 mg/mL to 200 mg/mL, from 3.4 mg/mL to 200 mg/mL, from 3.5 mg/mL to 200 mg/mL, from 3.6 mg/mL to 200 mg/mL, from 3.7 mg/mL to 200 mg/mL, from 3.8 mg/mL to 200 mg/mL, from 3.9 mg/mL to 200 mg/mL, from 4.0 mg/mL to 200 mg/mL, from 5.0 mg/mL to 200 mg/mL, from 6.0 mg/mL to 200 mg/mL, from 7.0 mg/mL to 200 mg/mL, from 8.0 mg/mL to 200 mg/mL, from 9.0 mg/mL to 200 mg/mL, from 10 mg/mL to 200 mg/mL, from 15 mg/mL to 200 mg/mL, from 20 mg/mL to 200 mg/mL, from 25 mg/mL to 200 mg/mL, from 30 mg/mL to 200 mg/mL, from 35 mg/mL to 200 mg/mL, from 40 mg/mL to 200 mg/mL, from 45 mg/mL to 200 mg/mL, from 50 mg/mL to 200 mg/mL, from 55 mg/mL to 200 mg/mL, from 60 mg/mL to 200 mg/mL, from 65 mg/mL to 200 mg/mL, from 70 mg/mL to 200 mg/mL, from 75 mg/mL to 200 mg/mL, from 80 mg/mL to 200 mg/mL, from 85 mg/mL to 200 mg/mL, from 90 mg/mL to 200 mg/mL, from 95 mg/mL to 200 mg/mL, from 100 mg/mL to 200 mg/mL, from 105 mg/mL to 200 mg/mL, from 110 mg/mL to 200 mg/mL, from 115 mg/mL to 200 mg/mL, from 120 mg/mL to 200 mg/mL, from 125 mg/mL to 200 mg/mL, from 130 mg/mL to 200 mg/mL, from 135 mg/mL to 200 mg/mL, from 140 mg/mL to 200 mg/mL, from 145 mg/mL to 200 mg/mL, from 150 mg/mL to 200 mg/mL, from 155 mg/mL to 200 mg/mL, from 160 mg/mL to 200 mg/mL, from 165 mg/mL to 200 mg/mL, from 170 mg/mL to 200 mg/mL, from 175 mg/mL to 200 mg/mL, from 180

mg/mL to 200 mg/mL, from 185 mg/mL to 200 mg/mL, from 190 mg/mL to 200 mg/mL, or from 195 mg/mL to 200 mg/mL.

[0901] In some embodiments, the instructions for diluting or solubilizing the compound as described herein in the diluent comprise instructions for diluting or solubilizing the compound as described herein to a concentration of from 0.1 mg/mL to 200 mg/mL, from 0.1 mg/mL to 195 mg/mL, from 0.1 mg/mL to 190 mg/mL, from 0.1 mg/mL to 185 mg/mL, from 0.1 mg/mL to 180 mg/mL, from 0.1 mg/mL to 175 mg/mL, from 0.1 mg/mL to 170 mg/mL, from 0.1 mg/mL to 165 mg/mL, from 0.1 mg/mL to 160 mg/mL, from 0.1 mg/mL to 155 mg/mL, from 0.1 mg/mL to 150 mg/mL, from 0.1 mg/mL to 145 mg/mL, from 0.1 mg/mL to 140 mg/mL, from 0.1 mg/mL to 135 mg/mL, from 0.1 mg/mL to 130 mg/mL, from 0.1 mg/mL to 125 mg/mL, from 0.1 mg/mL to 120 mg/mL, from 0.1 mg/mL to 115 mg/mL, from 0.1 mg/mL to 110 mg/mL, from 0.1 mg/mL to 100 mg/mL, from 0.1 mg/mL to 95 mg/mL, from 0.1 mg/mL to 90 mg/mL, from 0.1 mg/mL to 85 mg/mL, from 0.1 mg/mL to 80 mg/mL, from 0.1 mg/mL to 75 mg/mL, from 0.1 mg/mL to 70 mg/mL, from 0.1 mg/mL to 65 mg/mL, from 0.1 mg/mL to 60 mg/mL, from 0.1 mg/mL to 55 mg/mL, from 0.1 mg/mL to 50 mg/mL, from 0.1 mg/mL to 45 mg/mL, from 0.1 mg/mL to 40 mg/mL, from 0.1 mg/mL to 35 mg/mL, from 0.1 mg/mL to 30 mg/mL, from 0.1 mg/mL to 25 mg/mL, from 0.1 mg/mL to 20 mg/mL, from 0.1 mg/mL to 15 mg/mL, from 0.1 mg/mL to 10 mg/mL, from 0.1 mg/mL to 9 mg/mL, from 0.1 mg/mL to 8 mg/mL, from 0.1 mg/mL to 7 mg/mL, from 0.1 mg/mL to 6 mg/mL, from 0.1 mg/mL to 5 mg/mL, from 0.1 mg/mL to 4 mg/mL, from 0.1 mg/mL to 3.9 mg/mL, from 0.1 mg/mL to 3.8 mg/mL, from 0.1 mg/mL to 3.7 mg/mL, from 0.1 mg/mL to 3.6 mg/mL, from 0.1 mg/mL to 3.5 mg/mL, from 0.1 mg/mL to 3.4 mg/mL, from 0.1 mg/mL to 3.3 mg/mL, from 0.1 mg/mL to 3.2 mg/mL, from 0.1 mg/mL to 3.1 mg/mL, from 0.1 mg/mL to 3.0 mg/mL, from 0.1 mg/mL to 2.9 mg/mL, from 0.1 mg/mL to 2.8 mg/mL, from 0.1 mg/mL to 2.7 mg/mL, from 0.1 mg/mL to 2.6 mg/mL, from 0.1 mg/mL to 2.5 mg/mL, from 0.1 mg/mL to 2.4 mg/mL, from 0.1 mg/mL to 2.3 mg/mL, from 0.1 mg/mL to 2.2 mg/mL, from 0.1 mg/mL to 2.1 mg/mL, from 0.1 mg/mL to 2.0 mg/mL, from 0.1 mg/mL to 1.9 mg/mL, from 0.1 mg/mL to 1.8 mg/mL, from 0.1 mg/mL to 1.7 mg/mL, from 0.1 mg/mL to 1.6 mg/mL, from 0.1 mg/mL to 1.5 mg/mL, from 0.1 mg/mL to 1.4 mg/mL, from 0.1 mg/mL to 1.3 mg/mL, from 0.1 mg/mL to 1.2 mg/mL, from 0.1 mg/mL to 1.1 mg/mL, from 0.1 mg/mL to 1.0 mg/mL, from 0.1 mg/mL to 0.9 mg/mL, from 0.1 mg/mL to 0.8 mg/mL, from 0.1 mg/mL to 0.7 mg/mL, from 0.1 mg/mL to 0.6 mg/mL, from 0.1 mg/mL to 0.5 mg/mL, from 0.1 mg/mL to 0.4 mg/mL, from 0.1 mg/mL to 0.3 mg/mL, or from 0.1 mg/mL to 0.2 mg/mL.

[0902] One aspect of the disclosure relates to kits including the compound as described herein. The kits can further include one or more additional therapeutic regimens or agents.

[0903] Also disclosed herein, in some embodiments, are kits and articles of manufacture for use with one or more methods described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[0904] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[0905] For example, the container(s) include the composition of the invention, and optionally in addition with therapeutic regimens or agents disclosed herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[0906] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[0907] In some embodiments, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.,* as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

EXAMPLES

[0908] The present disclosure will be more specifically illustrated by the following Examples. However, it should be understood that the present disclosure is not limited by these examples in any manner.

Example 1: Mechanism of TANGO (Targeted Augmentation of Nuclear Gene Output).

[0909] TANGO uses ASOs to specifically increase protein expression by targeting naturally occurring non-productive alternative splicing events. TANGO can reduce non-productive messenger RNAs (mRNA), which are normally targeted for degradation by nonsense-mediated mRNA decay (NMD) as shown in **FIG. 1A** and **1B**. In turn, TANGO can increase productive mRNA and protein. TANGO can specifically increase expression of canonical target mRNA and full-length protein in tissues with endogenous gene expression. As these events are naturally occurring, TANGO can upregulate the wild-type alleles in the context of autosomal dominant haploinsufficiency, thus providing a potentially unique opportunity to treat diseases.

Example 2: Experimental administration of antisense oligomer ASO-22 to mice.

[0910] Mice were administered a single intracerebroventricular (ICV) injection of ASO-22 (sequence set forth in SEQ ID NO: 42) or vehicle (PBS) at postnatal day P2 or P14. Mice were monitored for survival out to 14 weeks. To monitor for seizures, mice are implanted with an 8201-EEG Headmount (Pinnacle Technology, Inc., Lawrence, KS) and seizure activity was continuously monitored from P22-P46. ASO-22 Measurement: ASO-22 levels were measured by Liquid Chromatography Mass Spectrometry (LCMS) *SCN1A* gene expression measurement Productive *Scn1a* mRNA transcripts were measured using TaqMan qPCR assays. $Na_V1.1$ Protein measurement: $Na_V1.1$ protein was measured using a Mesoscale Discovery electrochemiluminescence (MSD-ECL) assay which utilizes $Na_V1.1$ expression in wild-type mouse brain tissue lysates as a standard.

Example 3: Monitoring survival of mice after ASO-22 administration at postnatal day 2.

[0911] Mice groups were monitored for survival after ASO-22 was administered. **FIG. 2** shows an exemplary survival curve demonstrating 100% long term survival benefit provided by a SCN1A-targeting ASO (termed as "ASO-22") in Dravet mouse model. WT and heterozygous Dravet mice (+/-), F1 offspring from 129S-*Scn1a*^{tm1Kea} x C57BL/6J crosses, received a single dose ICV injection of 20 μg PBS or ASO-22 blindly on postnatal day 2, and their survival was monitored until 14 weeks. As depicted, Dravet mice receiving PBS treatment started to die from about postnatal day 20, whereas all mice of other three groups, including Dravet mice receiving ASO-22 treatment group, survived at least 70 days. Kaplan-Meier curve showing DS and WT littermate mice monitored to 14 weeks for survival. Administration of ASO-22 significantly ($p<0.0001$; **** = $p< 0.0001$ on **FIG. 2**) improved survival in the Dravet mouse model. 33/34 survived up to 14 weeks, compared with 14/62 animals in PBS-treated group. ASO-22 administration at P2 was able to prevent SUDEP (Sudden Unexpected Death in Epilepsy) in the DS mouse model.

Example 4: Monitoring of seizures in mice.

[0912] EEG recording was performed on the mice to monitor seizures. **FIG. 3** shows experimental design for the EEG seizure monitoring study in DS mice (n=21/group) and their WT littermates (n=11-12/group). Mice received a 20 μg ICV injection of ASO-22 or PBS vehicle at P2, underwent surgery for EEG head mounts at P20, and were continuously monitored by EEG from P22 to P46. WT mice injected with ASO-22 had normal EEGs throughout the monitoring period (data not shown). **FIG. 4A** shows representative traces from three channels during a seizure event recorded in different parts of the brain of a PBS-injected DS mouse, including the frontal cortex, the hippocampus, and the Parietal cortex. As shown in **FIG. 4B**, the number of recorded spontaneous seizures in the mice were shown to be reduced significantly in DS mice demonstrating a robust seizure freedom. In all mice, seizures were predominantly generalized as observed by the similar data obtained in the different areas of the brain. **FIG. 4C** is a summary of effect of ASO-22 on total number of spontaneous seizures (generalized and focal) recorded between P22 and P46 in DS mice dosed with PBS (n=21) or ASO-22 (n=21). *Indicates $p<0.05$. Additionally, as shown in **FIG. 4D**, the number of seizure-free mice increased after ASO-22 administration at P2, while the number of mice having 2 or more seizures decreased compared to control. Wild type mice did not have any seizure regardless of treatment. A 50% increase (76% vs 48%) in the number of mice that experienced no seizures following administration of ASO-22 at postnatal day 2 and monitored by EEG between postnatal day 22 and day 46. Reductions in the number of mice that experienced two or more seizures following administration of ASO-22 at postnatal day 2 compared to placebo (14% vs 38%). An 80% reduction (3 vs 15) in the average number of spontaneous seizures detected between postnatal day 22 and day 46 after treatment with ASO-22 compared to placebo ($p<0.05$). ASO-22 administration at P14 was able to significantly reduces SUDEP in the DS mouse model. Furthermore, administration of ASO-22 significantly prolonged latency to first seizure in DS mice during the recording period ($p<0.05$, **FIG. 4E**). There were non-statistically significant trends suggesting increased numbers of seizure-free DS mice (48% PBS vs 76% ASO-22) and decreased

numbers of DS mice having 2 or more seizures (38% PBS vs 14% ASO-22) over the assessment period following ASO-22 administration.

Example 5: Detection of ASO-22 exposure and protein expression levels in mice brains.

[0913] Mice brains were collected in order to detect exposure of the ASO to the brain tissue as well as detect the protein expression levels in the brain tissue. **FIG. 5A** shows the experiment timeline. Wild type (WT) or heterozygous Dravet mice (HET) F1 mice from 129S-*Scn1a*^{tm1Kea} x C57BL/6J crosses were subjected to an intracerebroventricular (ICV) injection at postnatal day 2 of 20 μg of ASO-22 or PBS. The brains of the mice were collected at 7 weeks from a subset of mice in all mice groups. A second collection of brains was performed at 14 weeks from another subset of mice in all mice groups. The brain tissues were shown to have a robust and long-lasting exposure to ASO-22 (~13 μg/g at 7 weeks; **FIG. 5B** and ~8 μg/g at 14 weeks**; FIG. 5E**) as measured using Liquid Chromatography-Mass Spectrometry (LC-MS). The expression levels of *Scn1a* productive transcript were increased after ASO-22 administration by ~1.5-2 fold in both WT and DS mice at 7 weeks (**FIG. 5C**) and 14 weeks (**FIG. 5F**). **FIG. 5D** (7 weeks) and **FIG. 5G** (14 weeks) shows an increase in $Na_V1.1$ protein in ASO-22 treated DS mice. $Na_V1.1$ protein increased in ASO-22 treated DS mouse brains to levels indistinguishable from PBS-treated WT brains at 7 weeks and 14 weeks. $Na_V1.1$ protein in the brains of ASO-22 injected WT animals also increased over PBS treated WT mice with no obvious adverse effects.

Example 6: Monitoring survival of mice after ASO-22 administration at postnatal day 2.

[0914] Mice groups were monitored for survival after ASO-22 was administered on P14. **FIG. 6A** shows a study design timeline with the mice injected on P14 and monitored until P90. **FIG. 6B** shows an exemplary survival curve demonstrating long term survival benefit provided by a *SCN1A* targeting ASO in Dravet mouse model. WT and heterozygous Dravet mice (+/-), F1 offspring from 129S-*Scn1a*^{tm1Kea} x C57BL/6J crosses, received a single dose ICV injection of 60 μg PBS or ASO blindly on postnatal day 14 (which was around the time of disease onset), and their survival was monitored until P90. As depicted, Dravet mice receiving PBS treatment started to die from about postnatal day 20 resulting in a lower survival rate at P90 than the DS mouse treated with ASO-22. 47/74 of the PBS treated DS mice survived up to P90 whereas 45/53 ($p<0.005$) of the DS mice treated with ASO-22 survived up to P90.

Example 7: Detection of ASO-22 exposure and protein expression levels in mice brains.

[0915] Mice brains were collected in order to detect exposure of the ASO to the brain tissue as well as detect the protein expression levels in the brain tissue. **FIG. 7A** shows the experiment timeline. Wild-type (WT) or heterozygous Dravet mice (HET) F1 mice from 129S-*Scn1a*^{tm1Kea} x C57BL/6J crosses were subjected to an intracerebroventricular (ICV) injection at postnatal day 14 of 60 μg of ASO-22 or PBS. The brains of the mice were collected at P35 from a subset of mice in all mice groups. A second collection of brains was performed at P90 from another subset of mice in all mice groups. The brain tissues were shown to have a robust and long-lasting exposure to ASO-22 (~36 μg/g at P35; **FIG. 7A** and ~10 μg/g at P90; **FIG. 7D**) as measured using LCMS. The expression levels of *Scn1a* productive transcript were increased after ASO-22 administration by ~1.5-fold in both WT and DS mice at P90 (**FIG. 7E**) with no significant change at P35 (**FIG. 7B**). **FIG. 7F** shows an increase in $Na_V1.1$ proteins in

ASO-22 treated DS mice at P90 with no significant change at P35 (**FIG. 7C**). $Na_V1.1$ protein increased in ASO-22 treated DS mouse brains to levels indistinguishable from PBS-treated WT brains at P90. $Na_V1.1$ protein in the brains of ASO-22 injected WT animals also increased over PBS treated WT mice with no obvious adverse effects.

Example 8: Administration of ASOs to cynomolgus monkeys.

[0916] 2- to 3-year-old naïve cynomolgus monkeys were administered a single bolus intrathecal lumbar (IT-L) injection of artificial cerebrospinal fluid (aCSF) or one or two dose levels of ASO-22 antisense oligomer (ASO) on the first study day. Two dose levels of an optimized ASO that was active in targeting a nonproductive alternative splicing event in *Scn1a* in rodent was evaluated in cynomolgus monkeys for safety, brain biodistribution, target engagement and pharmacodynamics. After a single intrathecal lumbar bolus injection (IT-L) of the ASO, animals were sacrificed and ASO, *Scn1a* mRNA and $Na_V1.1$ protein levels were measured on Day 3 (48 hours post dose) and on Day 29 (28 days post dose). **FIG. 8** shows the treatment, dosing and number of animals used for an exemplary study.

[0917] After dosing, the animals underwent a standard clinical and neurological observation and blood samples were collected. CSF and brains were collected at necropsy. Separate punches of various regions were collected for ASO-22 concentration levels, gene expression and protein expression measurements. ASO-22 levels were measured by liquid chromatography mass spectrometry (LCMS) in tissues and by hybridization enzyme-linked immunosorbent assay (HELISA) in plasma and CSF. Productive and non-productive (NMD-inducing) *Scn1a* mRNA transcripts were measured using TaqMan qPCR in order perform *SCN1A* gene expression measurements. $Na_V1.1$ protein was measured using a Mesoscale Discovery Electrochemiluminescence (MSD-ECL) assay which utilizes a recombinant fragment of $Na_V1.1$ as a standard. The ASO was well tolerated at both dose levels with no changes on physical and neurological exams, no changes in food intake, body weight, hepatic function or platelet counts, no complement system activation, and no abnormal histopathology was observed in all tissues examined.

Example 9: Detection of ASO-22 ASO in the brain tissues of cynomolgus monkeys.

[0918] The brains of 2-3-year-old naïve cynomolgus monkeys were analyzed for levels of the ASO-22 ASO using LCMS. Cynomolgus monkeys were sacrificed at Study Day 3 and Study Day 29 to observe the levels of ASO-22 in various brain tissues for the various doses. **FIG. 9A** shows the levels of ASO-22 in various area of the brains of the monkeys on Study Day 3. At the low dose, ASO-22 exposure was below the limit of quantitation (BLQ) in most of the brain regions. At the high dose, the ASO-22 was detectable, primarily detected in the cortex and the cerebellum. **FIG. 9B** shows the levels of the ASO-22 at Study Day 29. At the low dose, the brain tissue exposure was BLQ in most regions of the brain. For the high dose level, exposure in the cortical brain regions was generally higher than in the deeper structures and the level of exposure was generally increased from Day 3. ASO-22 is observed to distribute broadly in the non-human primate brain at the higher dose level.

Example 10: Detection of $Na_V1.1$ expression in the brain tissues of cynomolgus monkeys.

[0919] The brains of 2-3-year-old naïve cynomolgus monkeys were analyzed for levels of the $Na_V1.1$ expression. Cynomolgus monkeys were sacrificed at Study Day 3 and Study Day 29 to observe the

expression levels of $Na_V1.1$ in various brain tissues for the various doses. **FIG. 10A** shows the levels of ASO-22 in various area of the brains of the monkeys on Study Day 3. All brain regions assessed had measurable levels of $Na_V1.1$, with midbrain, motor cortex, occipital cortex and motor cortex being the highest. No or marginal change in $Na_V1.1$ levels in brain tissues were observed at the low or high dose levels of ASO-22. **FIG. 10B** shows the levels of the ASO-22 at Study Day 29. No or marginal change in $Na_V1.1$ level in brain tissues were observed at the low dose of ASO-22. At the high dose of ASO-22, $Na_V1.1$ protein level increased by 1.2- to 3-fold in motor cortex, occipital cortex, parietal cortex, and prefrontal cortex compared to aCSF treated animals.

Example 11: Detection of *SCN1A* expression in the brain tissues of cynomolgus monkeys.

[0920] The brains of 2- to 3-year-old naïve cynomolgus monkeys were analyzed for levels of the *SCN1A* expression. Levels of productive *SCN1A* gene and levels of total *SCN1A* gene expression were determined in order to evaluate the target engagement of the ASO-22 ASO. Cynomolgus monkeys were sacrificed at Study Day 3 and Study Day 29 to observe the expression levels of *SCN1A* in various brain tissues for the various doses. **FIG. 11A** shows the percentage of productive *SCN1A* gene expression/total *SCN1A* gene expression in various area of the brains of the monkeys on Study Day 3. No significant changes in percentage of productive gene expression were observed for either dosage compared to the control aCSF expression at Day 3 for any of the brain regions, indicating that limited target engagement had occurred. **FIG. 11B** shows the percentage of productive *SCN1A* gene expression/total *SCN1A* gene expression in various area of the brains of the monkeys on Study Day 29. Significant target engagement as determined by measurement of productive *SCN1A* gene expression/total *SCN1A* gene expression was observed in prefrontal cortex, parietal cortex, occipital cortex and limbic lobe on Day 29 at the high dose of ASO-22.

Example 12: Detection of ASO-22 ASO in the plasma and CSF of cynomolgus monkeys.

[0921] The plasma and CSF of 2- to 3-year-old naïve cynomolgus monkeys were analyzed for levels of ASO-22 after the intrathecal administration of ASO-22. **FIG. 12A** shows the plasma pharmacokinetics of the ASO-22 in the monkeys for low and high doses. Plasma levels were observed at timepoints from 1 hour from the administration up until 29 days from administration. ASO-22 reached mean peak plasma levels approximately 1 hour (first time of collection) for the low dose and 2 hours for the high dose. The concentrations declined in a biphasic manner. Peak and total exposures of each compound increased with increasing dose. Measured levels of ASO-22 in pre-dose and aCSF-dosed samples were below the limit of quantification of each assay.

[0922] **FIG. 12B** shows the levels of ASO-22 in the cynomolgus monkey CSF on day 3 and day 29. At Day 3, the observed CSF exposure in the low and high dose groups were similar. CSF ASO-22 levels decreased markedly from Day 3 to Day 29 for both doses suggesting a transition from distribution to clearance phase during this period. Mean exposure levels were variable, but slightly higher in the high compared to the low dose group at Day 29.

Example 13: Identification of NMD-inducing exon inclusion events in *SCN1A* transcripts by RNAseq using Next-Generation Sequencing (NGS).

[0923] Whole-transcriptome shotgun sequencing was carried out using next-generation sequencing to reveal a snapshot of transcripts produced by the *SCN1A* gene to identify NIE inclusion events. For this purpose, polyA+ RNA from nuclear and cytoplasmic fractions of HCN (human cortical neurons) was isolated and cDNA libraries constructed using Illumina's TruSeq Stranded mRNA library Prep Kit. The libraries were pair-end sequenced resulting in 100-nucleotide reads that were mapped to the human genome (Feb. 2009, GRCh37/hg19 assembly). Briefly, mapped reads visualized using the UCSC genome browser (operated by the UCSC Genome Informatics Group (Center for Biomolecular Science & Engineering, University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064) and described by, *e.g.,* Rosenbloom, *et al.*, 2015, "The UCSC Genome Browser database: 2015 update," Nucleic Acids Research 43, Database Issue, doi: 10.1093/nar/gku1177) and the coverage and number of reads can be inferred by the peak signals. The height of the peaks indicates the level of expression given by the density of the reads in a particular region. The upper panel shows a graphic representation of the *SCN1A* gene to scale. The conservation level across 100 vertebrate species is shown as peaks. The highest peaks correspond to exons (black boxes), while no peaks are observed for the majority of the introns (lines with arrow heads). Peaks of conservation were identified in intron 20 (NM_006920), shown in the middle panel. Inspection of the conserved sequences identified an exon-like sequence of 64 bp (bottom panel, sequence highlighted in grey) flanked by 3' and 5' splice sites (underlined sequence). Inclusion of this exon leads to a frameshift and the introduction of a premature termination codon in exon 21 rendering the transcript a target of NMD.

[0924] Exemplary *SCN1A* gene, pre-mRNA, exon, and intron sequences are summarized in **Table 1**. The sequence for each exon or intron is summarized in **Table 2**.

Table 1. List of target *SCN1A* gene and pre-mRNA sequences.

Species	SEQ ID NO:	Sequence Type
Human	SEQ ID NO: 1	*SCN1A* gene (NC_000002.12)
	SEQ ID NO: 2	*SCN1A* pre-mRNA (encoding *e.g.,* *Scn1a* mRNA NM_006920.5)
	SEQ ID NO: 3	Exon 20 gene
	SEQ ID NO: 4	Intron 20 gene
	SEQ ID NO: 5	Exon 21 gene
	SEQ ID NO: 6	Exon 20x gene
	SEQ ID NO: 7	Exon 20 pre-mRNA
	SEQ ID NO: 8	Intron 20 pre-mRNA
	SEQ ID NO: 9	Exon 21 pre-mRNA
	SEQ ID NO: 10	Exon 20x pre-mRNA
Mouse	SEQ ID NO: 11	*SCN1A* gene (NC_000068.7)

Species	SEQ ID NO:	Sequence Type
	SEQ ID NO: 12	*SCN1A* pre-mRNA (encoding *e.g.*, *Scn1a* mRNA NM_001313997.1)
	SEQ ID NO: 13	Exon 21 gene
	SEQ ID NO: 14	Intron 21 gene
	SEQ ID NO: 15	Exon 22 gene
	SEQ ID NO: 16	Exon 21x gene
	SEQ ID NO: 17	Exon 21 pre-mRNA
	SEQ ID NO: 18	Intron 21 pre-mRNA
	SEQ ID NO: 19	Exon 22 pre-mRNA
	SEQ ID NO: 20	Exon 21x pre-mRNA

Table 2. Sequences of target exon or intron in *SCN1A* pre-mRNA transcripts.

SEQ ID NO:	Sequence Type	Sequence
SEQ ID NO: 7	Exon 20 pre-mRNA	GUUUCAUUGGUCAGUUUAACAGCAAAUGCCUUGGGUUACUC AGAACUUGGAGCCAUCAAAUCUCUCAGGACACUAAGAGCUC UGAGACCUCUAAGAGCCUUAUCUCGAUUUGAAGGGAUGAGG
SEQ ID NO: 8	Intron 20 pre-mRNA	guaagaaaaaugaaagaaccugaaguauuguauauagccaaaauuaaacuaaauuaaauuuag aaaaaggaaaaucuaugcaugcaaaaggaauggcaaauucuugcaaaauugcuacuuuauugu uuuaucuguugcauauuuacuucuaggugauaugcaagagaaauaggccucucuugaaauga uauaauaucauuuaucugcugugcuuauuuaaaugacuuuauuuccuaauccaucuugggag uuuccuuacaaaucuauauacaaaaaaaagcugaugcauuauuaaaguacuauguguaaugau auaaugguaaucuaaaguaaaauucuauaucagguacuuauucuuugugaugauauacuguac uuaacgaguuuuccugaaaauaaugugaaucacacaugugccuaaguaugaguguuaagaaa aaaaugaaaggaguuguuaaaacuuuugucuguauaaugccaaaguuugcauuauuugaaua uauucaagauuagaugguuagauauuaaguguugacugaauuuauaaaacuaguaaauacuaa cuuaaagauuacauacaaauccacaucauuuuuauaacaauaaaguaaaacacuuauaaugaac agaaaauauaaauuuugacucauuacuauagguaauuuauacauuaaccuuaacuugcaucuua uuggucagagucacacaaaauguuauuuuauccuuuucaaagaugcaauaaucauuuuccau caugcauaacagauuagaaauuuugccauuauugacuuauuuuccaugccuuuuuuuacggc augaagcauuaguuuauagauauauaauauaaaaaauuaguucugcuuuuuuuuaaaaaaaa auauuaucaaaacaaaacacugaauugugugauuccaauagaaaaacacugcucuuucaccuc cuaagguguaguuacuuuuauggaaacuaagcuguauuguagacuuccauuugcacuuugua gauuguuuauagccuuauguucucuucucaagucuuauuauaaaugucacuuuguaagaacg uaggacuugucuucgauuucccuaacauauaugaaaacuuuguccucauuaucgacaacucag aacaauauaauacaaguaguccucuuuuauuucucacagagagccucaaauuuucaccaaaau guuaacagaaauuaucucugggguguauaagaauuaagucuguuuuccaauuaaaugucacu

SEQ ID NO:	Sequence Type	Sequence
		uuguuuuguuucagacuggcaguuucaguucuggagaaaaaaaaugucauuuguguacauuc uacuugaaaacauguugccugaaucaaaauaauauauuuuauauggcuugugaaaucugaac aaugcuaaacauuugaaaauauuauaaaccuuuuacauuugaccauuugaaaguuuauuaaau ucauuggucaagugcucagauauuuccauacauuacacuucauuucuauaaaaaaagcugaucu uaucgguauacuuuuaauuuucucagaaauaaccauaucuauaauuauuaaucaauaaugccu uuuauauuaaaagaggguuaguuuuugaaacuuggaguuuuagacauaaaauccuuauaaaug cugauagugauauaacuaauaguuuaaauggucagauuuaugaauauggcucuauuccucau aaugacaacauacacacagcacuaaaaugacuaaucucuucaauacguguuuggcauuguaga gucaaaauaacguuauaauugauucuauuuuuuauacuucuaguguuuggauauuuuauuu uguaaaaauauaaucaugaaugauggugagguuggauauaagaaugaugauuaugauuggga agugagauuugaacaugcucagaaacucucauuuaauucuuugcccuagcagcauaaaaucac aauagcugcgucaaagcguaacucaggcacucauuuuauuuuuguuguucuguuauuuuuuc aaagcaugugcuuuuaugcaacauuacugaauaaagcauguuguacagugcuugauaagaag uuagaaaguaacaaauaaaauuaucaucacguugcacuuuguguuuugcauguuuuaugcaca uuucuggcugacagcuuuuaaacauuuauuguauuucaaauuuccaguccaaauuuuucaac uuguaaaauuaaacugagugaauugaugucgugaauaucuaggguaaaauaaaauuuguguu uaaauuuguauuuuuaauuuccuaaccuaggaaaucuuaaauaccuucuuuuucaaaagaac ucaagucuuaauggauagggaaacagacggagagcaucaugaacaaaaaguaacaccaaaugu ucugucauaucagauuucuaacuaauaacaaacuauauauuucuauuuuguauaggauaauc uugcuccaacuuggaugggguggagcgcugguuccucccccugagcccuuuauuauggguacu guauuaccccuuuugcuaccuuuaauccuugcacugugacuuauguguaguggggugaggg agggauugggaaggguacuauuauugcaccacaguagggaaaauacauuauuuacauccuaa ucccccucuuuucaauugucuuaaauuucauuugaaaaaaaaaaaaaaccuuuaugaauuuaccc ucuguggauuuuaaccccaaugguugauaucuuuauuaaguuucauugaauaugauuuagu uauguguauauggaguuauccaucuuuggggagauuacuggauugggugagggcgggggacc cuggguguagaaugauuaugugaaaaaacaauuuaacuuguuaagcucaugauacuguuugag gcauacagccccugcuguuuaguacauuggucuggguccugaaaauuaccaguuagauacca ucaguugauuauugauauguaugagcagauacuagggugcaauauuucagguuucauaagac ugguauugauugugaccacucucauuuuuuauuguguaaguucauaugggguuauuuucaa aauguuaacaaggcaaaaauauauuaagaaauaguugaauaagcacaugugaauuguguugu aaacaaaaaguuagaauaaaaaaaauccacuuauuugaauuaugcagaauagaauacauaccuag aaauaaaacaaaaacgucuuaucaugaguauuaagauaaaauuuaaggcauaaacucacuucu uagaauaaguaacucccaacuaacuuucuaggauuuuaaaacauaacacagugaaaacauacau aaacauaacucuacauuuuauuuauucuuaaaguuuaaguguauuauacaagaagaagaguu uauauucgagagacagaaaaagucagaauuuuuguuuggaucaccaauauaucauagcuuaca aaaaaacugucuuaauuaaaacccacaacauaaauuuuuuuagauuuuuaagaaagauucuauu auucuucuuuauacuuaaaaauggaugauuccuacuuugcccacuuuuauuuuuauucacau

SEQ ID NO:	Sequence Type	Sequence
		agauuuucuuuauuucuauuagagaagcacuagaauucaugaauaguguugauuugaaguuc
		aaaguaauuaauucagauaaaaagacauuucugcauguaugaaaauuucuaaugugaauuug
		cauauuuaauuaucaauccuucauuuaguguagacuuauuuuuuaaaaaugcagguaaugaac
		cagaaauagaauugguugugcuagaguagagaaacuuuauuugaugauuguuuugaaaaaaa
		agcuucugagaagaaacaaccucuaguacaguauuaauucauuaagauagcuccuuucucaga
		cauuuccuuucauguagccugaaaguucaauuugaaauuuguucuuuccaauuuauucagac
		uaauucugccuacuuucuucccccauaagaaccaauuacugcagcuuuauugagacugaaaa
		aaguuaauacaccuccuucuuugcugaaccaaggaauggcuuggaacucuugggaaaagacaa
		ucuuuucuaugaucuuucauugucuaaauuuaauacaucauaaauaugacuauagcuuuguau
		aauaaacucccccaauacugugccagauguuuucuaagauaaaguuauuuuauguucacaaaaa
		aaauaaaacuuuucucugggccaaauguaugccaacuuugcaaaucauauccugaagugcacu
		gcugcagaguacaugcuugcgucauaaaauuccauagaguucgcuuuaacucuaaaucaauccc
		caguuucaaaguaaaccucucaaacauauuaccuaagcacaaacuucucccugugcucaguuc
		cuuaauuauucucaucccauauucagaaauaacauuuaaaaauuaugcuuugaucaauaaaua
		cuaaucuaaacuuugcuucauuaacccauucauuuuugucaaccauuauuuuauuccuauau
		ucaaagcucucugguauguucuuauauucaagacacucaaggcccuggaagauucacgaacau
		auguuugcaucuuaaauuuuuagaaaaucuuacaaucugucaggauuacacugaacucuagu
		acagaguaauauggguaccagauaagugggagcaacucuuccacguagacuggaaacagcacu
		aaaugcuauuuauaggcuacuuucugaacuuaacuuguuuuaaccucauuuuucucauaugc
		caaaugagaacgcaauacugaauuaucuguacaguucuguucaguacuagaauucugauucu
		ugaauucaaaggggaaaacauuccucuuuauuuuggaggcuaaacuggggacaaaguuagg
		cuccaugaaagaagugcuauuugaacuaaagccuuuaagaggggagaguauuucagaagagg
		agcuauuagacaaggaauuucaauguaaauggcaucucaaucaccuggcaauuauauuagcac
		acgguuauuauauuaauugaaguggcaugaaguauagaugaccagggaaguuaaaacuggaa
		auauagauuguggagugaugugaauaccaagguaagaaaaauauuuguuaguuaccagagag
		ccaauaaauaacuuucaagugggacuuggggaagauuaauucaucuuacauagauuaaaugaa
		ggagaaggguuaggagacagaugacagugcaaguaugaaauaacagagggcaguucuaggugg
		ugacugugagaauggaaaagagguggcaaagcugagaaacguuucaaagaaaaaaugugagac
		agguaaugugaaaagaaaaucgagaaauagguauagauaaucaguguucugcucauacucuaa
		auuggguguugaaggcaaaauacguauuuuaauuaguacucuguguauacacacuagaaaca
		gcauuguaaucuggauaguggacaaaauauucagaaaagaagggaaauaguaacuugauuuc
		aauuuccaaaucucuaaucugaaagaaaucuaauucuauucauccauuuaaaauaaauuauau
		aacgagaauuuaugaaguccauuguauuaaugcagacagucagaugagauaaggcaaagugu
		cacgugucagcuugguaguugcaucggccacaucauuugguucugccuggauaacucaacca
		aauuaauuuuucauacucaucccccuccaccuuugucauuacugguauucuuauuuucuuugg
		cccacuuaucacacuguuuuauguucccagaaggccuagaguucuuuacaggcuuuaaacag
		ggaucagaaguauaagaaauuggcucauguauuuuuuuuucagacaggcaguuaaaaaaaau

SEQ ID NO:	Sequence Type	Sequence
		uguucuaaaaauacacuggcaucaaauggcaaauagaagauguuuugacgacuacuuccauug gaucagacugacaagaauaauacaagcacauagguggaauuaaacuuagcuauuaauguccaa guuugaggcagcugccccuuauaaagcauuuuagggucuguuuuuagcuuccccucuuagccac uccugugcagcuccagugggagguauggaggaaaaagcaaggaagccaucccuauguuguuu ccaaacaugaacacucaagauuuuuaacuagugguccagaaguaaagaggggaaaacauccu ucuauagaaaaaaaaaaaaguagauaauaauuugaacacagaacuucaugugaucacaucagau uugagaacuauguauggcaucccucuuuuucuuauuuuccuaagaaaugauuucuauuaugu uucauuugaaauaaguuuuuugaauuaaacucaguaaaugaaacaacugacaugacuggagc uugaaauaaacgaugugaugaucuaaugaaauacauaaugcaaauugucuugcuucuuaugc aaaaauuauuagucauagcaaugcaugaauaauuaaagacaauuauauuagguauuuaauaau auuuuuuauauuuaucaucugaauuuuuaaguuauuuuaaaaauauauuggucaaaucaacu cagguccaaauguuuuaguuuuguucuuuaauauauugccuuuuuaaaaugaguuaaacuuc uguauaggcuuuuuaacuuuucuuuauucugauaacacaauucugacuucaucuggcagcaa guuccucugauuuuccuuuuccuuuaaccuuuuaaugcuucucccucccuuuuuuuuaaaaa cauuuuuguuucauuucuugguuauauugccuauaguuguuuuccuaaguguauugcuuaa gaaaaaaaaaugaauuuuaagauuuuuuugaaccuugcuuuuacauauccuagaauaaauagc auugauagaaaaaaagaauggaaagaccagagauuacuaggggaauuuuuuuucuuuauuaa cagauaagaauucugacuuuucuuuuuuuccauuuguguauuag
SEQ ID NO: 9	Exon 21 pre-mRNA	GUGGUUGUGAAUGCCCUUUUAGGAGCAAUUCCAUCCAUCAU GAAUGUGCUUCUGGUUUGUCUUAUAUUCUGGCUAAUUUUCA GCAUCAUGGGCGUAAAUUUGUUUGCUGGCAAAUUCUACCAC UGUAUUAACACCACAACUGGUGACAGGUUUGACAUCGAAGA CGUGAAUAAUCAUACUGAUUGCCUAAAACUAAUAGAAAGAA AUGAGACUGCUCGAUGGAAAAAUGUGAAAGUAAACUUUGAU AAUGUAGGAUUUGGGUAUCUCUCUUUGCUUCAAGUU
SEQ ID NO: 10	Exon 20x pre-mRNA	gauaaucuugcuccaacuuggaugggguggagcgcugguuccuccccugagcccuuuauuau gg
SEQ ID NO: 17	Exon 21 pre-mRNA	GUUUCAUUGGUCAGUUUAACAGCAAAUGCCUUGGGUUACUC UGAACUCGGGGCCAUCAAAUCCCUAAGGACACUAAGAGCUCU GAGACCCCUAAGAGCCUUAUCACGAUUUGAAGGGAUGAGG
SEQ ID NO: 18	Intron 21 pre-mRNA	guaagaaaaaggaaaacucugcagcguuguauauugucaaagcuaggcugaguucaacuuaac uaacgaaaaacacgugcaugcaaaaggaauggcaacccuuugcaaacuugcuacuuuacccuu uucucuguugcauauuuacuucuuggugauaugcaagagaaaaucggccucuuugaaaauga uuuaauaucauuuaucugcuuugcuaauuaaaaugaccuuaguucauaaucgaucuugggag uuuccuuauaaauuccuaauacaaaggggagggcagauacucucuuaaagaacuaaguuga gucauguaauaauuaccuagagauaauuuuguuucauaucguucuccucuaugacagcccau caguacuuaagggauccuauggaaaguaaugugaaucacaaauguguaugaauacaaaggaaa

SEQ ID NO:	Sequence Type	Sequence
		aaaugaagaauuguuaaauguuuugucuuuacaaugccaaaauucucauuauuugaauauau ccaagggcagauauuaaccauugacuggaguauaauaauacugccucaacuguaacuaaauua augacauugaauaaguaagacacuaauuuaauuacuauaaauacauacacaucuuaugacaau acagcugauaaggaaaaagaacauguauuuuuauucauugccauacauggcucgucaaccuua acuuaaaccucgguucucaguuacacagaguuuuauguugcucuuuugagcaaagcauuauu ccccucuccauaauucaacacguaucagauuuuugcauuuauuggcucauuguuaugaugau uauuucaaagcauuauacaaucauuuauagaagaugugccgugugaaaauuauuuuuuuauu aagauccaaaauuuacgcucuuuaaaccaaucagaugaaauguauaaggcaaagagugcucau uguccugacacuuacaaaccaaggcuccaacaaacaggcuccucucugcaccacauagagggcu uucagccuguguccccccauaaaaaccuauuauaaaauuuuauuauacuauacuguaagaaacc uguccaauuuuuuaauuucucuagcacauaugaaaacuucucuucaguagauccaaguaagcac aaaggagcuuugauucucacacaagaaaucacauuuguauuaaaaauguaucauaaauuuucu cccaauuaugcaaaacuuaaaugcuuuuccaauuaaaagagcacuuucguuucagaauagcaa uuucaguugucaaggaaaacauuguuuuuauacauuuuauauaaaaauacaugagcuaaauu uaaauucacauuuuucaacuuuuuauggguuuuuuuauguuucuuuuucuuucgcauuuuuu aacaauccagccauuaccucuccucccuguccccccuccuauaguuucucaucucauuccuccu cccccuugccucugagaggaugcucccucccucacuaggccucccucuucccagggcuucaa guuccucaaggauuauacacaucuucucccacugagaccaggccaggcaguccucugcuucug cccagccuguguauguuccugcuugguagcucagucucuggaagcucccuggggucugggu uaguugggacugcuggucuuccuauggaguuacccucccccuucaacuucuucaaucccuuccc cuaauucaaccacagguauccagacuucaguccaaugguugaguguaaauauuggcaucugu cucugucagcuguuguuaggggcucagaggacagccaugcuaggcuccugccuacaagcagc acaccauaacaucaguaauagugucaggccuuuaaugaauaaugcuacguauauaaggguugu uagauuauacuucaacuuugaucuuuuagaauauuauuaaauccagucguuuauuuuuuaua uguaauauugacuuuccauaacaaaugagucuauuuuccuuuuguguagaaauaacuuuauc aauuauuguuaauaaaugcuuuugucaauuauuguugauaugcuucucuuuuuuaaaacugg agucaucaaaacaaaaauucuggguagauauuacgaagcugacuccuuggucagcuuggcaca uagugagaccacaaauaucucaaggucacggcaauuccucaccaccaguuuggcauugugaag ucaaaaccaaccuucuguugauucuggguuuuuguauuucuaguaugagacauuuucuacuuu guaagaguauauaacuguggauggcggcgaggguugggcaugaugaugauuguaagcgggaa gugagcuagaguaucuucagaaacucucacuuuauccuccuuggcagcauagaaccgcaaucg cuguguccgagugucaaccaggcagucauuuuguuuuggguuuuuugucacucuuucaaag caugugcuucuacgcaacacuaccaaacacagcaugcugcauagugcuugagaaggaguuaga aaguaacaaacgaguuaucaucacguugcccuuuguguuuugcaugucuuaugcacacuuuu ggcugacagcuuuugaacauuuauuguauuucaaauuuccaguccaaauuuuuuuuucaacu ugugaaauugaacggaaugaaccgaugucgugaauaccuagggucaaauaaaacuuguauuu aaauucguaguuuuaauuucccaagcugggaaaaucguaaaaaccuuuuccaaagaacucaag

SEQ ID NO:	Sequence Type	Sequence
		ucuuaguugcuagggaaacaggcagugagcaucauauacaaaaaguaacaccaaauguucugu cauaucagcuuucuaacuaauaauaaacuauauauuucuauuuuauauaggauaaucuugcu ccaacuuggaugggguggagcgguguuccucccccucagcccuuuauuauggguacuguauu accccuuuugcuaccuuuaauccuugcacugugacuuauguguaguggggauugagggaggga gugggaagguacaauugcaccacaguagggacaauacaggauuuauuuccaaauccacuacu uuuaaugagcuuaaacuucuuuuggggaaaaaaaaaguuaucucugacuuaccaucuguggau uauaaccccagaaguacauaucuuuauuacguuucacugaauaugauuuagcuauuuauacu ucauuguccauuuauggggaaauuacucaauuggugagggugggggacccugguguaggau gcugaugaaaacguuuucauuugucaagcucaugguagugacagagcauauaguccuuauuu uuucaacacacugcucuggucccucaaugggccagucacauuccaucaguugaucguugaug ugugcgagcaguggcuaaagguacaacaggccagguaucucaggguugccaaugguuaugau cauucucaucuuuauugcauaaaaaauguguuauuugcagaaaguagcaaggcaagaucccug ugaaacaagggaauacaaaaaaaaaaaaagaugugcuuuaaguuauaaaaccaaaacaugugaa aagucaacuucauugaaguauaaagaauaggauaugcaugaaaaacaaaaaaaucaugagcac uaagaaauuggguguauaagccaacuccuuguaagcuaccccaauuaacuucccagaaucuuag aaggcaucacagugcaccccaaaauaaaaagccaaacugacacuucugcuuccucuuaaaaugu aggagucuuggauaagaaagauaauuuuuuauuguuuggaagaaaaaaaaauguuuggauaa uugaggcauuuaucuaucaaaaauauuuaucuuaauaaaauuucacaacacugauuuaguug uuggcuuuucuaaaaauuuuuuauauuucauauuaagaacucaugauuuuuacuuuccauuu uuuaaauucuuauucacauaugguuuuucucuauuucuuagaaaagcuauagaacccauggu uuccggugacuuaaaaaacuaaucuaaaugucuucacuuagaugauacuuucaaaugcacuga aauuucuaauaucaacaagaauauuugccugguccuaaauuuuucacugauuuaauaaaaagua ugaacccuaaagaagaaauagacuugaagaacugguugugugacaauacagaaauucugcugg gagauguccuuuuaaaacauuguuagaagagacaaccucuacaauccacccauuaagcauacu ucucucuuagacaucuccuuuuauguaccuuauaaccucaauguguucuuuccaauugacuu agaccaacacuucccagcgcaucccacaugggagccaauuacugacucucccuagagacugcaa agaauuaauauuguagaaccaagggaugguugggcucuugggagaggcaauccguuugugau cuuuugcucuggauguuaaugaaaucgcaacuuuaaguggauuuucaguggcaaauccucug auccuaugccaaauguucucuaagacaaacauccuuguaaaauaaaugucucacugggccaaa ucuauggcaaauuugcacguuuuccugaacugcauuccuauauaguauuugccauccugaau ucacuaaugggcauuacuuuuaauucaaaaccagucccuucuucaaaggaaaucucucccauu uauuacauuaugcaaacugcuuucuuaugcaguggguuaaauccuuagccaggcaaguaugag gacuggaauuuggauauccagaacccucagaaaugucggaugggcauaguagcuuacaugua auuccagagcuagaaagaugaaacuagcccuguccucaagcucugaauucaguuggugcaaua aauaagaaagaaucccccccccccgaccccuacaucucuuuccucuacaucuauacauguauuuc ccauacagcucuaugcuuccacauauaugcucacauaugugcaugcacacuugcacacauaug uacacuugacacauugaagcaucauaaucuaacaauuggaauauaagaaaauauuuaacuuuc

SEQ ID NO:	Sequence Type	Sequence
		acacagagcagucagagaaaaccauaagagguugaaacucuugaaaaaacuugcaggauaaaca gaaaagaguaugagaugccaauucuggucuacuuucugaaccuaacuuguuuuaccuucauu agucuaauuuuuccaaaugaacccaagcaccaaauuguccuuauugcucuuuccaguacuaaa uuauaauuccucaauucgaaggcaaacacucucaucuuuguuaaggauguguagaguuagac ucaauaaacgacauguauauuugagcuaaagccuggaggagggagauuauuucaagggcaag uacuuggcagggaguuucaaagaaagaaggcucucaauucucagacuaacaccuuagcgugga gugacugucacagaggagggugaaguguaugucaccaguuagggaagcugaaaggggaaaug uaucaggcuugugagaauccuucagcagccaagucuagcaccugagcacaaaccccagaacug accccacauggugaaaggagaggaauaauuccugcaaauuuuccugugaccuccacccaagu gcuauagaaaaugcaugcaugcccacaugcacacacaaauaaacauaguugcaaacuguuuug aggaaaauaaccucacaaacugucgagugauguaaaugccaaagaaagagaaauguuuucuaa uggcuagagaaccauuaaggaauuuuucaaaaugggacaugggauagauaaauuuaguaucc auacugaaagaaggcaagcaaauaaaaucugauaagaauguaauucuuaguaaccgaggacag agcgaagauagagaacagggccaauggccaagguggaaagguuugaaggaagcagcaugaaac cuacagacuuguaccaaaauguucaugucaugaguguuaaaagugaaaagcuugcauguua guauggauuucauauccucggcagacagagcaccucacugugagugggagaugaaguauuca gaaaugagaaacaacuacucaauuucaguguucauaucucaaauccaauaaacaacuuuaggg guacaauuuuuuuaaaaaauuacauuaaaaauguuuuuaaaucucuucuuaauaauuuaaaaau uaaauugaaaauaacuuuaaaaaguaauauauacaggaaagccugugugcuaaauuuuuuagg gaggccauaaagggagauaguugcucauuaauuucuacacaucagccuaucuuuggcuucug ccuugauagcgcacucugaauuaucuucuucauguucaucccucaucuuuauuguuacuggu uucauuucccuuggccacauagcccacuauuuuguauucccaauggauauuguuccuuaca aaguucagccagggcucagaaguacaaggaauuggcucuuauacuucugucagacaggcaaaa acuucuaaaauuauacuauaauaaaaaucaaagagaugauauucauaauuaaacuaacaaaagu ggcaggccccccccucccccaacaugaguagaauuaaucugacguccauguucaagucugaaac acacuugccaauuaagagcacauuagggccagccuuuaucucccucuuaguuacuaaugugca guucaauggugagcuauagagaaggaagccaagacuaccauaugucaaauauaaaaaaaaaaa aucccauuuuaaaucuguagucccgaauuaaggacaagagagagggaaauaucuuugacauua gaaaauggagaaaauauuuuagcacaggacuuuacucagucacaucagaguugauaaguacgu augacaucccucuuuuuccuguuuuccugagaaaaugaucucucuaguguuucauuuaagau aaguuuauugaauuaaacucaguaaaugaaacaacugacaugacuggagcuugaaauaaacga ugugaugaucuacugaaauacaugaugcuaaauugucuugcuucuuaugcaaaaacuacuau uaguuauagcaaugcauggauaauuaaggccaaaaauauauuagauguuaaaaauaguuuua uauuuauacaucugaauuuuaauuuauauuuaaaguauauugguccaaucaauucaugccca aauguuuuaguucuauucuuugagauacguuuuguuuuggguuuuuuuuuuaugagcuaa ucucuugccuaggaguuccuacuucucucuccuccuuuuauuuuuucuaauaaacuacacau gugcuucauccaggagcuaacuucucccauuuugcuuuuccuuuagcaccuuuuuuauauu

SEQ ID NO:	Sequence Type	Sequence
		agauuucuuucuuuucuccaucucuuugcauauugccuauauuucuuuuccuaagcauaaua uuuaaaaaagacugaguuuuauguuaagauuauuucugcuuugcucuuacacagauaggaua aguagucuugauagaaaauaaaucaaugauuccuaggggaugucuuuuugcuuuuaaucaa uaaggauucugacuucucuuucucuccauuuguguauuag
SEQ ID NO: 19	Exon 22 pre-mRNA	GUGGUUGUGAAUGCCCUGUUAGGAGCAAUUCCAUCCAUCAU GAAUGUGCUUCUGGUUUGCCUUAUAUUCUGGCUAAUUUUCA GCAUCAUGGGCGUAAAUUUGUUUGCUGGCAAAUUCUACCAC UGUGUUAACACCACAACUGGUGACAUAUUUGAGAUCAGCGA AGUCAAUAAUCAUUCUGAUUGCCUAAAACUAAUAGAAAGAA AUGAGACCGCCCGGUGGAAAAAUGUGAAAGUAAACUUUGAU AAUGUAGGAUUUGGGUAUCUUUCUUUGCUUCAAGUU
SEQ ID NO: 20	Exon 21x pre-mRNA	gauaaucuugcuccaacuuggaugggguggagcgggugguccucccccucagcccuuuauuau gg

Example 14: *SCN1A* Exon 20x region ASO walk.

[0925] An ASO walk was performed for *SCN1A* exon 20x region targeting sequences immediately upstream of the 3' splice site, across the 3'splice site, exon 20x, across the 5' splice site, and downstream of the 5' splice site using 2′-MOE ASOs, PS backbone. ASOs were designed to cover these regions by shifting 5 nucleotides at a time. A list of ASOs targeting *SCN1A* is summarized in **Table 3**. Sequences of ASOs are summarized in **Table 4A** and **Table 4B** and **Table 5A** and **Table 5B.**

Table 3. List of ASOs targeting *SCN1A*.

Gene SEQ ID NO:	Pre-mRNA SEQ ID NO:	ASOs SEQ ID NO:	NIE
SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NOs: 21-67, 210-256, 304-1099	Exon 20x
SEQ ID NO: 11	SEQ ID NO: 12	SEQ ID NOs: 68-114, 257-303	Exon 21x

Table 4A. Sequences of ASOs targeting human *SCN1A*.

ASO Name	SEQ ID NO:	Sequence name	ASO sequence
ASO-1A	21	SCN1A-IVS19X-81	GATGCTCTCCGTCTGTTT
ASO-2	22	SCN1A-IVS19X-76	TTCATGATGCTCTCCGTC

ASO Name	SEQ ID NO:	Sequence name	ASO sequence
ASO-3	23	SCN1A-IVS19X-71	TTTTGTTCATGATGCTCT
ASO-4	24	SCN1A-IVS19X-66	TTACTTTTTGTTCATGAT
ASO-5	25	SCN1A-IVS19X-61	TGGTGTTACTTTTTGTTC
ASO-6	26	SCN1A-IVS19X-56	ACATTTGGTGTTACTTTT
ASO-7	27	SCN1A-IVS19X-51	ACAGAACATTTGGTGTTA
ASO-8	28	SCN1A-IVS19X-46	ATATGACAGAACATTTGG
ASO-9	29	SCN1A-IVS19X-41	ATCTGATATGACAGAACA
ASO-10	30	SCN1A-IVS19X-36	TAGAAATCTGATATGACA
ASO-11	31	SCN1A-IVS19X-31	TTAGTTAGAAATCTGATA
ASO-12	32	SCN1A-IVS19X-26	TGTTATTAGTTAGAAATC
ASO-13	33	SCN1A-IVS19X-21	TAGTTTGTTATTAGTTAG
ASO-14	34	SCN1A-IVS19X-16	ATATATAGTTTGTTATTA
ASO-15	35	SCN1A-IVS19X-11	TAGAAATATATAGTTTGT
ASO-16	36	SCN1A-IVS19X-6	CAAAATAGAAATATATAG
ASO-17	37	SCN1A-IVS19X-3	ATACAAAATAGAAATATA
ASO-18	38	SCN1A-IVS19X-1	CTATACAAAATAGAAATA
ASO-19	39	SCN1A-I19X/E20X+2	TCCTATACAAAATAGAAA
ASO-20	40	SCN1A-I19X/E20X+4	TATCCTATACAAAATAGA
ASO-21	41	SCN1A-I19X/E20X+6	ATTATCCTATACAAAATA
ASO-22	42	SCN1A-Ex20X+1	AGTTGGAGCAAGATTATC
ASO-23	43	SCN1A-Ex20X+6	ATCCAAGTTGGAGCAAGA
ASO-24	44	SCN1A-Ex20X+11	ACCCCATCCAAGTTGGAG
ASO-25	45	SCN1A-Ex20X+16	GCTCCACCCCATCCAAGT
ASO-26	46	SCN1A-Ex20X+21	CCAGCGCTCCACCCCATC
ASO-27	47	SCN1A-Ex20X-24	GAACCAGCGCTCCACCCC
ASO-28	48	SCN1A-Ex20X-19	GGGAGGAACCAGCGCTCC
ASO-29	49	SCN1A-Ex20X-3	ATAATAAAGGGCTCAGGG
ASO-30	50	SCN1A-Ex20X-1	CCATAATAAAGGGCTCAG
ASO-31	51	SCN1A-E20X/I20X-6	GTAATACAGTACCCATAA
ASO-32	52	SCN1A-E20X/I20X-4	GGGTAATACAGTACCCAT
ASO-33	53	SCN1A-IVS20X+13	TTAAAGGTAGCAAAAGGG
ASO-34	54	SCN1A-IVS20X+18	AAGGATTAAAGGTAGCAA
ASO-35	55	SCN1A-IVS20X+23	AGTGCAAGGATTAAAGGT
ASO-36	56	SCN1A-IVS20X+28	GTCACAGTGCAAGGATTA
ASO-37	57	SCN1A-IVS20X+33	CATAAGTCACAGTGCAAG

ASO Name	SEQ ID NO:	Sequence name	ASO sequence
ASO-38	58	SCN1A-IVS20X+38	CTACACATAAGTCACAGT
ASO-39	59	SCN1A-IVS20X+43	CCCCACTACACATAAGTC
ASO-40	60	SCN1A-IVS20X+48	CCTCACCCCACTACACAT
ASO-41	61	SCN1A-IVS20X+53	CCCTCCCTCACCCCACTA
ASO-42	62	SCN1A-IVS20X+58	CCAATCCCTCCCTCACCC
ASO-43	63	SCN1A-IVS20X+63	CCTTCCCAATCCCTCCCT
ASO-44	64	SCN1A-IVS20X+68	AGTACCCTTCCCAATCCC
ASO-45	65	SCN1A-IVS20X+73	ATAATAGTACCCTTCCCA
ASO-46	66	SCN1A-IVS20X+78	GTGCAATAATAGTACCCT
ASO-47	67	SCN1A-IVS20X+83	CTGTGGTGCAATAATAGT

Table 4B. Sequences of ASOs targeting human *SCN1A*.

SEQ ID NO:	Sequence name	ASO sequence
210	SCN1A-IVS19X-81	GAUGCUCUCCGUCUGUUU
211	SCN1A-IVS19X-76	UUCAUGAUGCUCUCCGUC
212	SCN1A-IVS19X-71	UUUUGUUCAUGAUGCUCU
213	SCN1A-IVS19X-66	UUACUUUUUGUUCAUGAU
214	SCN1A-IVS19X-61	UGGUGUUACUUUUUGUUC
215	SCN1A-IVS19X-56	ACAUUUGGUGUUACUUUU
216	SCN1A-IVS19X-51	ACAGAACAUUUGGUGUUA
217	SCN1A-IVS19X-46	AUAUGACAGAACAUUUGG
218	SCN1A-IVS19X-41	AUCUGAUAUGACAGAACA
219	SCN1A-IVS19X-36	UAGAAAUCUGAUAUGACA
220	SCN1A-IVS19X-31	UUAGUUAGAAAUCUGAUA
221	SCN1A-IVS19X-26	UGUUAUUAGUUAGAAAUC
222	SCN1A-IVS19X-21	UAGUUUGUUAUUAGUUAG
223	SCN1A-IVS19X-16	AUAUAUAGUUUGUUAUUA
224	SCN1A-IVS19X-11	UAGAAAUAUAUAGUUUGU
225	SCN1A-IVS19X-6	CAAAAUAGAAAUAUAUAG
226	SCN1A-IVS19X-3	AUACAAAAUAGAAAUAUA
227	SCN1A-IVS19X-1	CUAUACAAAAUAGAAAUA
228	SCN1A-I19X/E20X+2	UCCUAUACAAAAUAGAAA
229	SCN1A-I19X/E20X+4	UAUCCUAUACAAAAUAGA
230	SCN1A-I19X/E20X+6	AUUAUCCUAUACAAAAUA
231	SCN1A-Ex20X+1	AGUUGGAGCAAGAUUAUC

SEQ ID NO:	Sequence name	ASO sequence
232	SCN1A-Ex20X+6	AUCCAAGUUGGAGCAAGA
233	SCN1A-Ex20X+11	ACCCCAUCCAAGUUGGAG
234	SCN1A-Ex20X+16	GCUCCACCCCAUCCAAGU
235	SCN1A-Ex20X+21	CCAGCGCUCCACCCCAUC
236	SCN1A-Ex20X-24	GAACCAGCGCUCCACCCC
237	SCN1A-Ex20X-19	GGGAGGAACCAGCGCUCC
238	SCN1A-Ex20X-3	AUAAUAAAGGGCUCAGGG
239	SCN1A-Ex20X-1	CCAUAAUAAAGGGCUCAG
240	SCN1A-E20X/I20X-6	GUAAUACAGUACCCAUAA
241	SCN1A-E20X/I20X-4	GGGUAAUACAGUACCCAU
242	SCN1A-IVS20X+13	UUAAAGGUAGCAAAAGGG
243	SCN1A-IVS20X+18	AAGGAUUAAAGGUAGCAA
244	SCN1A-IVS20X+23	AGUGCAAGGAUUAAAGGU
245	SCN1A-IVS20X+28	GUCACAGUGCAAGGAUUA
246	SCN1A-IVS20X+33	CAUAAGUCACAGUGCAAG
247	SCN1A-IVS20X+38	CUACACAUAAGUCACAGU
248	SCN1A-IVS20X+43	CCCCACUACACAUAAGUC
249	SCN1A-IVS20X+48	CCUCACCCCACUACACAU
250	SCN1A-IVS20X+53	CCCUCCCUCACCCCACUA
251	SCN1A-IVS20X+58	CCAAUCCCUCCCUCACCC
252	SCN1A-IVS20X+63	CCUUCCCAAUCCCUCCCU
253	SCN1A-IVS20X+68	AGUACCCUUCCCAAUCCC
254	SCN1A-IVS20X+73	AUAAUAGUACCCUUCCCA
255	SCN1A-IVS20X+78	GUGCAAUAAUAGUACCCU
256	SCN1A-IVS20X+83	CUGUGGUGCAAUAAUAGU

Table 5A. Sequences of ASOs targeting mouse *SCN1A*.

SEQ ID NO:	Sequence name	ASO sequence
68	mScn1a-IVS20X-81	GATGCTCACTGCCTGTTT
69	mScn1a-IVS20X-76	TATATGATGCTCACTGCC
70	mScn1a-IVS20X-71	TTTTGTATATGATGCTCA
71	mScn1a-IVS20X-66	TTACTTTTTGTATATGAT
72	mScn1a-IVS20X-61	TGGTGTTACTTTTTGTAT
73	mScn1a-IVS20X-56	ACATTTGGTGTTACTTTT
74	mScn1a-IVS20X-51	ACAGAACATTTGGTGTTA
75	mScn1a-IVS20X-46	ATATGACAGAACATTTGG

SEQ ID NO:	Sequence name	ASO sequence
76	mScn1a-IVS20X-41	AGCTGATATGACAGAACA
77	mScn1a-IVS20X-36	TAGAAAGCTGATATGACA
78	mScn1a-IVS20X-31	TTAGTTAGAAAGCTGATA
79	mScn1a-IVS20X-26	TATTATTAGTTAGAAAGC
80	mScn1a-IVS20X-21	TAGTTTATTATTAGTTAG
81	mScn1a-IVS20X-16	ATATATAGTTTATTATTA
82	mScn1a-IVS20X-11	TAGAAATATATAGTTTAT
83	mScn1a-IVS20X-6	TAAAATAGAAATATATAG
84	mScn1a-IVS20X-3	ATATAAAATAGAAATATA
85	mScn1a-IVS20X-1	CTATATAAAATAGAAATA
86	mScn1a-I20X/E21X+2	TCCTATATAAAATAGAAA
87	mScn1a-I20X/E21X+4	TATCCTATATAAAATAGA
88	mScn1a-I20X/E21X+6	ATTATCCTATATAAAATA
89	mScn1a-Ex21X+1	AGTTGGAGCAAGATTATC
90	mScn1a-Ex21X+6	ATCCAAGTTGGAGCAAGA
91	mScn1a-Ex21X+11	ACCCCATCCAAGTTGGAG
92	mScn1a-Ex21X+16	GCTCCACCCCATCCAAGT
93	mScn1a-Ex21X+21	CCACCGCTCCACCCCATC
94	mScn1a-Ex21X-24	GAACCACCGCTCCACCCC
95	mScn1a-Ex21X-19	GGGAGGAACCACCGCTCC
96	mScn1a-Ex21X-3	ATAATAAAGGGCTGAGGG
97	mScn1a-Ex21X-1	CCATAATAAAGGGCTGAG
98	mScn1a-E21X/I21X-6	GTAATACAGTACCCATAA
99	mScn1a-E21X/I21X-4	GGGTAATACAGTACCCAT
100	mScn1a-IVS21X+13	TTAAAGGTAGCAAAAGGG
101	mScn1a-IVS21X+18	AAGGATTAAAGGTAGCAA
102	mScn1a-IVS21X+23	AGTGCAAGGATTAAAGGT
103	mScn1a-IVS21X+28	GTCACAGTGCAAGGATTA
104	mScn1a-IVS21X+33	CATAAGTCACAGTGCAAG
105	mScn1a-IVS21X+38	CTACACATAAGTCACAGT
106	mScn1a-IVS21X+43	TCCCACTACACATAAGTC
107	mScn1a-IVS21X+48	CTCAATCCCACTACACAT
108	mScn1a-IVS21X+53	CCTCCCTCAATCCCACTA
109	mScn1a-IVS21X+58	CACTCCCTCCCTCAATCC
110	mScn1a-IVS21X+63	CTTCCCACTCCCTCCCTC
111	mScn1a-IVS21X+68	GTACCCTTCCCACTCCCT

SEQ ID NO:	Sequence name	ASO sequence
112	mScn1a-IVS21X+73	CAATTGTACCCTTCCCAC
113	mScn1a-IVS21X+78	TGGTGCAATTGTACCCTT
114	mScn1a-IVS21X+83	TACTGTGGTGCAATTGTA

Table 5B. Sequences of ASOs targeting mouse *SCN1A*.

SEQ ID NO:	Sequence name	ASO sequence
257	mScn1a-IVS20X-81	GAUGCUCACUGCCUGUUU
258	mScn1a-IVS20X-76	UAUAUGAUGCUCACUGCC
259	mScn1a-IVS20X-71	UUUUGUAUAUGAUGCUCA
260	mScn1a-IVS20X-66	UUACUUUUUGUAUAUGAU
261	mScn1a-IVS20X-61	UGGUGUUACUUUUUGUAU
262	mScn1a-IVS20X-56	ACAUUUGGUGUUACUUUU
263	mScn1a-IVS20X-51	ACAGAACAUUUGGUGUUA
264	mScn1a-IVS20X-46	AUAUGACAGAACAUUUGG
265	mScn1a-IVS20X-41	AGCUGAUAUGACAGAACA
266	mScn1a-IVS20X-36	UAGAAAGCUGAUAUGACA
267	mScn1a-IVS20X-31	UUAGUUAGAAAGCUGAUA
268	mScn1a-IVS20X-26	UAUUAUUAGUUAGAAAGC
269	mScn1a-IVS20X-21	UAGUUUAUUAUUAGUUAG
270	mScn1a-IVS20X-16	AUAUAUAGUUUAUUAUUA
271	mScn1a-IVS20X-11	UAGAAAUAUAUAGUUUAU
272	mScn1a-IVS20X-6	UAAAAUAGAAAUAUAUAG
273	mScn1a-IVS20X-3	AUAUAAAAUAGAAAUAUA
274	mScn1a-IVS20X-1	CUAUAUAAAAUAGAAAUA
275	mScn1a-I20X/E21X+2	UCCUAUAUAAAAUAGAAA
276	mScn1a-I20X/E21X+4	UAUCCUAUAUAAAAUAGA
277	mScn1a-I20X/E21X+6	AUUAUCCUAUAUAAAAUA
278	mScn1a-Ex21X+1	AGUUGGAGCAAGAUUAUC
279	mScn1a-Ex21X+6	AUCCAAGUUGGAGCAAGA
280	mScn1a-Ex21X+11	ACCCCAUCCAAGUUGGAG
281	mScn1a-Ex21X+16	GCUCCACCCCAUCCAAGU
282	mScn1a-Ex21X+21	CCACCGCUCCACCCCAUC
283	mScn1a-Ex21X-24	GAACCACCGCUCCACCCC
284	mScn1a-Ex21X-19	GGGAGGAACCACCGCUCC
285	mScn1a-Ex21X-3	AUAAUAAAGGGCUGAGGG
286	mScn1a-Ex21X-1	CCAUAAUAAAGGGCUGAG

SEQ ID NO:	Sequence name	ASO sequence
287	mScn1a-E21X/I21X-6	GUAAUACAGUACCCAUAA
288	mScn1a-E21X/I21X-4	GGGUAAUACAGUACCCAU
289	mScn1a-IVS21X+13	UUAAAGGUAGCAAAAGGG
290	mScn1a-IVS21X+18	AAGGAUUAAAGGUAGCAA
291	mScn1a-IVS21X+23	AGUGCAAGGAUUAAAGGU
292	mScn1a-IVS21X+28	GUCACAGUGCAAGGAUUA
293	mScn1a-IVS21X+33	CAUAAGUCACAGUGCAAG
294	mScn1a-IVS21X+38	CUACACAUAAGUCACAGU
295	mScn1a-IVS21X+43	UCCCACUACACAUAAGUC
296	mScn1a-IVS21X+48	CUCAAUCCCACUACACAU
297	mScn1a-IVS21X+53	CCUCCCUCAAUCCCACUA
298	mScn1a-IVS21X+58	CACUCCCUCCCUCAAUCC
299	mScn1a-IVS21X+63	CUUCCCACUCCCUCCCUC
300	mScn1a-IVS21X+68	GUACCCUUCCCACUCCCU
301	mScn1a-IVS21X+73	CAAUUGUACCCUUCCCAC
302	mScn1a-IVS21X+78	UGGUGCAAUUGUACCCUU
303	mScn1a-IVS21X+83	UACUGUGGUGCAAUUGUA

[0926] Sequences of ASOs are summarized in **Table 6.**

Table 6. Sequences of ASOs targeting human *SCN1A.*

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-986	166864788	16686 4806	380	ATGAATTTAATAAACTTT	740	AUGAAUUUAAUAAACUUU
SCN1A-IVS22-981	166864783	16686 4801	381	GACCAATGAATTTAATAA	741	GACCAAUGAAUUUAAUAA
SCN1A-IVS22-976	166864778	16686 4796	382	CACTTGACCAATGAATTT	742	CACUUGACCAAUGAAUUU
SCN1A-IVS22-971	166864773	16686 4791	383	CTGAGCACTTGACCAATG	743	CUGAGCACUUGACCAAUG
SCN1A-IVS22-966	166864768	16686 4786	384	AATATCTGAGCACTTGAC	744	AAUAUCUGAGCACUUGAC
SCN1A-IVS22-961	166864763	16686 4781	385	ATGGAAATATCTGAGCAC	745	AUGGAAAUAUCUGAGCAC
SCN1A-IVS22-956	166864758	16686 4776	386	AATGTATGGAAATATCTG	746	AAUGUAUGGAAAUAUCUG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-951	166864753	166864771	387	AGTGTAATGTATGGAAAT	747	AGUGUAAUGUAUGGAAAU
SCN1A-IVS22-946	166864748	166864766	388	AATGAAGTGTAATGTATG	748	AAUGAAGUGUAAUGUAUG
SCN1A-IVS22-941	166864743	166864761	389	ATAGAAATGAAGTGTAAT	749	AUAGAAAUGAAGUGUAAU
SCN1A-IVS22-936	166864738	166864756	390	TTTTTATAGAAATGAAGT	750	UUUUUAUAGAAAUGAAGU
SCN1A-IVS22-931	166864733	166864751	391	CAGCTTTTTTATAGAAAT	751	CAGCUUUUUUAUAGAAAU
SCN1A-IVS22-926	166864728	166864746	392	AAGATCAGCTTTTTTATA	752	AAGAUCAGCUUUUUUAUA
SCN1A-IVS22-921	166864723	166864741	393	CCGATAAGATCAGCTTTT	753	CCGAUAAGAUCAGCUUUU
SCN1A-IVS22-916	166864718	166864736	394	GTATACCGATAAGATCAG	754	GUAUACCGAUAAGAUCAG
SCN1A-IVS22-911	166864713	166864731	395	TAAAAGTATACCGATAAG	755	UAAAAGUAUACCGAUAAG
SCN1A-IVS22-906	166864708	166864726	396	AAAATTAAAAGTATACCG	756	AAAAUUAAAAGUAUACCG
SCN1A-IVS22-901	166864703	166864721	397	CTGAGAAAATTAAAAGTA	757	CUGAGAAAAUUAAAAGUA
SCN1A-IVS22-896	166864698	166864716	398	TATTTCTGAGAAAATTAA	758	UAUUUCUGAGAAAAUUAA
SCN1A-IVS22-891	166864693	166864711	399	ATGGTTATTTCTGAGAAA	759	AUGGUUAUUUCUGAGAAA
SCN1A-IVS22-886	166864688	166864706	400	TAGATATGGTTATTTCTG	760	UAGAUAUGGUUAUUUCUG
SCN1A-IVS22-881	166864683	166864701	401	AATTATAGATATGGTTAT	761	AAUUAUAGAUAUGGUUAU
SCN1A-IVS22-876	166864678	166864696	402	TTAATAATTATAGATATG	762	UUAAUAAUUAUAGAUAUG
SCN1A-IVS22-871	166864673	166864691	403	ATTGATTAATAATTATAG	763	AUUGAUUAAUAAUUAUAG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-866	166864668	16686 4686	404	GCATTATTGATTAATAAT	764	GCAUUAUUGAUUAAUAAU
SCN1A-IVS22-861	166864663	16686 4681	405	AAAAGGCATTATTGATTA	765	AAAAGGCAUUAUUGAUUA
SCN1A-IVS22-856	166864658	16686 4676	406	AATATAAAAGGCATTATT	766	AAUAUAAAAGGCAUUAUU
SCN1A-IVS22-851	166864653	16686 4671	407	CTTTTAATATAAAAGGCA	767	CUUUUAAUAUAAAAGGCA
SCN1A-IVS22-846	166864648	16686 4666	408	AACCTCTTTTAATATAAA	768	AACCUCUUUUAAUAUAAA
SCN1A-IVS22-841	166864643	16686 4661	409	AAACTAACCTCTTTTAAT	769	AAACUAACCUCUUUUAAU
SCN1A-IVS22-836	166864638	16686 4656	410	TTCAAAAACTAACCTCTT	770	UUCAAAAACUAACCUCUU
SCN1A-IVS22-831	166864633	16686 4651	411	CAAGTTTCAAAAACTAAC	771	CAAGUUUCAAAAACUAAC
SCN1A-IVS22-826	166864628	16686 4646	412	AACTCCAAGTTTCAAAAA	772	AACUCCAAGUUUCAAAAA
SCN1A-IVS22-821	166864623	16686 4641	413	TCTAAAACTCCAAGTTTC	773	UCUAAAACUCCAAGUUUC
SCN1A-IVS22-816	166864618	16686 4636	414	TTATGTCTAAAACTCCAA	774	UUAUGUCUAAAACUCCAA
SCN1A-IVS22-811	166864613	16686 4631	415	GGATTTTATGTCTAAAAC	775	GGAUUUUAUGUCUAAAAC
SCN1A-IVS22-806	166864608	16686 4626	416	TATAAGGATTTTATGTCT	776	UAUAAGGAUUUUAUGUCU
SCN1A-IVS22-801	166864603	16686 4621	417	GCATTTATAAGGATTTTA	777	GCAUUUAUAAGGAUUUUA
SCN1A-IVS22-796	166864598	16686 4616	418	TATCAGCATTTATAAGGA	778	UAUCAGCAUUUAUAAGGA
SCN1A-IVS22-791	166864593	16686 4611	419	ATCACTATCAGCATTTAT	779	AUCACUAUCAGCAUUUAU
SCN1A-IVS22-786	166864588	16686 4606	420	GTTATATCACTATCAGCA	780	GUUAUAUCACUAUCAGCA

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-781	166864583	16686 4601	421	TATTAGTTATATCACTAT	781	UAUUAGUUAUAUCACUAU
SCN1A-IVS22-776	166864578	16686 4596	422	TAAACTATTAGTTATATC	782	UAAACUAUUAGUUAUAUC
SCN1A-IVS22-771	166864573	16686 4591	423	CCATTTAAACTATTAGTT	783	CCAUUUAAACUAUUAGUU
SCN1A-IVS22-766	166864568	16686 4586	424	TCTGACCATTTAAACTAT	784	UCUGACCAUUUAAACUAU
SCN1A-IVS22-761	166864563	16686 4581	425	ATAAATCTGACCATTTAA	785	AUAAAUCUGACCAUUUAA
SCN1A-IVS22-756	166864558	16686 4576	426	TATTCATAAATCTGACCA	786	UAUUCAUAAAUCUGACCA
SCN1A-IVS22-751	166864553	16686 4571	427	AGCCATATTCATAAATCT	787	AGCCAUAUUCAUAAAUCU
SCN1A-IVS22-746	166864548	16686 4566	428	AATAGAGCCATATTCATA	788	AAUAGAGCCAUAUUCAUA
SCN1A-IVS22-741	166864543	16686 4561	429	TGAGGAATAGAGCCATAT	789	UGAGGAAUAGAGCCAUAU
SCN1A-IVS22-736	166864538	16686 4556	430	CATTATGAGGAATAGAGC	790	CAUUAUGAGGAAUAGAGC
SCN1A-IVS22-731	166864533	16686 4551	431	GTTGTCATTATGAGGAAT	791	GUUGUCAUUAUGAGGAAU
SCN1A-IVS22-726	166864528	16686 4546	432	TGTATGTTGTCATTATGA	792	UGUAUGUUGUCAUUAUGA
SCN1A-IVS22-721	166864523	16686 4541	433	CTGTGTGTATGTTGTCAT	793	CUGUGUGUAUGUUGUCAU
SCN1A-IVS22-716	166864518	16686 4536	434	TAGTGCTGTGTGTATGTT	794	UAGUGCUGUGUGUAUGUU
SCN1A-IVS22-711	166864513	16686 4531	435	CATTTTAGTGCTGTGTGT	795	CAUUUUAGUGCUGUGUGU
SCN1A-IVS22-706	166864508	16686 4526	436	TTAGTCATTTTAGTGCTG	796	UUAGUCAUUUUAGUGCUG
SCN1A-IVS22-701	166864503	16686 4521	437	AGAGATTAGTCATTTTAG	797	AGAGAUUAGUCAUUUUAG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-696	166864498	16686 4516	438	ATTGAAGAGATTAGTCAT	798	AUUGAAGAGAUUAGUCAU
SCN1A-IVS22-691	166864493	16686 4511	439	CACGTATTGAAGAGATTA	799	CACGUAUUGAAGAGAUUA
SCN1A-IVS22-686	166864488	16686 4506	440	CCAAACACGTATTGAAGA	800	CCAAACACGUAUUGAAGA
SCN1A-IVS22-681	166864483	16686 4501	441	CAATGCCAAACACGTATT	801	CAAUGCCAAACACGUAUU
SCN1A-IVS22-676	166864478	16686 4496	442	CTCTACAATGCCAAACAC	802	CUCUACAAUGCCAAACAC
SCN1A-IVS22-671	166864473	16686 4491	443	TTTGACTCTACAATGCCA	803	UUUGACUCUACAAUGCCA
SCN1A-IVS22-666	166864468	16686 4486	444	GTTATTTTGACTCTACAA	804	GUUAUUUUGACUCUACAA
SCN1A-IVS22-661	166864463	16686 4481	445	ATAACGTTATTTTGACTC	805	AUAACGUUAUUUUGACUC
SCN1A-IVS22-656	166864458	16686 4476	446	CAATTATAACGTTATTTT	806	CAAUUAUAACGUUAUUUU
SCN1A-IVS22-651	166864453	16686 4471	447	AGAATCAATTATAACGTT	807	AGAAUCAAUUAUAACGUU
SCN1A-IVS22-646	166864448	16686 4466	448	AAAATAGAATCAATTATA	808	AAAAUAGAAUCAAUUAUA
SCN1A-IVS22-641	166864443	16686 4461	449	TATAAAAAATAGAATCAA	809	UAUAAAAAAUAGAAUCAA
SCN1A-IVS22-636	166864438	16686 4456	450	AGAAGTATAAAAAATAGA	810	AGAAGUAUAAAAAAUAGA
SCN1A-IVS22-631	166864433	16686 4451	451	ACACTAGAAGTATAAAAA	811	ACACUAGAAGUAUAAAAA
SCN1A-IVS22-626	166864428	16686 4446	452	TCCAAACACTAGAAGTAT	812	UCCAAACACUAGAAGUAU
SCN1A-IVS22-621	166864423	16686 4441	453	AAATATCCAAACACTAGA	813	AAAUAUCCAAACACUAGA
SCN1A-IVS22-616	166864418	16686 4436	454	AAATAAAATATCCAAACA	814	AAAUAAAAUAUCCAAACA

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-611	166864413	16686 4431	455	TTACAAAATAAAATATCC	815	UUACAAAAUAAAAUAUCC
SCN1A-IVS22-606	166864408	16686 4426	456	TATTTTTACAAAATAAAA	816	UAUUUUUACAAAAUAAAA
SCN1A-IVS22-601	166864403	16686 4421	457	GATTATATTTTTACAAAA	817	GAUUAUAUUUUUACAAAA
SCN1A-IVS22-596	166864398	16686 4416	458	TTCATGATTATATTTTTA	818	UUCAUGAUUAUAUUUUUA
SCN1A-IVS22-591	166864393	16686 4411	459	CATCATTCATGATTATAT	819	CAUCAUUCAUGAUUAUAU
SCN1A-IVS22-586	166864388	16686 4406	460	CTCACCATCATTCATGAT	820	CUCACCAUCAUUCAUGAU
SCN1A-IVS22-581	166864383	16686 4401	461	CCAACCTCACCATCATTC	821	CCAACCUCACCAUCAUUC
SCN1A-IVS22-576	166864378	16686 4396	462	TATATCCAACCTCACCAT	822	UAUAUCCAACCUCACCAU
SCN1A-IVS22-571	166864373	16686 4391	463	ATTCTTATATCCAACCTC	823	AUUCUUAUAUCCAACCUC
SCN1A-IVS22-566	166864368	16686 4386	464	TCATCATTCTTATATCCA	824	UCAUCAUUCUUAUAUCCA
SCN1A-IVS22-561	166864363	16686 4381	465	CATAATCATCATTCTTAT	825	CAUAAUCAUCAUUCUUAU
SCN1A-IVS22-556	166864358	16686 4376	466	CCAATCATAATCATCATT	826	CCAAUCAUAAUCAUCAUU
SCN1A-IVS22-551	166864353	16686 4371	467	ACTTCCCAATCATAATCA	827	ACUUCCCAAUCAUAAUCA
SCN1A-IVS22-546	166864348	16686 4366	468	ATCTCACTTCCCAATCAT	828	AUCUCACUUCCCAAUCAU
SCN1A-IVS22-541	166864343	16686 4361	469	TTCAAATCTCACTTCCCA	829	UUCAAAUCUCACUUCCCA
SCN1A-IVS22-536	166864338	16686 4356	470	GCATGTTCAAATCTCACT	830	GCAUGUUCAAAUCUCACU
SCN1A-IVS22-531	166864333	16686 4351	471	TCTGAGCATGTTCAAATC	831	UCUGAGCAUGUUCAAAUC

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-526	166864328	16686 4346	472	GAGTTTCTGAGC ATGTTC	832	GAGUUUCUGAG CAUGUUC
SCN1A-IVS22-521	166864323	16686 4341	473	AATGAGAGTTTC TGAGCA	833	AAUGAGAGUUU CUGAGCA
SCN1A-IVS22-516	166864318	16686 4336	474	AATTAAATGAGA GTTTCT	834	AAUUAAAUGAG AGUUUCU
SCN1A-IVS22-511	166864313	16686 4331	475	CAAAGAATTAA ATGAGAG	835	CAAAGAAUUAA AUGAGAG
SCN1A-IVS22-506	166864308	16686 4326	476	TAGGGCAAAGA ATTAAAT	836	UAGGGCAAAGA AUUAAAU
SCN1A-IVS22-501	166864303	16686 4321	477	GCTGCTAGGGCA AAGAAT	837	GCUGCUAGGGCA AAGAAU
SCN1A-IVS22-496	166864298	16686 4316	478	TTTATGCTGCTA GGGCAA	838	UUUAUGCUGCU AGGGCAA
SCN1A-IVS22-491	166864293	16686 4311	479	GTGATTTTATGC TGCTAG	839	GUGAUUUUAUG CUGCUAG
SCN1A-IVS22-486	166864288	16686 4306	480	CTATTGTGATTT TATGCT	840	CUAUUGUGAUU UUAUGCU
SCN1A-IVS22-481	166864283	16686 4301	481	CGCAGCTATTGT GATTTT	841	CGCAGCUAUUGU GAUUUU
SCN1A-IVS22-476	166864278	16686 4296	482	TTTGACGCAGCT ATTGTG	842	UUUGACGCAGCU AUUGUG
SCN1A-IVS22-471	166864273	16686 4291	483	TACGCTTTGACG CAGCTA	843	UACGCUUUGACG CAGCUA
SCN1A-IVS22-466	166864268	16686 4286	484	TGAGTTACGCTT TGACGC	844	UGAGUUACGCU UUGACGC
SCN1A-IVS22-461	166864263	16686 4281	485	GTGCCTGAGTTA CGCTTT	845	GUGCCUGAGUU ACGCUUU
SCN1A-IVS22-456	166864258	16686 4276	486	AATGAGTGCCTG AGTTAC	846	AAUGAGUGCCU GAGUUAC
SCN1A-IVS22-451	166864253	16686 4271	487	AATAAAATGAGT GCCTGA	847	AAUAAAAUGAG UGCCUGA
SCN1A-IVS22-446	166864248	16686 4266	488	ACAAAAATAAA ATGAGTG	848	ACAAAAAUAAA AUGAGUG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-441	166864243	16686 4261	489	GAACAACAAAA ATAAAAT	849	GAACAACAAAA AUAAAAU
SCN1A-IVS22-436	166864238	16686 4256	490	TAACAGAACAA CAAAAAT	850	UAACAGAACAAC AAAAAU
SCN1A-IVS22-431	166864233	16686 4251	491	AAAAATAACAG AACAACA	851	AAAAAUAACAG AACAACA
SCN1A-IVS22-426	166864228	16686 4246	492	TTTGAAAAAATA ACAGAA	852	UUUGAAAAAAU AACAGAA
SCN1A-IVS22-421	166864223	16686 4241	493	CATGCTTTGAAA AAATAA	853	CAUGCUUUGAA AAAAUAA
SCN1A-IVS22-416	166864218	16686 4236	494	AAGCACATGCTT TGAAAA	854	AAGCACAUGCUU UGAAAA
SCN1A-IVS22-411	166864213	16686 4231	495	CATAAAAGCAC ATGCTTT	855	CAUAAAAGCACA UGCUUU
SCN1A-IVS22-406	166864208	16686 4226	496	TGTTGCATAAAA GCACAT	856	UGUUGCAUAAA AGCACAU
SCN1A-IVS22-401	166864203	16686 4221	497	AGTAATGTTGCA TAAAAG	857	AGUAAUGUUGC AUAAAAG
SCN1A-IVS22-396	166864198	16686 4216	498	TATTCAGTAATG TTGCAT	858	UAUUCAGUAAU GUUGCAU
SCN1A-IVS22-391	166864193	16686 4211	499	TGCTTTATTCAG TAATGT	859	UGCUUUAUUCA GUAAUGU
SCN1A-IVS22-386	166864188	16686 4206	500	CAACATGCTTTA TTCAGT	860	CAACAUGCUUUA UUCAGU
SCN1A-IVS22-381	166864183	16686 4201	501	CTGTACAACATG CTTTAT	861	CUGUACAACAUG CUUUAU
SCN1A-IVS22-376	166864178	16686 4196	502	AAGCACTGTACA ACATGC	862	AAGCACUGUACA ACAUGC
SCN1A-IVS22-371	166864173	16686 4191	503	TTATCAAGCACT GTACAA	863	UUAUCAAGCACU GUACAA
SCN1A-IVS22-366	166864168	16686 4186	504	ACTTCTTATCAA GCACTG	864	ACUUCUUAUCAA GCACUG
SCN1A-IVS22-361	166864163	16686 4181	505	TTCTAACTTCTT ATCAAG	865	UUCUAACUUCUU AUCAAG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-356	166864158	166864176	506	TTACTTTCTAACTTCTTA	866	UUACUUUCUAACUUCUUA
SCN1A-IVS22-351	166864153	166864171	507	ATTTGTTACTTTCTAACT	867	AUUUGUUACUUUCUAACU
SCN1A-IVS22-346	166864148	166864166	508	AATTTATTTGTTACTTTC	868	AAUUUAUUUGUUACUUUC
SCN1A-IVS22-341	166864143	166864161	509	ATGATAATTTATTTGTTA	869	AUGAUAAUUUAUUUGUUA
SCN1A-IVS22-336	166864138	166864156	510	ACGTGATGATAATTTATT	870	ACGUGAUGAUAAUUUAUU
SCN1A-IVS22-331	166864133	166864151	511	GTGCAACGTGATGATAAT	871	GUGCAACGUGAUGAUAAU
SCN1A-IVS22-326	166864128	166864146	512	ACAAAGTGCAACGTGATG	872	ACAAAGUGCAACGUGAUG
SCN1A-IVS22-321	166864123	166864141	513	AAAACACAAAGTGCAACG	873	AAAACACAAAGUGCAACG
SCN1A-IVS22-316	166864118	166864136	514	CATGCAAAACACAAAGTG	874	CAUGCAAAACACAAAGUG
SCN1A-IVS22-311	166864113	166864131	515	TAAAACATGCAAAACACA	875	UAAAACAUGCAAAACACA
SCN1A-IVS22-306	166864108	166864126	516	GTGCATAAAACATGCAAA	876	GUGCAUAAAACAUGCAAA
SCN1A-IVS22-301	166864103	166864121	517	GAAATGTGCATAAAACAT	877	GAAAUGUGCAUAAAACAU
SCN1A-IVS22-296	166864098	166864116	518	AGCCAGAAATGTGCATAA	878	AGCCAGAAAUGUGCAUAA
SCN1A-IVS22-291	166864093	166864111	519	CTGTCAGCCAGAAATGTG	879	CUGUCAGCCAGAAAUGUG
SCN1A-IVS22-286	166864088	166864106	520	AAAAGCTGTCAGCCAGAA	880	AAAAGCUGUCAGCCAGAA
SCN1A-IVS22-281	166864083	166864101	521	TGTTTAAAAGCTGTCAGC	881	UGUUUAAAAGCUGUCAGC
SCN1A-IVS22-276	166864078	166864096	522	ATAAATGTTTAAAAGCTG	882	AUAAAUGUUUAAAAGCUG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-271	166864073	166864091	523	ATACAATAAATGTTTAAA	883	AUACAAUAAAUGUUUAAA
SCN1A-IVS22-266	166864068	166864086	524	TTGAAATACAATAAATGT	884	UUGAAAUACAAUAAAUGU
SCN1A-IVS22-261	166864063	166864081	525	GAAATTTGAAATACAATA	885	GAAAUUUGAAAUACAAUA
SCN1A-IVS22-256	166864058	166864076	526	GACTGGAAATTTGAAATA	886	GACUGGAAAUUUGAAAUA
SCN1A-IVS22-251	166864053	166864071	527	ATTTGGACTGGAAATTTG	887	AUUUGGACUGGAAAUUUG
SCN1A-IVS22-246	166864048	166864066	528	GAAAAATTTGGACTGGAA	888	GAAAAAUUUGGACUGGAA
SCN1A-IVS22-241	166864043	166864061	529	AAGTTGAAAAATTTGGAC	889	AAGUUGAAAAAUUUGGAC
SCN1A-IVS22-236	166864038	166864056	530	TTTACAAGTTGAAAAATT	890	UUUACAAGUUGAAAAAUU
SCN1A-IVS22-231	166864033	166864051	531	TTAATTTTACAAGTTGAA	891	UUAAUUUUACAAGUUGAA
SCN1A-IVS22-226	166864028	166864046	532	TCAGTTTAATTTTACAAG	892	UCAGUUUAAUUUUACAAG
SCN1A-IVS22-221	166864023	166864041	533	TTCACTCAGTTTAATTTT	893	UUCACUCAGUUUAAUUUU
SCN1A-IVS22-216	166864018	166864036	534	ATCAATTCACTCAGTTTA	894	AUCAAUUCACUCAGUUUA
SCN1A-IVS22-211	166864013	166864031	535	ACGACATCAATTCACTCA	895	ACGACAUCAAUUCACUCA
SCN1A-IVS22-206	166864008	166864026	536	TATTCACGACATCAATTC	896	UAUUCACGACAUCAAUUC
SCN1A-IVS22-201	166864003	166864021	537	CTAGATATTCACGACATC	897	CUAGAUAUUCACGACAUC
SCN1A-IVS22-196	166863998	166864016	538	TTACCCTAGATATTCACG	898	UUACCCUAGAUAUUCACG
SCN1A-IVS22-191	166863993	166864011	539	TTATTTTACCCTAGATAT	899	UUAUUUUACCCUAGAUAU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-186	166863988	16686 4006	540	AAATTTTATTTT ACCCTA	900	AAAUUUUAUUU UACCCUA
SCN1A-IVS22-181	166863983	16686 4001	541	AACACAAATTTT ATTTTA	901	AACACAAAUUU UAUUUUA
SCN1A-IVS22-176	166863978	16686 3996	542	ATTTAAACACAA ATTTTA	902	AUUUAAACACA AAUUUUA
SCN1A-IVS22-171	166863973	16686 3991	543	TACAAATTTAAA CACAAA	903	UACAAAUUUAA ACACAAA
SCN1A-IVS22-166	166863968	16686 3986	544	AAAAATACAAA TTTAAAC	904	AAAAAUACAAA UUUAAAC
SCN1A-IVS22-161	166863963	16686 3981	545	AAATTAAAAATA CAAATT	905	AAAUUAAAAAU ACAAAUU
SCN1A-IVS22-156	166863958	16686 3976	546	TTAGGAAATTAA AAATAC	906	UUAGGAAAUUA AAAAUAC
SCN1A-IVS22-151	166863953	16686 3971	547	CTAGGTTAGGAA ATTAAA	907	CUAGGUUAGGA AAUUAAA
SCN1A-IVS22-146	166863948	16686 3966	548	ATTTCCTAGGTT AGGAAA	908	AUUUCCUAGGU UAGGAAA
SCN1A-IVS22-141	166863943	16686 3961	549	TTAAGATTTCCT AGGTTA	909	UUAAGAUUUCC UAGGUUA
SCN1A-IVS22-136	166863938	16686 3956	550	GGTATTTAAGAT TTCCTA	910	GGUAUUUAAGA UUUCCUA
SCN1A-IVS22-131	166863933	16686 3951	551	AAGAAGGTATTT AAGATT	911	AAGAAGGUAUU UAAGAUU
SCN1A-IVS22-126	166863928	16686 3946	552	TGAAAAAGAAG GTATTTA	912	UGAAAAAGAAG GUAUUUA
SCN1A-IVS22-121	166863923	16686 3941	553	TCTTTTGAAAAA GAAGGT	913	UCUUUUGAAAA AGAAGGU
SCN1A-IVS22-116	166863918	16686 3936	554	TGAGTTCTTTTG AAAAAG	914	UGAGUUCUUUU GAAAAAG
SCN1A-IVS22-111	166863913	16686 3931	555	AGACTTGAGTTC TTTTGA	915	AGACUUGAGUU CUUUUGA
SCN1A-IVS22-106	166863908	16686 3926	556	CATTAAGACTTG AGTTCT	916	CAUUAAGACUU GAGUUCU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS22-101	166863903	166863921	557	CTATCCATTAAGACTTGA	917	CUAUCCAUUAAGACUUGA
SCN1A-IVS22-096	166863898	166863916	558	TTTCCCTATCCATTAAGA	918	UUUCCCUAUCCAUUAAGA
SCN1A-IVS22-091	166863893	166863911	559	GTCTGTTTCCCTATCCAT	919	GUCUGUUUCCCUAUCCAU
SCN1A-IVS23+091	166863631	166863649	560	TTTCCCTACTGTGGTGCA	920	UUUCCCUACUGUGGUGCA
SCN1A-IVS23+096	166863626	166863644	561	TGTATTTTCCCTACTGTG	921	UGUAUUUUCCCUACUGUG
SCN1A-IVS23+101	166863621	166863639	562	AATAATGTATTTTCCCTA	922	AAUAAUGUAUUUUCCCUA
SCN1A-IVS23+106	166863616	166863634	563	ATGTAAATAATGTATTTT	923	AUGUAAAUAAUGUAUUUU
SCN1A-IVS23+111	166863611	166863629	564	TTAGGATGTAAATAATGT	924	UUAGGAUGUAAAUAAUGU
SCN1A-IVS23+116	166863606	166863624	565	AGGGATTAGGATGTAAAT	925	AGGGAUUAGGAUGUAAAU
SCN1A-IVS23+121	166863601	166863619	566	AAAGAGGGAATTAGGATG	926	AAAGAGGGAAUUAGGAUG
SCN1A-IVS23+126	166863596	166863614	567	ATTGAAAAGAAGGGATTA	927	AUUGAAAAGAAGGGAUUA
SCN1A-IVS23+131	166863591	166863609	568	AGACAATTGAAAAGAGGG	928	AGACAAUUGAAAAGAGGG
SCN1A-IVS23+136	166863586	166863604	569	ATTTAAGACAATTGAAAA	929	AUUUAAGACAAUUGAAAA
SCN1A-IVS23+141	166863581	166863599	570	ATGAAATTTAAGACAATT	930	AUGAAAUUUAAGACAAUU
SCN1A-IVS23+146	166863576	166863594	571	TTCAAATGAAATTTAAGA	931	UUCAAAUGAAAUUUAAGA
SCN1A-IVS23+151	166863571	166863589	572	TTTTTTTCAAATGAAATT	932	UUUUUUUCAAAUGAAAUU
SCN1A-IVS23+156	166863566	166863584	573	TTTTTTTTTTTCAAATG	933	UUUUUUUUUUUCAAAUG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+161	166863561	166863579	574	AAGGTTTTTTTTTTTTTC	934	AAGGUUUUUUUUUUUUUC
SCN1A-IVS23+166	166863556	166863574	575	TCATAAAGGTTTTTTTTT	935	UCAUAAAGGUUUUUUUUU
SCN1A-IVS23+171	166863551	166863569	576	TAAATTCATAAAGGTTTT	936	UAAAUUCAUAAAGGUUUU
SCN1A-IVS23+176	166863546	166863564	577	GAGGGTAAATTCATAAAG	937	GAGGGUAAAUUCAUAAAG
SCN1A-IVS23+181	166863541	166863559	578	CCACAGAGGGTAAATTCA	938	CCACAGAGGGUAAAUUCA
SCN1A-IVS23+186	166863536	166863554	579	AAAATCCACAGAGGGTAA	939	AAAAUCCACAGAGGGUAA
SCN1A-IVS23+191	166863531	166863549	580	GGGTTAAAATCCACAGAG	940	GGGUUAAAAUCCACAGAG
SCN1A-IVS23+196	166863526	166863544	581	CATTGGGATTAAAATCCA	941	CAUUGGGAUUAAAAUCCA
SCN1A-IVS23+201	166863521	166863539	582	TCAACCATTAGGGTTAAA	942	UCAACCAUUAGGGUUAAA
SCN1A-IVS23+206	166863516	166863534	583	AGATATCAACCATTGGGA	943	AGAUAUCAACCAUUGGGA
SCN1A-IVS23+211	166863511	166863529	584	AATAAAGATATCAACCAT	944	AAUAAAGAUAUCAACCAU
SCN1A-IVS23+216	166863506	166863524	585	AACTTAATAAAGATATCA	945	AACUUAAUAAAGAUAUCA
SCN1A-IVS23+221	166863501	166863519	586	AATGAAACTTAATAAAGA	946	AAUGAAACUUAAUAAAGA
SCN1A-IVS23+226	166863496	166863514	587	TATTCAATGAAACTTAAT	947	UAUUCAAUGAAACUUAAU
SCN1A-IVS23+231	166863491	166863509	588	AATCATATTCAATGAAAC	948	AAUCAUAUUCAAUGAAAC
SCN1A-IVS23+236	166863486	166863504	589	AACTAAATCATATTCAAT	949	AACUAAAUCAUAUUCAAU
SCN1A-IVS23+241	166863481	166863499	590	CACATAACTAAATCATAT	950	CACAUAACUAAAUCAUAU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+246	166863476	16686 3494	591	ATATACACATAA CTAAAT	951	AUAUACACAUA ACUAAAU
SCN1A-IVS23+251	166863471	16686 3489	592	ACTCCATATACA CATAAC	952	ACUCCAUAUACA CAUAAC
SCN1A-IVS23+256	166863466	16686 3484	593	GGATAACTCCAT ATACAC	953	GGAUAACUCCAU AUACAC
SCN1A-IVS23+261	166863461	16686 3479	594	AAGATGGATAA CTCCATA	954	AAGAUGGAUAA CUCCAUA
SCN1A-IVS23+266	166863456	16686 3474	595	CCCCAAAGATGG ATAACT	955	CCCCAAAGAUGG AUAACU
SCN1A-IVS23+271	166863451	16686 3469	596	AATCTCCCCAAA GATGGA	956	AAUCUCCCCAAA GAUGGA
SCN1A-IVS23+276	166863446	16686 3464	597	CCAGTAATCTCC CCAAAG	957	CCAGUAAUCUCC CCAAAG
SCN1A-IVS23+281	166863441	16686 3459	598	CCAATCCAGTAA TCTCCC	958	CCAAUCCAGUAA UCUCCC
SCN1A-IVS23+286	166863436	16686 3454	599	CCTCACCAATCC AGTAAT	959	CCUCACCAAUCC AGUAAU
SCN1A-IVS23+291	166863431	16686 3449	600	CCCGCCCTCACC AATCCA	960	CCCGCCCUCACC AAUCCA
SCN1A-IVS23+296	166863426	16686 3444	601	GGTCCCCCGCCC TCACCA	961	GGUCCCCCGCCC UCACCA
SCN1A-IVS23+301	166863421	16686 3439	602	ACCAGGGTCCCC CGCCCT	962	ACCAGGGUCCCC CGCCCU
SCN1A-IVS23+306	166863416	16686 3434	603	TCTACACCAGGG TCCCCC	963	UCUACACCAGGG UCCCCC
SCN1A-IVS23+311	166863411	16686 3429	604	ATCATTCTACAC CAGGGT	964	AUCAUUCUACAC CAGGGU
SCN1A-IVS23+316	166863406	16686 3424	605	ACATAATCATTC TACACC	965	ACAUAAUCAUUC UACACC
SCN1A-IVS23+321	166863401	16686 3419	606	TTTTCACATAAT CATTCT	966	UUUUCACAUAA UCAUUCU
SCN1A-IVS23+326	166863396	16686 3414	607	TTGTTTTTTCAC ATAATC	967	UUGUUUUUUCA CAUAAUC

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+331	166863391	16686 3409	608	TTAAATTGTTTTTTCACA	968	UUAAAUUGUUUUUUCACA
SCN1A-IVS23+336	166863386	16686 3404	609	ACAAGTTAAATTGTTTTT	969	ACAAGUUAAAUUGUUUUU
SCN1A-IVS23+341	166863381	16686 3399	610	GCTTAACAAGTTAAATTG	970	GCUUAACAAGUUAAAUUG
SCN1A-IVS23+346	166863376	16686 3394	611	CATGAGCTTAACAAGTTA	971	CAUGAGCUUAACAAGUUA
SCN1A-IVS23+351	166863371	16686 3389	612	AGTATCATGAGCTTAACA	972	AGUAUCAUGAGCUUAACA
SCN1A-IVS23+356	166863366	16686 3384	613	CAAACAGTATCATGAGCT	973	CAAACAGUAUCAUGAGCU
SCN1A-IVS23+361	166863361	16686 3379	614	TGCCTCAAACAGTATCAT	974	UGCCUCAAACAGUAUCAU
SCN1A-IVS23+366	166863356	16686 3374	615	CTGTATGCCTCAAACAGT	975	CUGUAUGCCUCAAACAGU
SCN1A-IVS23+371	166863351	16686 3369	616	AGGGACTGTATGCCTCAA	976	AGGGACUGUAUGCCUCAA
SCN1A-IVS23+376	166863346	16686 3364	617	ACAGCAGGGACTGTATGC	977	ACAGCAGGGACUGUAUGC
SCN1A-IVS23+381	166863341	16686 3359	618	ACTAAACAGCAAGGGCTG	978	ACUAAACAGCAAGGGCUG
SCN1A-IVS23+386	166863336	16686 3354	619	AATGTACTAAACAGCAGG	979	AAUGUACUAAACAGCAGG
SCN1A-IVS23+391	166863331	16686 3349	620	AGACCAATGTACTAAACA	980	AGACCAAUGUACUAAACA
SCN1A-IVS23+396	166863326	16686 3344	621	GACCCAGACCAATGTACT	981	GACCCAGACCAAUGUACU
SCN1A-IVS23+401	166863321	16686 3339	622	TTCAGGACCCAGACCAAT	982	UUCAGGACCCAGACCAAU
SCN1A-IVS23+406	166863316	16686 3334	623	TAATTTTCAGGACCCAGA	983	UAAUUUUCAGGACCCAGA
SCN1A-IVS23+411	166863311	16686 3329	624	ACTGGTAATTTTCAGGAC	984	ACUGGUAAUUUUCAGGAC

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+416	166863306	16686 3324	625	ATCTAACTGGTA ATTTTC	985	AUCUAACUGGU AAUUUUC
SCN1A-IVS23+421	166863301	16686 3319	626	ATGGTATCTAAC TGGTAA	986	AUGGUAUCUAA CUGGUAA
SCN1A-IVS23+426	166863296	16686 3314	627	AACTGATGGTAT CTAACT	987	AACUGAUGGUA UCUAACU
SCN1A-IVS23+431	166863291	16686 3309	628	TAATCAACTGAT GGTATC	988	UAAUCAACUGA UGGUAUC
SCN1A-IVS23+436	166863286	16686 3304	629	ATCAATAATCAA CTGATG	989	AUCAAUAAUCA ACUGAUG
SCN1A-IVS23+441	166863281	16686 3299	630	TACATATCAATA ATCAAC	990	UACAUAUCAAU AAUCAAC
SCN1A-IVS23+446	166863276	16686 3294	631	GCTCATACATAT CAATAA	991	GCUCAUACAUAU CAAUAA
SCN1A-IVS23+451	166863271	16686 3289	632	TATCTGCTCATA CATATC	992	UAUCUGCUCAUA CAUAUC
SCN1A-IVS23+456	166863266	16686 3284	633	CCTAGTATCTGC TCATAC	993	CCUAGUAUCUGC UCAUAC
SCN1A-IVS23+461	166863261	16686 3279	634	TGCACCCTAGTA TCTGCT	994	UGCACCCUAGUA UCUGCU
SCN1A-IVS23+466	166863256	16686 3274	635	AATATTGCACCC TAGTAT	995	AAUAUUGCACCC UAGUAU
SCN1A-IVS23+471	166863251	16686 3269	636	CCTGAAATATTG CACCCT	996	CCUGAAAUAUU GCACCCU
SCN1A-IVS23+476	166863246	16686 3264	637	TGAAACCTGAAA TATTGC	997	UGAAACCUGAA AUAUUGC
SCN1A-IVS23+481	166863241	16686 3259	638	TCTTATGAAACC TGAAAT	998	UCUUAUGAAACC UGAAAU
SCN1A-IVS23+486	166863236	16686 3254	639	ACCAGTCTTATG AAACCT	999	ACCAGUCUUAUG AAACCU
SCN1A-IVS23+491	166863231	16686 3249	640	TCAATACCAGTC TTATGA	1000	UCAAUACCAGUC UUAUGA
SCN1A-IVS23+496	166863226	16686 3244	641	CACAATCAATAC CAGTCT	1001	CACAAUCAAUAC CAGUCU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+501	166863221	16686 3239	642	GTGGTCACAATC AATACC	1002	GUGGUCACAAUC AAUACC
SCN1A-IVS23+506	166863216	16686 3234	643	TGAGAGTGGTCA CAATCA	1003	UGAGAGUGGUC ACAAUCA
SCN1A-IVS23+511	166863211	16686 3229	644	AAAAATGAGAG TGGTCAC	1004	AAAAAUGAGAG UGGUCAC
SCN1A-IVS23+516	166863206	16686 3224	645	CAATAAAAAAT GAGAGTG	1005	CAAUAAAAAAU GAGAGUG
SCN1A-IVS23+521	166863201	16686 3219	646	TTACACAATAAA AAATGA	1006	UUACACAAUAA AAAAUGA
SCN1A-IVS23+526	166863196	16686 3214	647	TGAACTTACACA ATAAAA	1007	UGAACUUACACA AUAAAA
SCN1A-IVS23+531	166863191	16686 3209	648	CCATATGAACTT ACACAA	1008	CCAUAUGAACUU ACACAA
SCN1A-IVS23+536	166863186	16686 3204	649	TAACCCCATATG AACTTA	1009	UAACCCCAUAUG AACUUA
SCN1A-IVS23+541	166863181	16686 3199	650	GAAAATAACCCC ATATGA	1010	GAAAAUAACCCC AUAUGA
SCN1A-IVS23+546	166863176	16686 3194	651	ATTTTGAAAATA ACCCCA	1011	AUUUUGAAAAU AACCCCA
SCN1A-IVS23+551	166863171	16686 3189	652	TTAACATTTTGA AAATAA	1012	UUAACAUUUUG AAAAUAA
SCN1A-IVS23+556	166863166	16686 3184	653	CCTTGTTAACAT TTTGAA	1013	CCUUGUUAACAU UUUGAA
SCN1A-IVS23+561	166863161	16686 3179	654	TTTTGCCTTGTT AACATT	1014	UUUUGCCUUGU UAACAUU
SCN1A-IVS23+566	166863156	16686 3174	655	TATATTTTTGCC TTGTTA	1015	UAUAUUUUUGC CUUGUUA
SCN1A-IVS23+571	166863151	16686 3169	656	CTTAATATATTT TTGCCT	1016	CUUAAUAUAUU UUUGCCU
SCN1A-IVS23+576	166863146	16686 3164	657	TATTTCTTAATA TATTTT	1017	UAUUUCUUAAU AUAUUUU
SCN1A-IVS23+581	166863141	16686 3159	658	TCAACTATTTCT TAATAT	1018	UCAACUAUUUCU UAAUAU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+586	166863136	16686 3154	659	CTTATTCAACTATTTCTT	1019	CUUAUUCAACUAUUUCUU
SCN1A-IVS23+591	166863131	16686 3149	660	ATGTGCTTATTCAACTAT	1020	AUGUGCUUAUUCAACUAU
SCN1A-IVS23+596	166863126	16686 3144	661	TTCACATGTGCTTATTCA	1021	UUCACAUGUGCUUAUUCA
SCN1A-IVS23+601	166863121	16686 3139	662	CACAATTCACATGTGCTT	1022	CACAAUUCACAUGUGCUU
SCN1A-IVS23+606	166863116	16686 3134	663	TACAACACAATTCACATG	1023	UACAACACAAUUCACAUG
SCN1A-IVS23+611	166863111	16686 3129	664	TTGTTTACAACACAATTC	1024	UUGUUUACAACACAAUUC
SCN1A-IVS23+616	166863106	16686 3124	665	ACTTTTTGTTTACAACAC	1025	ACUUUUUGUUUACAACAC
SCN1A-IVS23+621	166863101	16686 3119	666	TTCTAACTTTTTGTTTAC	1026	UUCUAACUUUUUGUUUAC
SCN1A-IVS23+626	166863096	16686 3114	667	TTTTATTCTAACTTTTTG	1027	UUUUAUUCUAACUUUUUG
SCN1A-IVS23+631	166863091	16686 3109	668	GATTTTTTTATTCTAACT	1028	GAUUUUUUUAUUCUAACU
SCN1A-IVS23+636	166863086	16686 3104	669	AAGTGGATTTTTTTATTC	1029	AAGUGGAUUUUUUUAUUC
SCN1A-IVS23+641	166863081	16686 3099	670	CAAATAAGTGGATTTTTT	1030	CAAAUAAGUGGAUUUUUU
SCN1A-IVS23+646	166863076	16686 3094	671	TAATTCAAATAAGTGGAT	1031	UAAUUCAAAUAAGUGGAU
SCN1A-IVS23+651	166863071	16686 3089	672	CTGCATAATTCAAATAAG	1032	CUGCAUAAUUCAAAUAAG
SCN1A-IVS23+656	166863066	16686 3084	673	CTATTCTGCATAATTCAA	1033	CUAUUCUGCAUAAUUCAA
SCN1A-IVS23+661	166863061	16686 3079	674	GTATTCTATTCTGCATAA	1034	GUAUUCUAUUCUGCAUAA
SCN1A-IVS23+666	166863056	16686 3074	675	GGTATGTATTCTATTCTG	1035	GGUAUGUAUUCUAUUCUG

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+671	166863051	16686 3069	676	TTCTAGGTATGT ATTCTA	1036	UUCUAGGUAUG UAUUCUA
SCN1A-IVS23+676	166863046	16686 3064	677	TTTATTTCTAGG TATGTA	1037	UUUAUUUCUAG GUAUGUA
SCN1A-IVS23+681	166863041	16686 3059	678	TTTGTTTTATTTC TAGGT	1038	UUUGUUUUAUU UCUAGGU
SCN1A-IVS23+686	166863036	16686 3054	679	ACGTTTTTGTTTT ATTTC	1039	ACGUUUUUGUU UUAUUUC
SCN1A-IVS23+691	166863031	16686 3049	680	ATAAGACGTTTT TGTTTT	1040	AUAAGACGUUU UUGUUUU
SCN1A-IVS23+696	166863026	16686 3044	681	TCATGATAAGAC GTTTTT	1041	UCAUGAUAAGA CGUUUUU
SCN1A-IVS23+701	166863021	16686 3039	682	AATACTCATGAT AAGACG	1042	AAUACUCAUGA UAAGACG
SCN1A-IVS23+706	166863016	16686 3034	683	ATCTTAATACTC ATGATA	1043	AUCUUAAUACUC AUGAUA
SCN1A-IVS23+711	166863011	16686 3029	684	ATTTTATCTTAA TACTCA	1044	AUUUUAUCUUA AUACUCA
SCN1A-IVS23+716	166863006	16686 3024	685	CTTAAATTTTAT CTTAAT	1045	CUUAAAUUUUA UCUUAAU
SCN1A-IVS23+721	166863001	16686 3019	686	TATGCCTTAAAT TTTATC	1046	UAUGCCUUAAA UUUUAUC
SCN1A-IVS23+726	166862996	16686 3014	687	GAGTTTATGCCT TAAATT	1047	GAGUUUAUGCC UUAAAUU
SCN1A-IVS23+731	166862991	16686 3009	688	GAAGTGAGTTTA TGCCTT	1048	GAAGUGAGUUU AUGCCUU
SCN1A-IVS23+736	166862986	16686 3004	689	TCTAAGAAGTGA GTTTAT	1049	UCUAAGAAGUG AGUUUAU
SCN1A-IVS23+741	166862981	16686 2999	690	CTTATTCTAAGA AGTGAG	1050	CUUAUUCUAAG AAGUGAG
SCN1A-IVS23+746	166862976	16686 2994	691	AGTTACTTATTC TAAGAA	1051	AGUUACUUAUU CUAAGAA
SCN1A-IVS23+751	166862971	16686 2989	692	TTGGGAGTTACT TATTCT	1052	UUGGGAGUUAC UUAUUCU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+756	166862966	16686 2984	693	GTTAGTTGGGAG TTACTT	1053	GUUAGUUGGGA GUUACUU
SCN1A-IVS23+761	166862961	16686 2979	694	AGAAAGTTAGTT GGGAGT	1054	AGAAAGUUAGU UGGGAGU
SCN1A-IVS23+766	166862956	16686 2974	695	ATCCTAGAAAGT TAGTTG	1055	AUCCUAGAAAG UUAGUUG
SCN1A-IVS23+771	166862951	16686 2969	696	TTAAAATCCTAG AAAGTT	1056	UUAAAAUCCUA GAAAGUU
SCN1A-IVS23+776	166862946	16686 2964	697	ATGTTTTAAAAT CCTAGA	1057	AUGUUUUAAAA UCCUAGA
SCN1A-IVS23+781	166862941	16686 2959	698	GTGTTATGTTTT AAAATC	1058	GUGUUAUGUUU UAAAAUC
SCN1A-IVS23+786	166862936	16686 2954	699	TCACTGTGTTAT GTTTTA	1059	UCACUGUGUUA UGUUUUA
SCN1A-IVS23+791	166862931	16686 2949	700	TGTTTTCACTGT GTTATG	1060	UGUUUUCACUG UGUUAUG
SCN1A-IVS23+796	166862926	16686 2944	701	ATGTATGTTTTC ACTGTG	1061	AUGUAUGUUUU CACUGUG
SCN1A-IVS23+801	166862921	16686 2939	702	TGTTTATGTATG TTTTCA	1062	UGUUUAUGUAU GUUUUCA
SCN1A-IVS23+806	166862916	16686 2934	703	AGTTATGTTTAT GTATGT	1063	AGUUAUGUUUA UGUAUGU
SCN1A-IVS23+811	166862911	16686 2929	704	TGTAGAGTTATG TTTATG	1064	UGUAGAGUUAU GUUUAUG
SCN1A-IVS23+816	166862906	16686 2924	705	TAAAATGTAGAG TTATGT	1065	UAAAAUGUAGA GUUAUGU
SCN1A-IVS23+821	166862901	16686 2919	706	ATAAATAAAATG TAGAGT	1066	AUAAAUAAAAU GUAGAGU
SCN1A-IVS23+826	166862896	16686 2914	707	TAAGAATAAATA AAATGT	1067	UAAGAAUAAAU AAAAUGU
SCN1A-IVS23+831	166862891	16686 2909	708	AACTTTAAGAAT AAATAA	1068	AACUUUAAGAA UAAAUAA
SCN1A-IVS23+836	166862886	16686 2904	709	ACTTAAACTTTA AGAATA	1069	ACUUAAACUUU AAGAAUA

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+841	166862881	16686 2899	710	AATACACTTAAA CTTTAA	1070	AAUACACUUAA ACUUUAA
SCN1A-IVS23+846	166862876	16686 2894	711	TGTATAATACAC TTAAAC	1071	UGUAUAAUACA CUUAAAC
SCN1A-IVS23+851	166862871	16686 2889	712	CTTCTTGTATAA TACACT	1072	CUUCUUGUAUA AUACACU
SCN1A-IVS23+856	166862866	16686 2884	713	CTCTTCTTCTTGT ATAAT	1073	CUCUUCUUCUUG UAUAAU
SCN1A-IVS23+861	166862861	16686 2879	714	ATAAACTCTTCT TCTTGT	1074	AUAAACUCUUCU UCUUGU
SCN1A-IVS23+866	166862856	16686 2874	715	CGAATATAAACT CTTCTT	1075	CGAAUAUAAAC UCUUCUU
SCN1A-IVS23+871	166862851	16686 2869	716	TCTCTCGAATAT AAACTC	1076	UCUCUCGAAUAU AAACUC
SCN1A-IVS23+876	166862846	16686 2864	717	TTCTGTCTCTCG AATATA	1077	UUCUGUCUCUCG AAUAUA
SCN1A-IVS23+881	166862841	16686 2859	718	ACTTTTTCTGTCT CTCGA	1078	ACUUUUUCUGUC UCUCGA
SCN1A-IVS23+886	166862836	16686 2854	719	TTCTGACTTTTTC TGTCT	1079	UUCUGACUUUU UCUGUCU
SCN1A-IVS23+891	166862831	16686 2849	720	AAAAATTCTGAC TTTTTC	1080	AAAAAUUCUGA CUUUUUC
SCN1A-IVS23+896	166862826	16686 2844	721	CAAACAAAAATT CTGACT	1081	CAAACAAAAAU UCUGACU
SCN1A-IVS23+901	166862821	16686 2839	722	TGATCCAAACAA AAATTC	1082	UGAUCCAAACAA AAAUUC
SCN1A-IVS23+906	166862816	16686 2834	723	ATTGGTGATCCA AACAAA	1083	AUUGGUGAUCC AAACAAA
SCN1A-IVS23+911	166862811	16686 2829	724	GATATATTGGTG ATCCAA	1084	GAUAUAUUGGU GAUCCAA
SCN1A-IVS23+916	166862806	16686 2824	725	GCTATGATATAT TGGTGA	1085	GCUAUGAUAUA UUGGUGA
SCN1A-IVS23+921	166862801	16686 2819	726	TGTAAGCTATGA TATATT	1086	UGUAAGCUAUG AUAUAUU

Sequence name	Chr2 Start	Chr2 End	SEQ ID NO:	ASO sequence	SEQ ID NO:	ASO sequence
SCN1A-IVS23+926	166862796	16686 2814	727	TTTTTTGTAAGC TATGAT	1087	UUUUUUGUAAG CUAUGAU
SCN1A-IVS23+931	166862791	16686 2809	728	ACAGTTTTTTTG TAAGCT	1088	ACAGUUUUUUU GUAAGCU
SCN1A-IVS23+936	166862786	16686 2804	729	TTAAGACAGTTT TTTTGT	1089	UUAAGACAGUU UUUUUGU
SCN1A-IVS23+941	166862781	16686 2799	730	TTTAATTAAGAC AGTTTT	1090	UUUAAUUAAGA CAGUUUU
SCN1A-IVS23+946	166862776	16686 2794	731	TGGGTTTTAATT AAGACA	1091	UGGGUUUUAAU UAAGACA
SCN1A-IVS23+951	166862771	16686 2789	732	TGTTGTGGGTTT TAATTA	1092	UGUUGUGGGUU UUAAUUA
SCN1A-IVS23+956	166862766	16686 2784	733	AATTATGTTGTG GGTTTT	1093	AAUUAUGUUGU GGGUUUU
SCN1A-IVS23+961	166862761	16686 2779	734	AAAAAAATTATG TTGTGG	1094	AAAAAAAUUAU GUUGUGG
SCN1A-IVS23+966	166862756	16686 2774	735	AATCTAAAAAA ATTATGT	1095	AAUCUAAAAAA AUUAUGU
SCN1A-IVS23+971	166862751	16686 2769	736	TTAAAAATCTAA AAAAAT	1096	UUAAAAAUCUA AAAAAAU
SCN1A-IVS23+976	166862746	16686 2764	737	CTTTCTTAAAAA TCTAAA	1097	CUUUCUUAAAA AUCUAAA
SCN1A-IVS23+981	166862741	16686 2759	738	AGAATCTTTCTT AAAAAT	1098	AGAAUCUUUCU UAAAAAU
SCN1A-IVS23+986	166862736	16686 2754	739	ATAATAGAATCT TTCTTA	1099	AUAAUAGAAUC UUUCUUA

Table 7A. Exemplary ASOs to correct intron retention.

SEQ ID NO:	Name	Sequence (5'-3')	Retained Intron
115	SCN1A-IVS21+6	CAGAGAAAAUAGUGUUCA	21
116	SCN1A-IVS21+11	AUAUUCAGAGAAAAUAGU	21
117	SCN1A-IVS21+16	UAAAAAUAUUCAGAGAAA	21
118	SCN1A-IVS21+21	AACAAUAAAAAUAUUCAG	21
119	SCN1A-IVS21+26	UUCCAAACAAUAAAAAUA	21

SEQ ID NO:	Name	Sequence (5'-3')	Retained Intron
120	SCN1A-IVS21+31	UAUUAUUCCAAACAAUAA	21
121	SCN1A-IVS21+36	UUUGUUAUUAUUCCAAAC	21
122	SCN1A-IVS21+41	AUUAUUUUGUUAUUAUUC	21
123	SCN1A-IVS21+46	AUGUCAUUAUUUUGUUAU	21
124	SCN1A-IVS21+51	GAUGUAUGUCAUUAUUUU	21
125	SCN1A-IVS21+56	UAAUAGAUGUAUGUCAUU	21
126	SCN1A-IVS21+61	CUAAAUAAUAGAUGUAUG	21
127	SCN1A-IVS21+66	AGGAACUAAAUAAUAGAU	21
128	SCN1A-IVS21+71	UUCUUAGGAACUAAAUAA	21
129	SCN1A-IVS21+76	ACUUUUUCUUAGGAACUA	21
130	SCN1A-IVS21+81	UAUAUACUUUUUCUUAGG	21
131	SCN1A-IVS21-16	UGCAUGUUUUACUUUGGA	21
132	SCN1A-IVS21-21	GUUUUACUUUGGAGUAAA	21
133	SCN1A-IVS21-26	ACUUUGGAGUAAAAAUAA	21
134	SCN1A-IVS21-31	GGAGUAAAAAUAAUUUAG	21
135	SCN1A-IVS21-36	AAAAAUAAUUUAGACCUG	21
136	SCN1A-IVS21-41	UAAUUUAGACCUGAUGUU	21
137	SCN1A-IVS21-46	UAGACCUGAUGUUUAAUA	21
138	SCN1A-IVS21-51	CUGAUGUUUAAUAAAUAU	21
139	SCN1A-IVS21-56	GUUUAAUAAAUAUUCUUA	21
140	SCN1A-IVS21-61	AUAAAUAUUCUUACUGAU	21
141	SCN1A-IVS21-66	UAUUCUUACUGAUAUAAU	21
142	SCN1A-IVS21-71	UUACUGAUAUAAUUUUCA	21
143	SCN1A-IVS21-76	GAUAUAAUUUUCAAAAGG	21
144	SCN1A-IVS21-81	AAUUUUCAAAAGGGAAUA	21
145	SCN1A-IVS21-27	CUUUGGAGUAAAAAUAAU	21
146	SCN1A-IVS21-28	UUUGGAGUAAAAAUAAUU	21
148	SCN1A-IVS21-29	UUGGAGUAAAAAUAAUUU	21
149	SCN1A-IVS21-30	UGGAGUAAAAAUAAUUUA	21
150	SCN1A-IVS21-32	GAGUAAAAAUAAUUUAGA	21
151	SCN1A-IVS21-33	AGUAAAAAUAAUUUAGAC	21
152	SCN1A-IVS21-34	GUAAAAAUAAUUUAGACC	21
153	SCN1A-IVS21-35	UAAAAAUAAUUUAGACCU	21
154	SCN1A-IVS21-72	UACUGAUAUAAUUUUCAA	21
155	SCN1A-IVS21-73	ACUGAUAUAAUUUUCAAA	21

SEQ ID NO:	Name	Sequence (5'-3')	Retained Intron
156	SCN1A-IVS21-74	CUGAUAUAAUUUUCAAAA	21
157	SCN1A-IVS21-75	UGAUAUAAUUUUCAAAAG	21
158	SCN1A-IVS21-77	AUAUAAUUUUCAAAAGGG	21
159	SCN1A-IVS21-78	UAUAAUUUUCAAAAGGGA	21
160	SCN1A-IVS21-79	AUAAUUUUCAAAAGGGAA	21
161	SCN1A-IVS21-80	UAAUUUUCAAAAGGGAAU	21
162		CAAGGAUUAAAGGUAGCA	21

Table 7B. Exemplary ASOs to correct intron retention.

SEQ ID NO:	Name	Sequence (5'-3')	Retained Intron
163	SCN1A-IVS21+6	CAGAGAAAATAGTGTTCA	21
164	SCN1A-IVS21+11	ATATTCAGAGAAAATAGT	21
165	SCN1A-IVS21+16	TAAAAATATTCAGAGAAA	21
166	SCN1A-IVS21+21	AACAATAAAAATATTCAG	21
167	SCN1A-IVS21+26	TTCCAAACAATAAAAATA	21
168	SCN1A-IVS21+31	TATTATTCCAAACAATAA	21
169	SCN1A-IVS21+36	TTTGTTATTATTCCAAAC	21
170	SCN1A-IVS21+41	ATTATTTTGTTATTATTC	21
171	SCN1A-IVS21+46	ATGTCATTATTTTGTTAT	21
172	SCN1A-IVS21+51	GATGTATGTCATTATTTT	21
173	SCN1A-IVS21+56	TAATAGATGTATGTCATT	21
174	SCN1A-IVS21+61	CTAAATAATAGATGTATG	21
175	SCN1A-IVS21+66	AGGAACTAAATAATAGAT	21
176	SCN1A-IVS21+71	TTCTTAGGAACTAAATAA	21
177	SCN1A-IVS21+76	ACTTTTTCTTAGGAACTA	21
178	SCN1A-IVS21+81	TATATACTTTTTCTTAGG	21
179	SCN1A-IVS21-16	TGCATGTTTTACTTTGGA	21
180	SCN1A-IVS21-21	GTTTTACTTTGGAGTAAA	21
181	SCN1A-IVS21-26	ACTTTGGAGTAAAAATAA	21
182	SCN1A-IVS21-31	GGAGTAAAAATAATTTAG	21
183	SCN1A-IVS21-36	AAAAATAATTTAGACCTG	21
184	SCN1A-IVS21-41	TAATTTAGACCTGATGTT	21
185	SCN1A-IVS21-46	TAGACCTGATGTTTAATA	21
186	SCN1A-IVS21-51	CTGATGTTTAATAAATAT	21
187	SCN1A-IVS21-56	GTTTAATAAATATTCTTA	21

SEQ ID NO:	Name	Sequence (5'-3')	Retained Intron
188	SCN1A-IVS21-61	ATAAATATTCTTACTGAT	21
189	SCN1A-IVS21-66	TATTCTTACTGATATAAT	21
190	SCN1A-IVS21-71	TTACTGATATAATTTTCA	21
191	SCN1A-IVS21-76	GATATAATTTTCAAAAGG	21
192	SCN1A-IVS21-81	AATTTTCAAAAGGGAATA	21
193	SCN1A-IVS21-27	CTTTGGAGTAAAAATAAT	21
194	SCN1A-IVS21-28	TTTGGAGTAAAAATAATT	21
195	SCN1A-IVS21-29	TTGGAGTAAAAATAATTT	21
196	SCN1A-IVS21-30	TGGAGTAAAAATAATTTA	21
197	SCN1A-IVS21-32	GAGTAAAAATAATTTAGA	21
198	SCN1A-IVS21-33	AGTAAAAATAATTTAGAC	21
199	SCN1A-IVS21-34	GTAAAAATAATTTAGACC	21
200	SCN1A-IVS21-35	TAAAAATAATTTAGACCT	21
201	SCN1A-IVS21-72	TACTGATATAATTTTCAA	21
202	SCN1A-IVS21-73	ACTGATATAATTTTCAAA	21
203	SCN1A-IVS21-74	CTGATATAATTTTCAAAA	21
204	SCN1A-IVS21-75	TGATATAATTTTCAAAAG	21
205	SCN1A-IVS21-77	ATATAATTTTCAAAAGGG	21
206	SCN1A-IVS21-78	TATAATTTTCAAAAGGGA	21
207	SCN1A-IVS21-79	ATAATTTTCAAAAGGGAA	21
208	SCN1A-IVS21-80	TAATTTTCAAAAGGGAAT	21
209		CAAGGATTAAAGGTAGCA	21

Example 15: Alternative splicing of *SCN1A* pre-mRNA that results in NMD is conserved in multiple species and in a DS patient.

[0927] Bioinformatic analysis of human brain samples revealed an exon inclusion event in the *SCN1A* gene that leads to a frameshift and the introduction of a premature termination codon. This example demonstrates validation of this non-productive splicing event in various species, including in a human DS patient.

[0928] **FIG. 13A** shows a schematic representation and validation of this non-productive splicing event by RT-PCR of human cells treated with or without the translation inhibitor, cycloheximide (CHX). The productive (canonical) isoform (bottom band) does not contain the alternative exon and translates into functional $Na_V1.1$ protein. The non-productive isoform contains the alternative exon (top band). DMSO: Dimethyl sulfoxide, CHX: Cycloheximide.

[0929] BLAST searches of the NCBI database identified highly conserved homologs of this *SCN1A* NMD-inducing exon in multiple species and the results were verified by RT-PCR (**FIG. 13B**). Moreover, the presence of the NMD-inducing exon inclusion event is retained in brain tissues from a DS patient

(**FIG. 13B**), suggesting that the level of the NMD-exon inclusion event is unchanged between healthy and DS individuals. **FIG. 13B** shows TBE-PAGE of the RT-PCR products of *SCN1A* transcripts in cerebral cortex from a healthy female subject, a DS patient, a cynomolgus monkey, a DS mouse, a WT mouse (C57BL/6J) and a Sprague Dawley rat. Canonical *SCN1A* transcript is represented by the lower bands and product corresponding to the NMD-exon inclusion is represented by the upper bands. Patient variants located in the NMD-inducing exon region that was identified here have been shown to cause an increase in NMD-exon inclusion levels and a reduction of productive mRNA leading to DS. *See* Carvill *et al.*, *Am J Hum Genet* **103**, 1022-1029 (2018).

[0930] RT-PCR analysis was also performed to measure the inclusion level of the NMD-inducing exon and productive *Scn1a* mRNA in coronal brain sections from P0-P20 and 10-month-old WT C57BL/6J mice (**FIG. 13C**). Densitometric measurement of the RT-PCR products showed that the NMD-inducing exon containing transcript (upper band) is largely unchanged during development while the productive mRNA (lower band) increases (**FIG. 13D**). Productive *Scn1a* transcript levels (**FIG. 13D**) begin to increase dramatically around P7-8. As shown in **FIG. 13D**, expression of *Scn1a* transcripts was first normalized to endogenous *Gapdh* and then to the *Scn1a* productive transcript at P0. Data are presented as mean ± SD in the figure (n=2 or 3 samples from individual animals for each data point). Expression of *Scn1a* productive transcript was fit to a four-parameter non-linear curve. Expression of *Scn1a* non-productive transcript was best fit to a linear curve. These results suggested that it may be possible to increase total productive transcript levels by converting NMD-exon containing transcripts to productive transcripts and that the impact of this manipulation would be the greatest during early postnatal brain development.

Example 16: ASO administration increases *SCN1A* expression in cultured human cells and mouse brain.

[0931] A series of ASOs were designed, which bind to human *SCN1A* exon 20X and the surrounding intronic sequences. All ASOs used in the initial screening were based on 2'-methoxy-ethyl (MOE) modification of the oligonucleotide with a phosphorothioate backbone. ASOs were screened in human neural progenitor cells by free uptake, followed by analysis of *SCN1A* productive and exon 20X-containing nonproductive transcripts with RT-PCR and qPCR. As shown in **FIG. 14A**, a total of 47 ASOs were screened at 20 μM. Nucleobase sequences of the 47 ASOs are summarized in **Table 4A**. A non-targeting ASO (NT) and no ASO control (-) were included. *RPL32* was used as loading control. A number of ASOs were identified that significantly decreased the NMD-inducing exon inclusion and increased productive transcript expression (**FIGS. 14A-14C**). The most active ASO (ASO-22, indicated by the arrows in **FIGS. 14A-14C**) was selected for further evaluation. It was confirmed that the effect of ASO-22 is dose-dependent (**FIG. 15**). A non-targeting ASO control (NT) had no effect on the level of either transcript isoform (**FIG. 15**).

[0932] Dose-response relationships for ASO-22 were determined in human neural progenitor cells using free uptake or nucleofection delivery methods. The EC50 values were 3 μM, determined by free uptake, and 529 nM, determined by nucleofection (**FIG. 14D**). The specificity of ASO-22 was also assessed by

measuring its effect on the expression of four highly homologous VGSC α subunit genes in treated cells. No change in the expression levels of *SCN2A, SCN3A, SCN8A,* or *SCN9A* were observed in ReNcells following 20, 8 or 3 μM ASO treatment via free uptake (**FIG. 14E**). These results indicate that ASO-22 potently and specifically increases productive *Scn1a* mRNA in human neural progenitor cells.

[0933] **FIG. 14A** shows ASO screen in ReNcells. TBE PAGE of RT-PCR products corresponding to *SCN1A* productive (lower bands, 549 bp) and non-productive mRNA containing exon 20X (upper bands, 613 bp) in ReNcells after gymnotic (free) uptake of ASO. **FIG. 14B** shows percentage of exon 20X inclusion in *SCN1A* transcript, as quantified from the RT-PCR products shown in **FIG. 14A**. PCR products were quantified by densitometry and plotted as percentage of the exon 20X-containing mRNA over total (exon 20X-containing and productive mRNA). n=1 for each ASO treatment group; n=2 for NT; n=11 for sham. **FIG. 14C** shows expression of *SCN1A* productive mRNA in ASO-treated ReNcells determined by SYBR green qPCR. Expression of *SCN1A* productive mRNA was first normalized to endogenous *RPL32* and then to no ASO control (-). qPCR results were presented as mean ± SD for each treatment. n=1 for each ASO treatment; n=2 for NT; n=10 for sham. **FIG. 14D** demonstrates the dose-response relationship of ASO-22 in ReNcells with free uptake and nucleofection. Expression of *SCN1A* was normalized to endogenous *RPL32* and then to no ASO control. qPCR results were presented as mean ± SD. (n=2 for both treatments). Expression of *SCN1A* productive transcript was fit to four-parameter non-linear curves. **FIG. 14E** demonstrates effect of selected ASOs on expression of homologous VGSC α subunit genes in ReNcells. Expression of *SCN2A*, *3A*, *8A*, and *9A* in ReNcells was measured by probe-based qPCR, following gymnotic uptake of 20, 8 or 3 μM of ASO-22 or a non-target. ASO control (NT). *SCN* mRNA levels were first normalized to endogenous *Gapdh* and then to no ASO (-) treated cells. qPCR results were presented as mean ± SD for each analysis (n=4 for each ASO treatment; n=8 for no ASO control.

[0934] **FIGS. 15A-15C** shows dose-dependent effects of ASO-22 on splicing and expression of *Scn1a* mRNA in ReNcells. ReNcells were treated with 20, 8 or 3 μM of ASO-22 for 72 h by gymnotic uptake, followed by DMSO or cycloheximide (CHX) treatment for 3 h before harvesting. A non-targeting ASO control (NT) and no ASO control (sham) were included. **FIG. 15A** shows TBE PAGE of RT-PCR products corresponding to *SCN1A* productive mRNA (lower bands, 549 bp) and non-productive mRNA containing exon 20X (upper bands, 613 bp) in ReNcells. *RPL32* was used as the loading control. Expression of *SCN1A* transcript in ReNcells after gymnotic uptake of ASO-22 was quantified by probe-based qPCR. The levels of *SCN1A* productive (**FIG. 15B**) and non-productive (**FIG. 15C**) mRNA were measured separately with two qPCR assays (see description in the Methods). Transcript expression was first normalized to the endogenous *RPL32* signal and then to the no ASO (sham) control. Sham qPCR results are presented as mean ± SD for each group. (Independent repeats of experiment: n=1 for ASO-22 treatment; n=3 for sham; n=3 for sham + CHX).

[0935] To determine whether ASO-22 administration can upregulate productive mRNA and protein in a dose-dependent manner *in vivo*, P2 WT C57BL/6J mice were dosed with a single ICV injection of ASO-22 at 0.3, 1, 3, 5, 10, 20 or 30 μg and euthanized 5 days after treatment (**FIG. 16A**). Brain tissues were

collected and analyzed for changes in levels of non-productive and productive *Scn1a* transcripts, respectively, as well as $Na_V1.1$ protein. Inclusion of the NMD exon in *Scn1a* transcript decreased with increasing ASO dose (**FIG. 16B**). A dose-dependent increase in productive *Scn1a* expression was also observed using probe-based qPCR (**FIG. 16C**) and RT-PCR (**FIG. 17**), with a ~6-fold increase in expression level detected in the 10-μg dose group and no further increase was observed at 20 and 30 μg. Finally, expression levels of $Na_V1.1$ protein increased in a similar dose-dependent manner (**FIG. 16D** and **FIG. 18**). A non-targeting ASO control (NT) had no effect on the level of either *Scn1a* transcript or $Na_V1.1$. The expression of eight closely related VGSC α subunit genes plus Nax (*Scn7a*) were unaffected in the brains of mice that had received the ASO (**FIG. 16E**).

[0936] To determine the durability of the ASO-22 effect in brain, P2 WT mice ICV-injected with 10 μg of ASO-22 were examined for brain expression of *Scn1a* productive transcript levels at varying time points after injection (**FIG. 16F**). Increased levels of productive *Scn1a* transcript were observed for up to 30 days post injection (**FIG. 16G** and **FIG. 19**). Levels of $Na_V1.1$ protein also increased and were maintained during the 30-day observation period compared to PBS injection controls (**FIG. 16H** and **FIG. 20**).

[0937] **FIG. 16A** shows experimental design for ASO-22 dose-response relationship *in vivo*. **FIG. 16B** shows percentage of NMD-inducing exon inclusion in *Scn1a* transcript in mouse brains, as quantified by densitometry of TBE PAGE RT-PCR products (gels shown in **FIG. 17**). Quantification results are presented as mean ± SD (n=3-14 for each treatment group). Plotted data in **FIG. 16B** were fit to a four-parameter non-linear curve. Similar to PBS treated animals, the percentage of NMD-inducing exon inclusion for NT ASO treatment group was 45.8% ± 0.7%. **FIG. 16C** shows fold changes in expression of *Scn1a* productive transcript in mouse brains, as quantified by probe-based qPCR. qPCR results are presented as mean ± SD (n=3-14 for each treatment group). Plotted data were fit to a four-parameter non-linear curve. Similar to PBS treated animals, the fold change in *Scn1a* mRNA for the NT ASO treatment group was 0.9 ± 0.1. **FIG. 16D** shows fold changes in expression of $Na_V1.1$ protein in mouse, as quantified by the Meso Scale Discovery (MSD) method. Quantification results are presented as mean ± SD (n=3-8 for each treatment group). Plotted data were fit to a four-parameter non-linear curve. Similar to PBS treated animals, $Na_V1.1$ expression for the NT ASO treatment group was 16.8% ± 0.9% compared to adult brain. **FIG. 16E** shows effect of ASO-22 on expression of the 9 VGSC α subunit genes plus Nax (*Scn7a*) expressed in mouse brain. Expression of *Scn1a* productive transcript and the remaining 8 VGSC α subunit genes plus Nax (*Scn7a*) in mouse brains following ICV injection of PBS, a non-target ASO control (NT, 20 μg) or different doses of ASO-22 was measured by probe-based qPCR. Expression of each transcript was first normalized to endogenous *Gapdh* then compared to PBS injection controls. qPCR assays used here are listed in the Methods. Data are presented as mean ± SD (n=3-14 for each treatment group). **FIG. 16F** shows experimental design for assessment of duration of effect in mouse brains following ICV injection of ASO-22. **FIG. 16G** shows quantification of *Scn1a* productive transcript in mouse brains at selected days post injection of 10 μg of ASO-22 at P2. *Scn1a* transcript was first normalized to endogenous *Gapdh*, then compared to mouse brains 1 day after receiving the PBS injection. qPCR results were

presented as mean ± SD (n=4-9 for each treatment group). Plotted data were fit to a four-parameter non-linear curve. **FIG. 16H** shows fold changes in expression of $Na_V1.1$ protein in mouse brains at selected days post injection of 10 μg of ASO-22 at P2. $Na_V1.1$ protein expression was quantified by the MSD method. MSD results were presented as mean ± SD (n=4-5 randomly selected samples from each treatment group).

[0938] **FIG. 17** shows dose-dependent effects of ASO-22 on expression of *Scn1a* in ICV-injected neonatal mouse brains. WT C57BL/6J mice were ICV injected with PBS, a non-target (NT, 20 μg) control, 0.3, 1, 3, 5, 10, 20 or 30 μg of ASO-22 at P2. Brains were harvested 5 days after injection and analyzed for *Scn1a* mRNA expression. TBE PAGE of RT-PCR products shows *Scn1a* productive (bottom bands, 498 bp, indicated by *) and NMD-inducing transcript (upper bands, 562 bp, indicated by §) in mouse brains. Quantification of the percentage of exon 21X inclusion is shown in **FIG. 16B**. Quantification of the *Scn1a* productive mRNA expression by qPCR is shown in **FIG. 16C**. M: DNA ladder, NEB, N3231L.

[0939] **FIG. 18** shows dose-dependent effects of ASO-22 on expression of $Na_V1.1$ in ICV-injected neonatal mouse brains. WT C57BL/6J mice were ICV injected with 0.3, 1, 3 or 10 μg of ASO-22 or PBS at P2. Brains were harvested 5 days after injection and analyzed for $Na_V1.1$ expression. $Na_V1.1$ expression (~223 kDa, indicated by *) was assessed by immunoblotting of two randomly selected brain samples from each dosing group. 50 μg of protein was loaded per lane. Ponceau S-stained blots are included to show equal loading. Half input of protein from a brain injected with 10 μg of ASO was included for testing signal saturation of the immunoblotting. Brain samples from untreated *Scn1a*$^{+/-}$ and WT littermate mice were included as controls. Quantification of $Na_V1.1$ expression by Meso Scale Discovery (MSD) method is shown in **FIG. 16D**.

[0940] **FIG. 19** shows Expression of *Scn1a* mRNA in mouse brains at different post-injection days. WT C57BL/6J mice were ICV injected with 3 or 10 μg of ASO-22 or PBS at P2. Brains were harvested 1, 3, 5, 10, 20 or 30 days after injection and analyzed for *Scn1a* mRNA expression. TBE PAGE of RT-PCR products shows *Scn1a* productive (bottom bands, 498 bp, indicated by *) and NMD-inducing transcript (upper bands, 562 bp, indicated by §) in mouse brains. *Gapdh* was used as loading control. Quantification of the *Scn1a* productive mRNA expression by qPCR is shown in **FIG. 16G**. M: DNA ladder, NEB, N3231L.

[0941] **FIG. 20** shows expression of $Na_V1.1$ in mouse brains at different post-injection days. WT C57BL/6J mice were ICV injected with 10 μg of ASO-22 or PBS at P2. $Na_V1.1$ expression (~223 kDa, indicated by *) was assessed by immunoblotting of two randomly selected brain samples from the 10-, 20-, and 30-day post-injection mice. 50 μg of total protein was loaded per lane. Ponceau S-stained blots are included to show equal loading. Quantification of changes in $Na_V1.1$ expression by Meso Scale Discovery (MSD) method is shown in **FIG. 16H**.

Example 17: Treating Dravet syndrome.

[0942] Dravet syndrome (DS) is a rare infantile-onset drug-resistant developmental and epileptic encephalopathy with a poor long-term prognosis. Dravet syndrome affects an estimated 1:15,700

individuals in the United States, or a population of approximately 20,000 individuals (Wu *et al.*, 2015, Pediatrics, 136:e1310-5, of which entire content is incorporated herein by reference). Dravet syndrome is most commonly caused by a pathogenic mutation in the *SCN1A* gene (Scheffer 2012, Eur. J. Paediatr. Neurol. 16, Suppl 1:S5-8, of which entire content is incorporated herein by reference). Single nucleotide substitutions, small insertions or deletions, and even whole gene deletions have been reported, with at least 1257 different mutations in the *SCN1A* gene having been described in DS patients to date (Djémié *et al.*, 2016, Mol Genet Genomic Med. 4:457-64, of which entire content is incorporated herein by reference). The *SCN1A* gene codes for the sodium voltage-gated channel alpha subunit ($Na_V1.1$ protein). SCN1A ($Na_V1.1$ channel) mutations associated with DS are mostly truncating or missense mutations that lead to loss-of-function of the $Na_V1.1$ protein in >95% of cases (Catterall *et al.*, 2010, J. Physiol. 588:1849-59; Meng *et al.*, 2015, Hum Mutat. 2015;36:573–80, of which entire content is incorporated herein by reference). The mutations are heterozygous in DS patients and result in haploinsufficiency of the $Na_V1.1$ protein.

[0943] Several SCN1A mutations (Thr226Met, Val422Leu) have been identified in children with early infantile SCN1A encephalopathy, a profound developmental and epileptic encephalopathy that is phenotypically distinct from DS (Sadleir *et al.*, 2017, Neurology, 89:1035–42, of which entire content is incorporated herein by reference). Upon functional biophysical testing using dynamic action potential clamp assessment, the mutations found to be causative for the early infantile disease have been demonstrated to cause gain-of-function changes in the $Na_V1.1$ protein (Berecki *et al.*, 2019, Ann Neurol. 85:514-25, of which entire content is incorporated herein by reference). Several other mutations have been found using functional testing to cause gain-of-function changes in $Na_V1.1$ (V1611F, D1866Y, W1204R) that are also associated with a seizure phenotype that differs from DS (Meng *et al.*, 2015, Hum Mutat. 2015;36:573–80, of which entire content is incorporated herein by reference). In addition, Familial Hemiplegic Migraine (FHM), a disease not typically associated with epilepsy, has been shown in some cases to be associated with gain-of-function mutation in SCN1A (L263V, T1174S, Q1489K, F1499L, L1624P, L1649Q, L1670W) (Dhifallah *et al.*, 2018, Front Mol. Neurosci. 11: 232; Fan *et al.*, 2016, Cephalalgia. 36: 1238-47; Cestele *et al.*, 2013, Proc. Natl. Acad. Sci. USA. 2013;110:17546–51, of which entire content is incorporated herein by reference). Other potential gain-of-function SCN1A mutations have been associated with non-DS symptoms such as Rasmussen Syndrome (Arg1575Cys) (Depienne *et al.*, 2009, J. Med Genet. 46:183–91, of which entire content is incorporated herein by reference).

[0944] Loss of $Na_V1.1$ channels in inhibitory interneurons may cause epilepsy and premature death in patients with DS (Cheah *et al.*, 2012, PNAS. 109:14646-51, of which entire content is incorporated herein by reference). The loss of $Na_V1.1$ channels in other nerve cells likely contributes to the seizures, as well as other aspects of DS (Liu *et al.*, 2013, Ann Neurol. 74:128-39, of which entire content is incorporated herein by reference). Dravet syndrome is characterized by multiple seizure types and frequently progresses to status epilepticus or prolonged seizures lasting more than 5 minutes that require immediate intervention. Almost all patients (>90%) suffer from several comorbidities in addition to

seizures including motor and speech impairment, severe intellectual and developmental disabilities, learning difficulties, autism, Attention-Deficit/Hyperactivity Disorder, sleep and gait abnormalities, and behavioral difficulties (Lagae *et al.*, 2018, Dev. Med. Child Neurol. 60:63-72, of which entire content is incorporated herein by reference). As a result, DS patients have a remarkably low quality of life (Lagae *et al.*, 2018, Dev. Med. Child Neurol. 60:63-72, incorporated herein by reference).

[0945] Neurologic examination and cognition are usually normal in children with DS up to 2 years of age (Ragona *et al.*, 2011, Epilepsia. 52:386-92, of which entire content is incorporated herein by reference). However, among DS patients >4 years of age, nearly 100% have intellectual impairment (Genton *et al.*, 2011, Epilepsia. 52, Suppl 2:44-9; Ragona *et al.*, 2011, Epilepsia. 52:386-92, of which entire content is incorporated herein by reference). The degree of neurobehavioral impairment ranges from minor learning difficulty to intellectual disability. The time period between 1 year and 8 years of age (the Worsening Stage) is a critical interval for intervention **(FIG. 3)**. After 8 years of age, nearly 100% of DS patients have evidence of substantial intellectual disability (Gataullina and Dulac, 2017, Seizure 44:58-64, of which entire content is incorporated herein by reference). Cognitive impairment in DS is not purely a consequence of seizures. Patients with few seizures may have very severe encephalopathy, and conversely, patients with frequent seizures may have relatively little cognitive decline. In addition, there does not appear to be a correlation between cognitive outcome and SCN1A mutation type, whether a missense or truncating mutation (Ragona *et al.*, 2011, Epilepsia. 52:386-92, incorporated herein by reference). Longer use of contra-indicated medications (*e.g.,* sodium channel blockers) in the first 5 years of disease can have negative effects on cognitive outcome in people with DS (de Lange *et al.*, 2018, Epilepsia, 59:1154-65, of which entire content is incorporated herein by reference).

[0946] Dravet syndrome is among the most drug-resistant forms of epilepsy, with more than 90% of patients continuing to have uncontrolled seizures despite treatment with multiple antiepileptic drugs (AEDs), putting them at high risk for injury or death. The primary goal of therapy for DS is to reduce seizure frequency and severity; however, there remains a significant need for additional therapies for these patients that address the other comorbidities of DS. Dravet syndrome is associated with low quality of life (Lagae *et al.*, 2018, Dev. Med. Child. Neurol. 60:63-72, incorporated herein by reference). Reducing seizure frequency and improving cognition and gait will likely have a dramatic improvement in quality of life.

[0947] Therapeutic Agent

[0948] An exemplary therapeutic agent for treating Dravet syndrome is an antisense oligonucleotide or antisense oligomer (ASO) medicine that targets ribonucleic acid (RNA) splicing to increase protein levels for the treatment of severe genetic diseases. Specifically, Compound-A is an embodiment of an ASO for the treatment of DS, which is caused by mutations in the *SCN1A* gene. Dravet syndrome is most often caused by mutations in one allele of the *SCN1A* gene. These patients possess one wild-type allele and one mutant allele. While the $Na_V1.1$ protein is produced from the wild-type allele, the mutant allele is translated into non-functional protein and results in 50% of the normal protein expression in the patient.

Compound-A was designed to increase the level of productive SCN1A messenger RNA (mRNA) and consequently increase the expression of the sodium channel $Na_V1.1$ protein. That is, Compound-A binds to the *SCN1A* pre-mRNA and redirects the splicing machinery to decrease the amount of non-productive mRNA and increases productive mRNA, which is translated into increased $Na_V1.1$ protein from the wild-type allele. Restoring $Na_V1.1$ to physiological levels may reduce both the occurrence of seizures and other non-seizure comorbidities. This RNA-based approach may not be gene therapy, but rather RNA modulation, as it does not manipulate nor insert genetic deoxyribonucleic acid code.

[0949] Compound-A was developed to utilize TANGO (Targeted Augmentation of Nuclear Gene Output) technology to leverage a naturally occurring non-productive alternatively spliced exon in human and mouse SCN1A that leads to the incorporation of a premature termination codon and subsequent transcript (mRNA) degradation. These non-productive splicing events are a part of normal gene regulation, and the non-productive splicing events are part of the wild-type or normal sequence of the *SCN1A* gene. Non-productive splicing events amenable to TANGO are alternative splicing that lead to nonsense-mediated mRNA decay exons, or NMD exons. NMD exons are found in over 10% of gene transcripts and, like retained introns, are part of the wild-type sequence of the gene. Non-productive mRNA, which includes these NMD exons, is degraded in the cytoplasm of the cell by nonsense-mediated mRNA decay and is not translated into protein. Compound-A binds to the pre-mRNA and redirects the splicing machinery to prevent inclusion of the NMD exon. This splice-switching decreases non-productive mRNA and increases productive mRNA, which is translated into increased full-length functional protein from the wild-type allele. The TANGO mechanism upregulates expression of the wild-type allele, meaning the TANGO mechanism does not rely on targeting a specific mutation. TANGO ASOs decrease the amount of non-productive mRNA and increase the level of productive mRNA, leading to the generation of more protein. TANGO operates in a mutation-independent manner, given it utilizes one wild-type allele, and does not alter protein coding splicing isoforms.

[0950] *Scn1a* mRNA and $Na_V1.1$ protein levels in rodent brains peak at 4 weeks after birth. In mice the rise in $Na_V1.1$ channels begins at 10 days postnatal and continues through 4 weeks of age (Cheah *et al.*, 2013, Channels, 7:468–72, of which entire content is incorporated herein by reference). Human brain immunoblotting with subtype-specific antibodies showed that $Na_V1.1$ protein expression parallels that in rodent brain, with levels of $Na_V1.1$ being low at birth, steadily increasing to peak values by 20 months, and remaining steady through 30 months (Cheah *et al.*, 2013, Channels, 7:468–72, incorporated herein by reference). A separate study in human brain showed $Na_V1.1$ immunoreactive neurons and neurites increased during the late fetal and postnatal periods, reached their peaks 7 to 9 months after birth (Wang *et al.*, 2011, Brain Res. 1389:61-70, of which entire content is incorporated herein by reference). A similar pattern has been observed in non-human primates (NHPs) and humans. Although the absolute amount of NMD substrate is similar in brain tissues obtained from mice of different ages, because of the progressive increase in productive *Scn1a* mRNA and $Na_V1.1$ protein in the brain with age, the fold change in Scn1a and $Na_V1.1$ in Compound-A-treated mice is higher in younger animals than in older animals. Therefore, Compound-A treatment may be more effective in restoring $Na_V1.1$ protein back to

physiologically normal levels in pediatric DS patients. Preclinical testing in a neonatal mouse model of DS using Compound-A showed significant mortality benefit in animals 35 to 90 days postnatally (equivalent to a greater than 2-year-old human) (Arzimanoglou *et al.*, 2018, Pediatr. Drugs. 20:249-64, of which entire content is incorporated herein by reference).

[0951] Oligonucleotide-based compounds are developed for the treatment of human brain disorders by direct delivery inside the blood-brain barrier. Oligonucleotides dosed directly in the CNS have several unique pharmacokinetic (PK) and pharmacodynamic (PD) properties, including active uptake mechanisms, low systemic exposure, long half-lives ($t_{1/2}$), accumulation, and gradual release from subcellular depots (Khorkova and Wahlestedt, 2017, Nat. Biotechnol. 35:249-63, of which entire content is incorporated herein by reference). CNS delivery of ASOs, such as Compound-A, is not gene therapy (*i.e.,* therapies delivered or expressed using viral technology). Compound-A is a synthetically manufactured chemical product which the FDA categorizes as a small molecule. Compound-A is chemically synthesized and may not be regarded as a biologic.

Example 18: Pharmacological evaluation of the therapeutic agent in non-human models.

[0952] Initial target engagement, pharmacology, and efficacy studies with Compound-A were performed in mice, including both wild-type and a DS mouse model. The targeted non-productive splicing event in SCN1A is highly conserved across multiple species, including mice, non-human primates (NHPs), and humans. The target sequence for Compound-A is also identical across species.

[0953] Characterization of target engagement and pharmacology of Compound-A was done in wild-type mice. Neonate (postnatal day one) mice were administered a single dose of Compound-A by intracerebroventricular injection. On Day 5 of life the brains were isolated and were processed for RNA and protein. Treatment with Compound-A resulted in a dose-dependent reduction of non-productive *Scn1a* mRNA. Furthermore, the reduction of non-productive mRNA was associated with an increase of productive *Scn1a* mRNA and an increase in $Na_V1.1$ protein.

[0954] Compound-A pharmacology and efficacy were also investigated in transgenic mice with a heterozygous deletion of Scn1a. This model was created by introducing a targeted deletion in the first coding exon of the Scn1a gene; these mice exhibit many aspects of the DS phenotype including seizures and premature lethality and has been previously used to evaluate new AEDs for DS. Neonate (postnatal day two) and wild-type littermate controls were administered a single dose of either placebo (consisting of a phosphate-buffered solution) or Compound-A by intracerebroventricular injection. A single injection of Compound-A restored $Na_V1.1$ protein in DS mice to levels that are near those of the wild-type mice at both 7 and 14 weeks. Compound-A treated samples showed an increase in expression of the *SCN1A* gene, but not any of the other SCN family members. These results demonstrate that Compound-A is highly specific for SCN1A among the highly homologous family of sodium channel genes, indicating a low likelihood of off-target activities. In addition to an increase in $Na_V1.1$ protein, the administration of a single dose of Compound-A in DS mice resulted in a significant reduction in premature mortality. Treatment with Compound-A resulted in 97% survival of DS mice for the 90-day postnatal observation period compared with 23% survival of placebo-treated mice. The 90-day postnatal mouse is equivalent to

a greater than 2-year-old human (Arzimanoglou *et al.*, 2018, Pediatr Drugs. 20:249-64, incorporated herein by reference).

[0955] In sum, preclinical data obtained with Compound-A demonstrate proof-of-mechanism and clinical efficacy for Compound-A. Compound-A engages the target and elicits the predicted pharmacology in wild-type mice brain. Administration of a single dose of Compound-A in DS mice resulted in a significant reduction ($p<0.0001$) in premature mortality.

[0956] The pharmacology, distribution, and tolerability of Compound-A were also evaluated in cynomolgus monkeys. Pre-pubescent monkeys were administered a single dose of Compound-A or control solution by intrathecal (IT) injection at a dose range that coincides with the estimated therapeutic dose range and stays below the maximum tolerated dose based on tolerability in monkeys and published data for molecules of similar chemistry. The animals (n=3 for treatment groups and n=2 for control groups) were sacrificed at 2 days or 28 days after dosing. A two-fold increase in the $Na_V1.1$ protein was observed. The increase in $Na_V1.1$ was also correlated with the presence of Compound-A in brain tissue.

Example 19: Pharmacological evaluation of therapeutic agent in human patients.

[0957] DS is a highly drug-resistant form of genetic epilepsy, associated with multiple severe comorbidities. The Worsening Stage (between 1 and 8 years of age) is a critical window for therapeutic intervention to reduce the occurrence and severity of comorbidities such as intellectual disability. It is therefore crucial to develop novel therapeutics for the treatment of DS that may be administered to the pediatric population.

[0958] The safety and PK endpoints are, for example, the safety profile and PK of single or multiple doses of Compound-A. Safety variables for analysis include, but are not limited to, the incidence, type, and severity of AEs, vital signs, ECG/Holter, laboratory and physical examination parameters. The PK parameters may be obtained by non-compartmental analysis from plasma concentrations of Compound-A that may include, but are not limited to, Maximum plasma concentration (Cmax), Time to maximum plasma concentration (Tmax), Area under the plasma concentration-time curve from time 0 to infinity and to the last measurable concentration ($AUC_{0-\infty}$, AUC_{0-t}), and Fold change in Cmax and AUC compared with dose levels. Exposure of Compound-A in CSF may be assessed by measuring concentrations of Compound-A.

[0959] The efficacy endpoints are, for example, evidence of dose effect and comparison between baseline and the end of treatment in: (i) percentage change from baseline in convulsive seizure frequency (as measured by paper diary) calculated over 4-week time periods; (ii) proportion of patients with ≥50%, ≥75%, and 100% reduction (compared with baseline) in convulsive seizure frequency (as measured by paper diary) calculated over 4-week time periods; (iii) change from baseline in overall clinical status as measured by the following scales: Caregiver Global Impression of Change (CaGIC), Clinical Global Impression of Change (CGIC), and Change from baseline in the patient's quality of life as measured by the EuroQol-5D (Youth) (EQ-5D-Y), or the EQ-VAS component of the EQ-5D-Y assessment.

[0960] Other efficacy endpoints include, but are not limited to, number and type of all convulsive and non-convulsive seizures, percentage change from baseline in total seizure frequency (as measured by

paper diary) calculated over, *e.g.,* 4-week time periods, proportion of patients with ≥50%, ≥75%, and 100% reduction (compared with baseline) in total seizure frequency (as measured by paper diary) calculated over, *e.g.,* 4-week time periods, change in 10-20 electroencephalogram (EEG) parameters, total sleep time measured by actigraphy and as weekly sleep duration (hours) by sleep diary, convulsive seizure frequency as measured by, *e.g.,* the Embrace2 wearable device, assessment of ambulation and gait as measured by the Gillette Functional Assessment Questionnaire (FAQ) 22-item skill set, and analysis of CSF, plasma, or serum samples for exploratory biomarkers (*e.g.,* $Na_V1.1$, neurofilament light chain, *etc.*).

[0961] Dose Levels

[0962] Single or multiple doses of Compound-A, *e.g.,* 0.1, 0.5, 1, 2.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg, are administered by intrathecal (IT) injection to patients with DS. The dose levels may be adjusted based on Safety Monitoring Committee (SMC) determination. Dose escalation between cohorts may be two-fold or lower increase for each dose level.

[0963] Patient population

[0964] Patients meeting the following criteria (Inclusion Criteria) may be eligible: (i) patient and/or authorized representative must be willing and able to give informed consent/assent and any authorizations according to local law for participation in the study; (ii) patient and their caregiver must be willing and able to comply with all elements of the protocol; (iii) patient must be up to18 years (inclusive) of age at Screening; (iv) patient must have DS as defined by: (a) onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia, (b) no past history of causal magnetic resonance imaging (MRI) lesion (MRI not required to confirm absence of lesion), (c) no other known etiology, and (d) normal development at seizure onset; (v) patient must have a documented pathogenic, likely pathogenic variant, or variant of uncertain significance in the *SCN1A* gene associated with DS. Patients who have SCN1A testing results of negative (no variants of clinical significance identified) may not be enrolled; (vi) patient has had at least 2 prior treatments for epilepsy that either had lack of adequate seizure control (requiring an additional AED) or had to be discontinued due to an AE(s); (vii) patient must be experiencing 4 or more convulsive seizures (Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic/Atonic (Drop Attacks), and Clonic) during the initial Observation Period; (viii) patient must currently be taking at least one AED at a dose which has been stable for at least 4 weeks prior to Screening; (ix) all epilepsy medications or interventions for epilepsy (including ketogenic diet or vagal nerve stimulator) must have been stable (including product type, dose, and setting) for at least 4 weeks prior to Screening; (x) any marijuana- or cannabinoid-based product or medication is allowed but treatment must have been stable for at least 4 weeks prior to Screening, including supplier, ratio, and dose; and (xi) patient must meet age-appropriate institutional guidelines for IT drug administration procedures.

[0965] Patients meeting the following criteria (Exclusion Criteria) may not be eligible: (i) patient has one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, or Asp1866Tyr; (ii) patient has a known pathogenic mutation in another gene that causes epilepsy (the pathogenic mutation must be homozygous in cases of known recessive disease); (iii) patient is currently being treated with a sodium channel blocker as maintenance treatment including: phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide; (iv) patient has clinically significant unstable medical conditions other than epilepsy; (v) patient has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to Screening or prior to dosing on Day 1, other than epilepsy; (vi) patient has a history of brain or spinal cord disease (other than epilepsy or DS) or a history of bacterial meningitis or brain malformation; (vii) patient has a spinal deformity or other condition that may alter the free flow of CSF or has an implanted CSF drainage shunt; (viii) patient has clinically significant (in the judgment of the Investigator) abnormal laboratory values at Screening or prior to dosing on Day 1; (ix) patient has AST or ALT >2.5-fold ULN, serum creatinine >ULN, or platelet count < the lower limit of normal at Screening and upon repeat testing; (x) patient has clinically relevant abnormalities in the 12-lead ECG measured at Screening or prior to dosing on Day 1; (xi) patient has a psychiatric or behavioral disorder which, in the opinion of the Investigator, may interfere with the patient's participation in the study; (xii) patient is currently taking, or in the past 4 weeks has taken, any anticoagulant (except aspirin); (xiii) female patients of childbearing potential and male patients whose partner is of childbearing potential, unless willing to ensure that they or their partner use effective contraception, for example, abstinence, oral contraception, double barrier, or intra-uterine device during the study and for 3 months thereafter; (xiv) patient who is pregnant, lactating, or planning pregnancy during the course of the study and for 3 months thereafter following the last dose of Compound-A; (xv) Patient who is currently enrolled in or has been part of a blinded clinical study involving an investigational product within 2 months prior to Screening; and (xvi) Patient has any other significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, may influence the results of the study, or may affect the patient's ability to participate in the study.

[0966] The mechanism of action of Compound-A may cause an increase in the levels of the gain-of-function mutated protein and treatment may lead to a worsening of symptoms. Patients carrying gain-of-function mutations in SCN1A may likely be excluded from the study because they do not meet the criteria for DS diagnosis.

[0967] Administration of Therapeutic Agents

[0968] The drug product is a concentrate intended for dilution with artificial cerebral spinal fluid (aCSF) solution followed by intrathecal administration. The diluent, aCSF, for administration is supplied with the drug product. The drug product may be produced with sufficient fill volume to allow withdrawal of, *e.g.*, 5.0 mL. The solution is a clear, colorless liquid that is essentially free of visible particles. Instructions regarding drug storage, preparation and dosing may be included.

[0969] *Mode of Administration*: diluted drug product may be administered as an IT slow bolus.

[0970] An exemplary drug product is provided in a kit comprised of 3 vials: 1 vial of drug product at an appropriate concentration; 1 vial of aCSF diluent; and 1 empty, sterile vial for mixing. It is suitably packaged in such a way as to protect the product from deterioration during transport and it is stored frozen at, *e.g.,* -20°C at the study site. Further information regarding storage and transport conditions may be provided. The study drug may be shipped on dry ice and stored on site at, *e.g.,* -20°C.

[0971] In addition to the therapeutic agents as described herein, for example, Compound-A, patients may take at least one AED during the study, and any AEDs the patient takes may be maintained at a stable dose prior to Screening and after dosing. For some examples, patients may take at least one AED during the study, and any AEDs the patient takes may be maintained at a stable dose for at least, *e.g.,* 4 weeks prior to Screening and for the first, *e.g.,* 12 weeks after dosing, in addition to the therapeutic agents as described herein, for example, Compound-A. Exemplary medications or interventions for epilepsy include, but are not limited to, ketogenic diet, vagal nerve stimulator, cannabinoid or marijuana-derived products. Exemplary rescue medications allowed for home use include, but are not limited to, lorazepam, midazolam, and diazepam. Lorazepam may be used at 0.1-0.2 mg/kg as needed (PRN) intrabuccally, sublingually, or intravenously. Midazolam may be used at 0.1-0.2 mg/kg PRN intranasally, intrabuccally, or intravenously. Diazepam may be used at 0.2-0.5 mg/kg PRN rectally or intravenously.

[0972] The exemplary medications that may not be concomitantly used with the therapeutic agents as described herein, for example, Compound-A, include, but are not limited to, sodium channel blockers as maintenance treatment (*e.g.,* phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide), anticoagulants (except aspirin), and any investigational product or device.

[0973] Study Assessments

[0974] *Epilepsy Genetic Panel Testing:* saliva samples are collected at Screening for determination of the patient's DS mutation and confirmation of eligibility. The samples are analyzed using a genetic epilepsy panel. The panel also analyzes genes associated with both syndromic and nonsyndromic causes of epilepsy (including SCN1A) and provides a comprehensive analysis for inherited epilepsy.

[0975] *Baseline Assessments:* exemplary patient demographic and baseline characteristic data to be collected on all patients include, but are not limited to, age at Screening, sex, race/ethnicity, age of DS disease onset, and diagnostic and treatment history for DS.

Example 20: Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A reduces seizures and rescues parvalbumin positive interneuron firing frequency in a mouse model of Dravet syndrome.

[0976] Dravet syndrome (DS) is a severe and progressive developmental and epileptic encephalopathy characterized by high seizure frequency and severity, intellectual disability, and a high risk of sudden unexpected death in epilepsy (SUDEP). Approximately 85% of DS cases are caused by spontaneous, heterozygous loss of function mutations in the *SCN1A* gene which encodes the voltage-gated sodium channel α subunit $Na_V1.1$. We developed a novel therapeutic approach to treat DS using antisense oligomers (ASOs) to increase the endogenous expression of *Scn1a* mRNA and $Na_V1.1$ protein. We are

testing this approach using the F2:129S-Scn1a+/- x C57BL/6J DS mouse model that has been shown previously to recapitulate many patient phenotypes.

[0977] Methods

[0978] Targeted Augmentation of Nuclear Gene Output (TANGO), which modulates naturally occurring, non-productive splicing events to increase target protein expression, was used to screen and identify an ASO (Compound-A) that can increase productive *Scn1a* mRNA and $Na_V1.1$ protein *in vivo*. We administered 20 μg TANGO ASO or PBS control to DS mice and wildtype (WT) littermates by single intracerebroventricular (ICV) injection at postnatal day (P)2. Mice were monitored by electroencephalography (EEG) pre (P13-19) and post (P20-40) weaning. DS mice were also crossed with WT mice hemizygous for a parvalbumin (PV)-tdTomato fluorescent reporter to produce DS mice expressing the tdTomato specifically in PV expressing interneurons. These mice received 20 μg ASO or PBS by ICV administration at P2 and then electrophysiological recordings were taken from tdTomato expressing cells in the somatosensory cortex between P17 and 23.

[0979] Results

[0980] No seizures were detected in any of the mice prior to day 16. Between P16-19, ASO-injected DS mice continued seizure free (0/5 animals) whereas 50% (4/8 animals) of PBS-injected control DS mice had seizures. When assessed after weaning (P20-40), 2/11 P2 ASO injected DS mice developed seizures and one animal died while 9/11 P2 PBS-injected control DS mice developed seizures and seven animals died. The firing frequency of PV interneurons in DS mice assessed between P17 to P23 was significantly impaired. DS PV interneurons fired at a significantly ($P< 0.05$) lower frequency than WT PV interneurons over a range of current injection steps. After ASO treatment at P2, the firing frequency of PV interneurons in DS mice was increased and was no longer significantly different from WT levels.

[0981] Conclusions

[0982] These results provide evidence that increased Scn1a and $Na_V1.1$ expression achieved using a TANGO ASO can greatly decrease seizures and death rates in a mouse model of *Scn1a*-linked DS. Further, the current data support the hypothesis that the improvement in DS phenotype is in part due to restoration of excitability of PV expressing interneurons.

Example 21: Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A reduces seizures and rescues parvalbumin positive interneuron firing frequency in a mouse model of Dravet syndrome.

[0983] Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy. DS is caused primarily by physiologically loss-of-function SCN1A mutations resulting in hypofunction of inhibitory interneurons. Patients suffer refractory seizures, cognitive and motor impairments, and have a substantial risk for SUDEP. There is a demand for therapeutic strategies that directly address genetic cause of disease.

[0984] Compound-A reduced seizure frequency and extended survival in DS mice with no significant deleterious effects observed in WT mice. Treatment with Compound-A rescues neuronal excitability of parvalbumin-positive inhibitory interneurons in DS mice, which supports the hypothesis that restoration

of excitability to inhibitory interneurons is a viable approach toward rescuing DS mice from seizures and death.

[0985] Potential future evaluations: collect electrophysiology recordings of voltage-gated sodium channel activity; explore effects on other inhibitory interneuron populations (SST, VIP, *etc.*); examine impact on network excitability (synaptic inhibition, *etc.*).

Example 22: BUTTERFLY, a 24-month observational study of Dravet Syndrome patients.

[0986] The BUTTERFLY study is the longest-running prospective natural history study of patients with genetically confirmed Dravet Syndrome (DS) to elucidate the natural trajectory of DS, seizure frequency, and associated comorbidities and establish a baseline for disease-modifying therapies in children and adolescents. BUTTERFLY was a multicenter, US-based, longitudinal, prospective, observational study. Patients participating in BUTTERFLY only received standard of care treatment with the best available antiseizure medications (ASM) and did not receive ASO-1.

[0987] Study Design

[0988] Key criteria for inclusion were that the participants (1) were between 2 and 18 years old and (2) diagnosed with DS comprising a documented mutation in SCN1A gene. Key criteria for exclusion were those who had (1) a gain-of-function SCN1A mutation or (2) were currently receiving treatment with sodium channel blockers.

[0989] Average change over time across the clinical measures was assessed using disease progression models (**Table 8**). Disease progression models used to evaluate study participants comprised Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P); Bayley Scales of Infant Development, Third Edition (BSID-III); Caregiver Global Impression of Change for Cognition (CaGI-C); Clinical Global Impression of Change for Cognition (CGI-C); Gillette FAQ, Gillette Functional Assessment Questionnaire; Vineland Adaptive Behavior Scales, Third Edition (Vineland-3 or VABS-III); and Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV). Patients' age at enrollment, age at seizure onset, sex, body mass index, *SCN1A* genotype, baseline scores, and baseline convulsive seizures were tested as covariates in mixed-effects models.

[0990] The study's primary objective was to determine participant neurodevelopmental status using Vineland-3, BSID-III, and WPPSI-IV from baseline to Month 24. The study's secondary objectives were to chronicle the number of countable convulsive seizures for every 4-week period before visits, determine the change relative to baseline in overall clinical status using CaGI-C and CGI-C, measure locomotor skills with Gillette FAQ, and assess executive function using BRIEF-P.

Table 8. Exams performed during various visits in the BUTTERFLY study.

	Visit 1 Baseline	Visit 2 Month 3	Visit 3 Month 6	Visit 4 Month 12	Visit 5 Month 18	Visit 6 Month 24
Vineland-3	√	√	√	√	√	√
BSID-III/WPPSI-IV	√	√	√	√	√	√
Gillette FAQ	√	√	√	√	√	√
BRIEF-P	√	√	√	√	√	√
CaGI-C/CGI-C		√	√	√	√	√

[0991] Baseline characteristics

[0992] BUTTERFLY patients were experiencing an average of 14.3 seizures/28 days despite receiving best available ASMs (**Table 9**). Overall, patients reported a mean (range) of 3.5 (0-7) ongoing seizure therapies at baseline. Most common anti-seizure medications (ASMs) taken during the study included clobazam (69.4%), fenfluramine (44.4%), stiripentol (38.9%), valproic acid (38.9%), cannabidiol (33.3%), and levetiracetam (22.2%).

Table 9. Summary of baseline characteristics and patient demographics.

Parameter	2–7 years (n=12)	8–12 years (n=12)	13–18 years (n=12)	All enrolled (N=36)
Gender, n (%)				
Female	5 (41.7)	7 (58.3)	10 (83.3)	22 (61.1)
Race, n (%)				
White	11 (91.7)	12 (100.0)	11 (91.7)	34 (94.4)
Asian	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.8)
Other	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.8)
Baseline convulsive seizure frequency per 28 days*				
Mean (SD)	7.9 (6.2)	13.6 (8.4)	21.6 (23.5)	14.3 (15.6)

*Number of patients for baseline convulsive seizure frequency were n=9 (2–7 years), n=8 (8–12 years), n=9 (13–18 years), and n=26 (all enrolled).

[0993] ***Neurodevelopmental assessments***

[0994] Adaptive behavior: Vineland-3

[0995] Growth scale values obtained from Vineland-3 were used for modeling disease progression. Disease progression modeling indicated no improvements in four of the six subdomains analyzed, with statistically significant improvements through Month 24 observed only in Receptive Communication (P=0.0189; n=32) (**FIG. 66A**) and Coping Skills (P=0.0114; n=32) (**FIG. 66B**). Modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit. Progression for neurotypical peers was plotted using normative tables from the Vineland-3 manual that show correlations between age equivalents and growth scale values. P-values are provided for statistically significant changes. The progression of BUTTERFLY patients diverged substantially from the expected progression

in neurotypical peers starting from the same mean developmental age-equivalent level. Baseline score, but not baseline seizure frequency, was a significant covariate across all analyzed subdomains.

[0996] ***Development across cognitive, language, and motor domains: BSID-III***

[0997] Disease progression modeling did not detect statistically significant changes in any BSID-III subtests through Month 24 (all Ps>0.21, n=10-13). The progression of BUTTERFLY patients in the BSID-III subtests diverged substantially compared to their expected progression in neurotypical peers starting from the same mean developmental age-equivalent level.

[0998] ***General intellectual functioning: WPPSI-IV***

[0999] Disease progression modeling for WPPSI-IV subtests indicated no statistically significant changes across any of the subtests through Month 24 (all Ps>0.12; n=9-11).

[1000] Overall clinical status

[1001] Disease progression modeling indicated a statistically significant improvement in CaGI-C (*P*=0.0352; n=14), but not in CGI-C (*P*=0.3006; n=14) (**FIGS. 67A-67B**). For both assessments, change was scored on a 7-point scale with improvement ranging from "very much improved" (scored as 1) to "very much worse" (scored as 7). *P*-values are provided for statistically significant changes. Mean CaGI-C and CGI-C scores at the end of Month 24 were 3.26 and 2.90, respectively, indicating participants "slightly improved." Baseline convulsive seizure frequency was a positively correlated predictor for both CaGI-C and CGI-C.

[1002] ***Convulsive seizure frequency, locomotor skills, and executive functioning.***

[1003] Disease progression modeling indicated that participants had no significant changes in convulsive seizure frequency through Month 24 (*P*=0.6280; n=23) (**FIG. 68A**). Disease progression modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit. Disease progression modeling indicated that study participants had no significant changes in locomotor skills (Gillette FAQ; *P*=0.5707; n=32) (**FIG. 68B**) or executive functioning (BRIEF-P; *P*=0.8867 for BRIEF-P global executive composite; n=33) through Month 24.

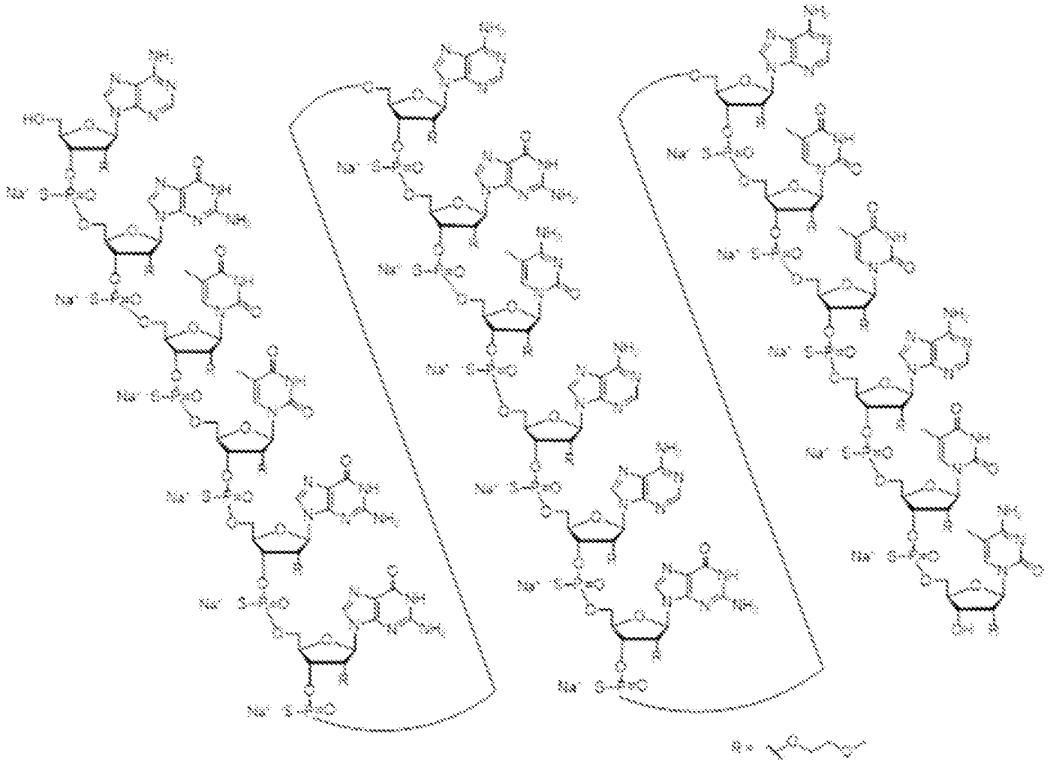
[1004] Study Findings

[1005] Despite treatment with standard ASMs, BUTTERFLY patients continued experiencing similarly high rates of seizures and fell further behind their neurotypical peers in aspects of cognition and behavior over 24 months. Modeling based on the Vineland-3 revealed statistically significant improvements only in Receptive Communication and Coping Skills; however, the magnitude of improvement differed substantially from neurotypical peers. Modeling based on the BSID-III and WPPSI-IV did not detect any statistically significant changes across the various subtests. Seizure frequency, Gillette FAQ scores, and BRIEF-P indexes remained stable, with no significant changes. Slight improvements in overall clinical status were observed by caregivers but not by clinicians.

Example 23: Safety and pharmacokinetics of antisense oligonucleotide Compound-A in children and adolescents with Dravet Syndrome: single ascending dose design for the open-label Phase 1/2a MONARCH and ADMIRAL clinical studies.

[1006] Condition or disease: Dravet Syndrome.

[1007] Intervention/treatment: Drug: Compound-A (also referred to herein as "ASO-1") is an antisense oligonucleotide compound according to chemical structure (II):



(II),

which is a sodium salt of *all-P-ambo*-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine. Compound-A has the nucleobase sequence set forth in SEQ ID NO: 42, with all nucleosides modified with 2'-MOE, all cytosines methylated at the 5' position, and all backbone linkages being phosphorothioate linkages.

[1008] Phase: Phase 1, Phase 2

[1009] Ages Eligible for Study: 2 Years to 18 Years (Child, Adult);

[1010] Sexes Eligible for Study: All;

[1011] Accepts Healthy Volunteers: No

[1012] Rationale

[1013] Dravet syndrome (DS) is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, beginning within the first year of life. It is characterized by high

seizure frequency and severity, intellectual disability, and a high risk of sudden unexpected death in epilepsy. Available therapies do not adequately control seizures in 90% of DS patients, and they do not address other aspects of the disease, including intellectual disability, developmental delays, motor and speech impairment, behavioral problems, sleep abnormalities, and an increased risk of sudden unexpected death in epilepsy. Complications of the disease often contribute to a poor quality of life for patients and their caregivers. In approximately 85% of cases, DS is caused by spontaneous, heterozygous loss of function mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_V1.1$). Upregulating $Na_V1.1$ may restore functioning neurons and prevent seizures and reduce non-seizure related comorbidities in DS.

[1014] Compound-A is an investigational new medicine for the treatment of Dravet syndrome. Compound-A is an antisense oligonucleotide treatment using a unique platform, Targeted Augmentation of Nuclear Gene Output (TANGO) (**FIG. 24**) that exploits naturally occurring nonproductive splicing events to increase $Na_V1.1$ protein expression. Compound-A is an antisense oligonucleotide (ASO) that is intended to increase the level of productive SCN1A messenger RNA (mRNA) and consequently increase the expression of the sodium channel $Na_V1.1$ protein. This RNA-based approach is not gene therapy, but rather RNA modulation, as it does not manipulate nor insert genetic deoxyribonucleic acid (DNA). Compound-A is designed to upregulate $Na_V1.1$ protein expression from the nonmutant (wild-type) copy of the *SCN1A* gene to restore physiological $Na_V1.1$ levels. $Na_V1.1$ levels are reduced in people with Dravet syndrome. Stoke has generated preclinical data demonstrating proof-of-mechanism for Compound-A.

[1015] In DS, patients have one functional gene copy and one mutated copy, resulting in half as much protein as needed to maintain health. These genes are transcribed into pre-messenger RNA (pre-mRNA); most pre-mRNA is productive, becoming a template for protein production, but some is non-productive pre-mRNA. Synthesized ASOs bind to specific stretches of pre-mRNA, reducing the synthesis of non-productive mRNA and increasing the synthesis of productive mRNA. The increased levels of productive mRNA from the functional gene copy increase protein production, thereby restoring the target protein to near normal levels.

[1016] Current treatments focus on seizure control. Compound-A may be the first precision medicine approach for DS. Compound-A has the potential to be the first disease-modifying therapy to address the genetic cause of DS by restoring physiological $Na_V1.1$ levels and reducing both occurrence of seizures and significant non-seizure comorbidities. This clinical study aims to primarily assess the safety, tolerability, and pharmacokinetics of intrathecally administered Compound-A. Secondary objectives aim to evaluate the effect of Compound-A on convulsive seizure frequency, overall clinical status, and quality of life in Dravet syndrome patients. The dose implications of this study may better inform future clinical trials on the appropriate and effective dosing for efficacy measures.

[1017] Study Design:

[1018] Open-label, Single and Multiple Ascending Doses (SAD and MAD) of Compound-A in 2–18y.

[1019] Study duration: 7-9 months / patient; Number of patients <80;

[1020] Sites: US; UK, Scotland, Ireland among others;

[1021] Cohorts: This phase 1/2a open-label single ascending dose study includes patients aged 2-18 years with disease onset prior to 12 months of age with recurrent seizures (focal motor, hemiconvulsive or generalized tonic-clonic) and genetically confirmed SCN1A variant.

[1022] Inclusion Criteria: Must have DS with onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia; No history of causal MRI lesion; No other known etiology; Normal development at seizure onset; Documented pathogenic, likely pathogenic variant, or variant of uncertain significance in the *SCN1A* gene associated with DS; Had at least 2 treatments for epilepsy that either had lack of adequate seizure control (requiring an additional AED) or had to be discontinued due to an AE(s); Currently be taking at least one AED at a dose which has been stable for at least 4 weeks prior to Screening; All epilepsy medications or interventions for epilepsy (including ketogenic diet or vagal nerve stimulator) must have been stable (including product type, dose, and setting) for at least 4 weeks prior to Screening.

[1023] Exclusion Criteria: Known pathogenic mutation in another gene that causes epilepsy; Currently being treated with an antiepileptic drug acting primarily as a sodium channel blocker including: phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide; Clinically significant unstable medical conditions other than epilepsy; Has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to Screening or prior to dosing on Day 1, other than epilepsy; Any other significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, may influence the results of the study, or may affect the patient's ability to participate in the study.

[1024] Dosing: Dose escalation based on safety and tolerability assessed by Safety Committee (with external reviewers), Dosing begins in 13 to 18 y cohorts, with internal safety team approving dosing in 2 to 12 y.

[1025] ***MONARCH and ADMIRAL studies: Single Ascending Dose arm***

[1026] Enrollment of patients in two age groups. A Sentinel group of patients aged 13 to 18 years of age, inclusive, and an expanded group of patients 2 to 12 years of age were to receive single doses. There was an option to dose up to 6 additional patients at each dose level and an option to expand the maximum tolerated dose level with 5 additional patients. In Single Ascending Doses arm (SAD), ASO-1 drug product is an antisense oligonucleotide administered as an intrathecal injection. Four dose levels were evaluated (10 mg, 20 mg, 30 mg, 45 mg, and 70 mg). In the MONARCH study, SAD regimes at 10 mg, 20 mg, 30 mg, and 45 mg dosages were administered to an expanded group of patients 2 to 12 years of age and 13-18 years of age. In the ADMIRAL study, SAD regimes at 30 mg, 45 mg, and 70 mg were administered to an expanded group of patients 2 to 12 years of age and 13-18 years of age. Dose escalation was based on safety and tolerability assessment by the Safety Monitoring Committee (including external reviewers). Dosing began in each cohort in 13- to 18-year-olds and an internal safety team approved dosing in younger patients (2-12 years).

[1027] ***MONARCH study: Multiple Ascending Doses arm***

[1028] Enrollment of patients in two age groups. A Sentinel group of 2 patients aged 13 to 18 years of age, inclusive, and an expanded group of 2 patients 2 to 12 years of age to receive multiple doses. There will be an option to dose up to 6 additional patients at each dose level and an option to expand the maximum tolerated dose level with 10 additional patients. In the Multiple Ascending Doses (MAD) arm, ASO-1 drug product is an antisense oligonucleotide administered as an intrathecal injection. Three dose levels are evaluated (20 mg, 30 mg and 45 mg). In the MONARCH study, MAD regimes at 20 mg, 30 mg, and 45 mg dosages were administered to an expanded group of patients 2 to 12 years of age and 13-18 years of age.

[1029] **FIGS. 33A-33C** show the study design and workflow of the SAD and MAD study assessments in the MONARCH and ADMIRAL Phase 1/2a clinical trials for ASO-1. For each patient in the study, there was a baseline period for monitoring seizure from Day -28 and Day -1 (in reference to 1st dose of study drug), and the patient was monitored continuously (adverse effect monitoring, physical examination, clinical laboratories, and plasma PK) for 225 days post administration in the SAD and MAD arms of the MONARCH study and 252 days in the SAD arm of the ADMIRAL study. **FIG. 33A** shows the study design and dosing schedule using the Single Ascending Dose (SAD) regime (MONARCH) before patients can become eligible to enroll in the LONGWING OLE. Study drug Compound-A was administered on Day 1 in SAD arm of the MONARCH study. **FIG. 33B** shows the study design and dosing schedule using the Multiple Ascending Dose (MAD) regime (MONARCH) before patients can become eligible to enroll in the LONGWING OLE. Compound-A was administered on Day 1, Day 29, and Day 57 in MAD arm of the MONARCH study. **FIG. 33C** shows the study design and dosing schedule using the Multiple Ascending Dose (MAD) regime (ADMIRAL) before patients can become eligible to enroll in the LONGWING OLE. Compound-A was administered on Day 1, Day 57, and Day 85 in SAD arm of the ADMIRAL study. The study protocol for ADMIRAL was amended to allow investigators to decide whether to administer two or three doses of ASO-1 (70 mg) in the ADMIRAL study before patients would be eligible to enroll in the LONGWING OLE. Baseline seizure diary entries were collected in the periods of Day -28 to Day -1, Day 1 to Day 28, Day 29 to Day 56, Day 57- Day 84, Day 85- Day 112, Day 113 to Day 140, Day 141 to Day 168, Day 169 to Day 196, Day 197 to Day 224 in the MONARCH Study. Baseline seizure entries were collected in the periods of Day -28 to Day -1, Day 1 to Day 28, Day 29 to Day 56, Day 57 to Day 84, Day 85 to Day 112, Day 113 to Day 140, Day 141 to Day 168, Day 169 to Day 196, Day 197 to Day 224, and Day 225 to Day 252 in the ADMIRAL Study.

[1030] Study visits included the following (**FIG. 26**): screening visit; a four-week observation period: no change to current anti-epileptic therapy, ketogenic diet, or vagal nerve stimulator settings, caregivers track child's seizure frequency during this period; Baseline visit: blood and urine analyses, quality of life, neurological, and general pediatric assessments; inpatient treatment period: patients are admitted on the day of dosing and discharged after completing post-dosage assessments: all patients received intrathecal administration of Compound-A; 3-month and 6-month follow-up period. Patients who completed the

study had the option to receive Compound-A in an open-label extension study if they met enrollment criteria.

[1031] Two cohorts based on age (2-12 and 13-18 years) were administered a single dose or multiple doses of ASO-1 administered intrathecally (IT). Each cohort enrolled up to 4 patients with an option to dose up to 6 additional patients per cohort at the same level based on clinical assessment for safety evaluation. All patients had a 28-day observation period evaluating seizure frequency. On Day 1, patients underwent cerebral spinal fluid (CSF) collection followed by a single IT administration of ASO-1 and 24-hour post-dose assessment. A follow-up period occurred about a year after dosing. Adverse events were monitored throughout the study. Plasma and CSF were collected at multiple timepoints. Patients kept a seizure/sleep diary the full duration of the study. The demographics for the initial 74 patients treated with >=1 dose of ASO-1 in the MONARCH and ADMIRAL studies are shown in **Table 10**. Enrolled patients have severe disease and are refractory to Standard treatment.

Table 10. Demographics for patients treated with ≥1 dose of ASO-1 in initial MONARCH/ADMIRAL studies.

	Total, n (%)
N	74
Age at Screening, y	
Mean (SD)	10.2 years (5.05)
Median (min, max)	10.5 years (2, 18)
Sex	
Female	39 (52.7%)
Male	35 (47.3%)
Number of Concomitant Anti-Seizure Medications (ASMs)	
≥3	60 (81.1%)
≥4	37 (50.0%)
Concomitant Fenfluramine	
%	36 (48.6%)
Baseline Convulsive Seizure Frequency per 28 days	
Median (min, max)	17.5 (1, 2335)

[1032] ***Outcome Measures:***

[1033] Primary Outcome Measures:

[1034] 1. Incidence proportion of adverse events [Time Frame: Screening until 6 months after single drug dosing Safety of Compound-A were evaluated by the proportion of subjects experiencing Adverse Events, Serious Adverse Events, and Adverse Events leading to drug discontinuation.

[1035] 2. Pharmacokinetic (PK) Parameters [Time Frame: Screening until 6 months after single drug dosing] Analysis of plasma concentrations of Compound-A.

[1036] 3. Exposure of Compound-A in Cerebrospinal Fluid (CSF) [Time Frame: Screening until 6 months after single drug dosing] Measurement of Compound-A concentrations.

[1037] Secondary Outcome Measures:

[1038] 1. Measurement of seizure frequency [Time Frame: Screening until 6 months after single drug dosing] Measured by paper diary.

[1039] 2. Change in clinical status [Time Frame: Screening until 6 months after single drug dosing] Change from baseline in overall clinical status as measured by the Caregiver Global Impression of Change (CaGIC).

[1040] Values of scales: a. Very much improved; b. Much improved; c. Minimally improved; d. No change; e. Minimally worse; f. Much worse; g. Very much worse.

[1041] 3. Change in clinical status [Time Frame: Screening until 6 months after single drug dosing] Change from baseline in overall clinical status as measured by the Clinical Global Impression of Change (CGI-C).

[1042] Values of scales: a. Very much improved; b. Much improved; c. Minimally improved; d. No change; e. Minimally worse; f. Much worse; g. Very much worse.

[1043] 4. Measurement of Quality of Life [Time Frame: Screening until 6 months after single drug dosing] Change from baseline in the patient health is measured by the EuroQOL quality of life questionnaire, youth version (EQ-5D-Y) instrument. The scale is scored from 0-100. The reference to a high score indicates a better outcome of quality of life.

[1044] Results

[1045] This study assessed the safety, tolerability, and pharmacokinetic profile of ascending doses of Compound-A in DS patients. In addition, the impact of Compound-A on frequency of convulsive seizures and quality of life may indicate the initial clinical effect of the individual doses.

Example 24: Interim safety, PK, CSF exposure, and seizure frequency data from a Phase 1/2a study of Compound-A in children and adolescents with Dravet Syndrome (DS).

[1046] This example describes some interim data obtained from a Phase 1/2a study of Compound-A in children and adolescents with DS. The data presented here illustrate the safety, pharmacokinetic (PK), and cerebrospinal fluid (CSF) exposure features of Compound-A in the tested subjects and their seizure frequency before and after administration of Compound-A. Patients in this study have severe disease. The interim data presented here show that single doses of Compound-A up to 30 mg and multiple doses of 20 mg were well-tolerated, and there were no safety concerns related to study drug. Moreover, dose-dependent increases in plasma exposure and CSF concentration were observed, and it was found that seizures were reduced in 12 of 17 (70.6%), including all 2- to 12-year-old patients, at days 29-84 as compared to baseline period.

[1047] **FIG. 29** shows the workflow of the SAD and MAD study assessments. For each patient in the study, there was a baseline period for monitoring seizure from Day -28 and Day -1 (in reference to 1st dose of study drug), and the patient was monitored continuously (adverse effect monitoring, physical examination, clinical laboratories, and plasma PK) for 169 days post administration in SAD study, and 225 days in MAD study. Study drug Compound-A was administered on Day 1 in SAD study, and was administered on Day 1, Day 29, and Day 57 in MAD study. Baseline seizure diary entries were collected

in the periods of Day -28 to Day -1, Day 1 to Day 85, and Day 141 to Day 169 in the SAD study, and in the periods of Day -28 to Day -1, and Day 1 to Day 225 in MAD study. CSF collection was performed on Day 1, Day 85, and Day 169 in SAD study, and on Day 1, Day 29/Week 4, Day 57/Week 8, and Day 141/Week 20 in the MAD study.

[1048] Cutoff date for data presented in this example was October 19, 2021, after all patients in Cohort A3 (30 mg SAD) completed visit 5 (day 85) and Cohort B1 (20 mg MAD) completed visit 7 (week 12). All received ≥1 dose of Compound-A.

[1049] ***Study Objectives***

[1050] Primary Assessments include Safety and Tolerability (Adverse events (AEs), vital signs, physical examination, electrocardiogram, laboratories), Pharmacokinetics (PK) (Compound-A plasma concentrations), and Cerebrospinal Fluid (CSF) Exposure (Compound-A CSF concentrations). Secondary Assessments include Convulsive seizure frequency (Daily paper seizure diary), Overall Clinical Status and Quality of Life (Caregiver and Clinical Global Impression of Change; EQ-5D-Y).

[1051] **Table 11** below summarizes the demographics of the tested subjects and the safety evaluation after they received administration of Compound-A. The most common treatment-emergent adverse effects (TEAEs) include headache (reported in 7 patients), vomiting (6 patients), seizure (5 patients), irritability (4 patients), back pain (3 patients), fall (3 patients), and pyrexia (3 patients). In addition, overall, there was no new clinically significant weakness reported on physical exam, there was no increase in seizures identified in 1 hour EEG recorded ~24 hours post-dose, and there were no clinically significant changes in laboratories assessed as related to study drug.

Table 11. Summary of Demographics and Safety.

	SAD			**MAD**	
	A1 (10 mg)	**A2 (20 mg)**	**A3 (30 mg)**	**B1 (20 mg)**	**Total**
Age at Screening, y					
n	5	4	7	6	22
Mean (SD)	11.2 (5.89)	10.8 (5.19)	9.1 (5.90)	13.7 (5.13)	11.1 (5.46)
Median (min, max)	13.0 (2, 18)	10.0 (6, 17)	10.0 (2, 16)	16.0 (4, 17)	13.0 (2, 18)
Age Group, n (%)					
2- to 12-year-old	2 (40)	2 (50)	4 (57.1)	2 (33.3)	10 (45.5)
13-18y	3 (60)	2 (50)	3 (42.9)	4 (66.7)	12 (54.5)
# patients (all ages) with TEAEs (treatment-emergent adverse effects)					
TEAEs, n (%)	4 (80.0)	4 (100.0)	7 (100.0)	6 (100.0)	21 (95.5)
TEAEs, related to study drug, n (%)	2 (40.0)	1 (25.0)	0	1 (16.7)	4 (18.2)
>=Grade 3 TEAEs, n (%)	0	1 (25.0)	1 (14.3)	1 (16.7)	3 (13.6)

	SAD			MAD	
	A1 (10 mg)	**A2 (20 mg)**	**A3 (30 mg)**	**B1 (20 mg)**	**Total**
>=Grade 3 TEAEs, related to study drug, n (%)	0	0	0	0	0
Serious TEAEs, n (%)	1 (20.0)	1 (25.0)	1 (14.3)	2 (33.3)	5 (22.7)
Serious TEAEs, related to study drug, n (%)	0	0	0	0	0
TEAEs leading to study withdrawal or death, n (%)	0	0	0	0	0

[1052] **Table 12** below summarizes the pharmacokinetic results in each cohort, and **FIG. 30** shows two plots summarizing CSF exposure of Compound-A in SAD cohorts and MAD cohorts, respectively. Dose-dependent increases in plasma exposure and CSF concentration were observed. Plasma AUC_{last} was similar for the 20 mg SAD cohort and 1st dose in the 20 mg MAD cohort. Last collection until which Compound-A CSF levels were detected was on day 169 for 10 and 20 mg, and day 85 for 30 mg. Overall, mean CSF concentration at day 85 increased from 10 to 30 mg. Mean CSF levels post 2nd dose were higher compared to levels post 1st dose indicating accumulation of Compound-A in CNS tissues with repeated monthly dosing.

Table 12. Plasma PK parameters of Compound-A.

Dose (mg)	**Plasma PK parameters**	
	N	AUC_{last} (h*ng/mL) (mean ± SD)
SAD 10	4	2450 ± 1690
SAD 20	4	6460 ± 2820
SAD 30	7	15300 ± 12100
MAD 20 (dose 1)	6	4450 ± 3110

[1053] Observed baseline convulsive seizure frequency over a period of 28 days in the tested subjects was calculated, with a Mean (SD) of 51.41 (131.4), and Median (min, max) of 16 (1.0, 630.0). 90.9% patients used at least three concomitant anti-seizure medications as maintenance therapy, and 72.7% used at least four concomitant anti-seizure medications as maintenance therapy. Most common medications were clobazam (68.2%) and fenfluramine (54.5%).

[1054] **FIGS. 31A and 31B** show two plots summarizing median percent change in seizure frequency from baseline level to the period between Day 29 and 84 post administration of Compound-A (in reference to 1st dose, Day 29-84) in 2- to 12-year-old subjects (**FIG. 31A**) and 13- to 18-year-old subjects (**FIG. 31B**), each combined by cohort. In 2- to 12-year-old subjects in all cohorts, there was a reduction in seizure frequency as measured: about 20% in Cohort A2 (20 mg, N=2), about 35% in both Cohort A3 (30 mg; N=2) and Cohort B1 (20 mg MAD, N=2), and about 70% in Cohort A1 (10 mg; N=1). In 13-18

y subjects, there was about 25% reduction in seizure frequency in Cohort B1 (20 mg MAD, N=2), and about 35% in Cohort A3 (30 mg; N=3). Note that when analyzing the seizure frequency data, Cohort A1 excludes patient with incorrect dosing, Cohort A3 excludes patients meeting minimum seizure count during observation but not during defined baseline; and Cohort B1 excludes patients who received only 2 doses prior to D84. Overall, seizures were reduced in 12 of 17 (70.6%), including all 2- to 12-year-old patients, at days 29-84 vs baseline period.

[1055] **FIGS. 32A and 32B** show two plots summarizing median percent change in seizure frequency from baseline in patients of all ages as combined by cohort in the period between Day 1 and Day 84 (**FIG. 32A**, Day 1-84) post administration, and in the period between Day 29-84 (**FIG. 32B**, Day 29-84), respectively.

Example 25: Interim Safety, PK, CSF Exposure, and seizure frequency data from a Phase 1/2a study of Compound-A in children and adolescents with Dravet Syndrome (DS).

[1056] **FIGS. 33A-33C** provide the study design for the Phase 1/2a clinical trials for ASO-1. **FIG. 34** shows a plot summarizing median percent change in seizure frequency from baseline in patients of all ages receiving 30 mg, 45 mg of ASO-1, and combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study (and in the period between Day 1 and Day 252 post administration in the ADMIRAL study). Overall, there was an observable beneficial effect of ASO-1 on convulsive Seizure Frequency in the 30 mg, 45 mg, and 70 mg Multiple Dose Cohorts (**FIG. 34**), with an average reduction of about 50%-60% (at the Day 225 period) in patients receiving the 45 mg dose, an average reduction of about 30% in patients receiving the 30 mg dose (at the Day 169 mark), and an average reduction of about 90% in patients receiving the 70 mg dose (at the end of the Day 252 mark). When measured through the period of Day 29 to 3-months post last dose administration, there was an average reduction of about 42% in patients receiving the 70 mg dose, an average reduction of about 30% in patients receiving the 45 mg dose, and an average reduction of about 18% in patients receiving the 30 mg dose (**FIG. 35**).

[1057] **FIGS. 36A-36B** show plots summarizing the percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg or 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study. **FIG. 36A** shows a plot summarizing the reduction in the percent in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study. **FIG. 36B** shows a plot summarizing the reduction in the percent in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 225 post administration in the MONARCH study.

[1058] **FIGS. 37A-37C** show plots summarizing percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg, 45 mg, or 70 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL

study. **FIG. 37A** shows a plot summarizing the reduction in the percent in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 30 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. When measured at the end of 3 months post administration of last dose, patients receiving 30 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 27% (**FIG. 39A**). When measured at the end of 6 months post administration of last dose, patients receiving 30 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 5% (**FIG. 39B**).

[1059] **FIG. 37B** shows a plot summarizing the reduction in the percent in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 45 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. When measured at the end of 3 months post administration of last dose, patients receiving 45 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 20% (**FIG. 39A**). When measured at the end of 6 months post administration of last dose, patients receiving 45 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 45% (**FIG. 39B**).

[1060] **FIG. 37C** shows a plot summarizing the reduction in the percent in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 70 mg of ASO-1 as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. When measured at the end of 3 months post administration of last dose, patients receiving 70 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 80% (**FIG. 39A**). When measured at the end of 6 months post administration of last dose, patients receiving 70 mg of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 90% (**FIG. 39B**).

[1061] Patients between about 2 and 18 years old who were treated with three doses of 70 mg showed a differentiated response compared with patients who were treated with two doses of 70 mg of ASO-1 (**FIG. 40A**). The one patient treated with two doses in these analyses did not show the same magnitude of response as patients treated with three doses. **FIG. 38** shows a plot summarizing percent change in seizure frequency from baseline in patients between ages 2-12 and between ages 13-18 years receiving 2 or 3 doses of 70 mg of ASO-1, as combined by cohort in the period between Day 1 and Day 252 post administration in the ADMIRAL study. Patients treated with 3 doses of 70 mg ASO-1 showed about 70% reduction in seizure frequency in patients between the age of 13-18 when measured at the end of the 3-month period following the administration of the last dose (**FIG. 40A**). In the case of patients between the age of 2-12 years treated with 3 doses of 70 mg ASO-1, a reduction in seizure frequency of greater than 85% was observed (**FIG. 40A**) when measured at the end of the 3-month period following the administration of the last dose.

[1062] Patients treated with 3 doses of 70 mg showed an average reduction in convulsive seizure frequency by about 80% by the D225-or D252 mark (**FIG. 39**). When measured at the end of 6 months post administration of the last dose, patients between the ages of 13-18 receiving two or three 70 mg

doses (n=3) of ASO-1 showed an average reduction in Convulsive Seizure Frequency (CSF) of about 75% (**FIG. 40B**). When measured at the end of 6 months post administration of last dose, patients receiving 70 mg of ASO-1 showed a reduction in Convulsive Seizure Frequency (CSF) of about 98% (**FIG. 40B**) in the patient between the ages of 2-12 (**FIG. 40B**).

[1063] In the Open-label Extension study, data indicated that there were sustained reductions in CSF with ASO-1 doses of 30 mg or 45 mg every four months (**FIG. 41**). Patients receiving ASO-1 for over one year of dosing showed an improvement in receptive communication as compared to observed natural history of the disease measured on the Vineland (VABS-III) scale (**FIG. 42A**). Data indicated that patients receiving ASO-1 for over one year of dosing showed an improvement in expressive communication as compared to natural history results of the disease measured on the Vineland (VABS-III) scale (**FIG. 42B**). Patients receiving ASO-1 for over one year of dosing showed an improvement in gross motor skills as compared to observed natural history of the disease measured on the Vineland (VABS-III) scale (**FIG. 43**). Patients receiving ASO-1 for over one year of dosing showed an improvement in executive function as compared to observed natural history of the disease measured on the Vineland (VABS-III) scale (**FIG. 44**). Patients receiving ASO-1 for over one year of dosing showed a substantial improvement in overall condition. For example, patients receiving ASO-1 for over one year of dosing showed a substantial improvement in overall condition when measured under the Clinician Global Impression of change (**FIG. 45A**). Further, patients receiving ASO-1 for over one year of dosing showed a substantial improvement in overall condition when measured under the Caregiver Global Impression of change (**FIG. 45B**).

[1064] For the behavioral measurements in **FIGS 42A-45B**, mixed model repeated measures were performed with AR(1) covariance structure. Baseline covariates in BUTTERFLY were matched to SWALLOWTAIL. Analysis included all patients who received 30 mg or 45 mg for all doses in SWALLOWTAIL. For CGI-C, BUTTERFLY sample size: n=32 at month 3, n=29 at month 12; and for CaGI-C, BUTTERFLY sample size: n=27 at month 3, n=24 at month 12. For both CGI-C and CaGI-C, SWALLOWTAIL sample size: n=25 at week 16, n=9 at week 48 and n=5 at week 64. CGI and CaGI in BUTTERFLY were adapted for cognition. CGI-C=Clinical Global Impression of Change and CaGI-C=Caregiver Global Impression of Change.

Example 26. Substantial and sustained reductions in seizure frequency were observed with 70-mg loading dosages in Phase 1/2.

[1065] ***Highly Refractory Patient Population***

[1066] The patient population participating in the clinical studies described herein is a highly refractory patient population. The Phase 1/2 studies comprised a cohort of 81 patients (62 patients from MONARCH and 19 patients from ADMIRAL) who were already taking the best available anti-seizure medications prior to participating in the study. **Table 13A** is a summary of participant statistics. About 85% of the patients were taking more than three concomitant anti-seizure medications (ASMs), and about 50% of the patients were taking fenfluramine. The median baseline convulsive seizure frequency in this patient cohort was about 17 convulsive seizures every 28 days. The open-label extension (OLE) studies

had more than 90% of the 81 patients enrolled, and more than 80% of the 81 patients remain in the OLE studies (n=68). **Table 13B** is a summary of baseline participant characteristics.

Table 13A. Participant statistics for patients in MONARCH and ADMIRAL studies.

	Phase 1/2*
N	81
***SCN1A* Variant Type**	
Missense, n (%)	37 (45.7)
Nonsense, n (%)	44 (54.3)
Age at screening, years	
Mean (SD)	9.9 (5.05)
Concomitant Anti-seizure Medications (ASM)	
≥3, n (%)	69 (85.2)
≥4, n (%)	44 (54.3)
Concomitant Fenfluramine	
Yes, n (%)	40 (49.4)
Baseline Convulsive Seizure Frequency per 28 Days	
n	77
Mean (SD)	70.63 (275.552)
Median (min, max)	17 (4.0, 2335.4)

Table 13B. Demographics for patients in MONARCH and ADMIRAL studies.

Parameter	**MONARCH (n=62)**	**ADMIRAL (n=19)**	**ALL ENROLLED (N=81)**
Age at screening, years			
Median (min, max)	10.0 (2, 18)	7.0 (3, 17)	10.0 (2,18)
Age group, n (%)			
2–12 years	35 (56.5)	11 (57.9)	46 (56.8)
≥13 years	27 (43.5)	8 (42.1)	35 (43.2)
Gender, n (%)			
Female	30 (48.4)	10 (52.6)	40 (49.4)
Male	32 (51.6)	9 (47.4)	41 (50.6)
Race*, n (%)			
Asian	5 (8.1)	0 (0)	5 (6.2)
Black or African American	5 (8.1)	0 (0)	5 (6.2)
White	52 (83.9)	19 (100.0)	71 (87.7)
Prefer not to answer	4 (6.5)	0 (0)	4 (4.9)
Baseline convulsive seizure frequency per 28 days†			
Median (range)	16 (4, 630.0)	21.3 (4, 2335.4)	17 (4, 2335.4)

*Multiple selections for race could be entered. †Includes n=58, n=19, and N=77 for MONARCH, ADMIRAL, and ALL ENROLLED, respectively. One patient who received an incorrect dose in Phase 1/2a and 3 patients who had <4 seizures in Phase 1/2a baseline were excluded.

[1067] *Clinically Evaluable Sets*

[1068] Certain criteria were considered when determining whether data should be excluded from the clinically evaluable data sets (**Table 14**). Patients who did not have a minimum number of seizures in the baseline period were excluded from analysis. Seizure data was censored for specific intervals with <50% diary days completed. Seizure data were also censored following modification to a patient's anti-seizure medications that could affect interpretation of seizure data.

Table 14. Criteria for exclusion from clinically evaluable data sets.

	Number of patients excluded from Seizure Analysis	**Number of patients with data censored at the time of event that could affect interpretation of seizure data**	
Cohort	<4 seizures in 28 prior to dosing	ASM modification	Missing Diary Days
70 mg SAD	1	0	1 patient in (1) 28-day interval (5-6 months after last dose)
30 mg MAD	0	4	0
45 mg MAD	0	4	0
70 mg MAD	0	2	0

[1069] Safety and tolerability

[1070] Overall, 59/62 patients (95.2%) in MONARCH and 19/19 patients (100%) in ADMIRAL experienced at least one treatment-emergent adverse event (TEAE) (**Table 15**).

[1071] Most TEAEs were mild or moderate, and no patients withdrew from either study due to TEAEs. TEAEs were deemed drug-related in 16 patients (25.8%) in MONARCH and in 8 patients (42.1%) in ADMIRAL, with cerebrospinal fluid protein increase and procedural vomiting being most common across both studies. One patient from ADMIRAL who received three 70 mg doses experienced suspected unexpected serious adverse reactions but completed the study.

Table 15. Summary of MONARCH and ADMIRAL TEAEs.

TEAE Category Number of patients (%)	**MONARCH (n=62)**	**ADMIRAL (n=19)**	**All enrolled (N=81)**
Any TEAE	**59 (95.2)**	**19 (100.0)**	**78 (96.3)**
Drug-related TEAEs	16 (25.8)	8 (42.1)	24 (29.6)
Procedure-related TEAEs	35 (56.5)	8 (42.1)	43 (53.1)
≥Grade 3 TEAE	**10 (16.1)**	**3 (15.8)**	**13 (16.0)**
TESAE	**12 (19.4)**	**6 (31.6)**	**18 (22.2)**
Drug-related TESAE	0	1 (5.3)	1 (1.2)
Potential DLT	**0**	**1 (5.3)**	**1 (1.2)**
TEAE leading to study withdrawal	**0**	**0 (0)**	**0**
TEAE leading to death†	**1 (1.6)**	**0 (0)**	**1 (1.2)**

*TEAE is defined in this study as an adverse event first identified, or identified to worsen in intensity, at a time occurring after first dose of study drug. †One patient in MONARCH died due to sudden

unexpected death in epilepsy (SUDEP) that was assessed as unrelated to ASO 1. DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

[1072] About 30% of patients experienced a study drug-related TEAE. The most common TEAEs comprised CSF protein elevations (13.6%) and procedural vomiting (4.9%). About 22% of patients experienced a TESAE. All TEAEs were unrelated to the ASO-1 study drug except for 1 patient with Suspected Unexpected Serious Adverse Reactions (SUSARs).

[1073] ***Two or three loading doses of 70 mg of ASO outperformed all other tested dose groups in reducing the frequency of convulsive seizures.***

[1074] Various loading doses were evaluated for effect on convulsive seizure frequency over time (**FIG. 46**). Patients were administered with either two or three of the same ASO loading dose (30 mg, 45 mg, or 70 mg). Patient cohorts that were administered either two or three loading doses of 70 mg of ASO were observed to have sustained reductions in the frequency of convulsive seizures over the course of 252 days from the first day of administration. Patients receiving two or three loading doses of either 30 mg, 45 mg, or 70 mg each were observed to have close to 50% reduction in convulsive seizure frequency by days 57-84. Patients in the 70-mg ASO loading dose cohort were observed to continue to have a reduction in convulsive seizure frequency to about a 60% reduction from baseline by days 85-112, and about a 75% reduction by days 113-140. The approximately 75% reduction in convulsive seizure frequency in the 70-mg loading dose cohort was maintained between days 113 and 224. By days 225-252, the 70-mg loading dose cohort still had about a 60% reduction in convulsive seizure frequency from baseline. Patients receiving two or three loading doses of either 30 mg or 45 mg were observed to experience higher frequencies of convulsive seizures after day 84. Those receiving the 30-mg dose returned to their baseline level of convulsive seizures by days 225-252, and those receiving the 45-mg dose experienced about a 35% reduction in convulsive seizure frequency relative to their baseline by days 225-252.

[1075] ***Two or three 70-mg loading doses provide similar levels of seizure reduction at three, four, and six months after the last loading dose administration.***

[1076] Single and multiple 70-mg loading doses were evaluated three, four, and six months after the last loading dose. Patients who were administered with one (Single Ascending Dose, or SAD), two (Multiple Ascending Doses, or MAD – 2 doses), or three (Multiple Ascending Doses, or MAD – 3 doses) 70-mg ASO loading doses were evaluated three, four, and six months after the last loading dose **(FIG. 47A-47C)**. Data for patients with changes in their anti-seizure medications were excluded from this study. 70 mg were administered in each dose of the one-loading-dose, two-loading-dose, and three-loading-dose cohorts (*e.g.,* the two-loading-dose cohort received one dose of 70 mg, followed by a later second dose of 70 mg). For those who were administered a single dose, "three months after the last dose" corresponds to days 57-84 (D57-D84), "four months after the last dose" corresponds to days 85-112 (D85-D112), and "six months after the last dose" corresponds to days 141-168 (D141-D168). For those who received two administered doses, "three months after the last dose" corresponds to days 113-140 (D113-D140), "four months after the last dose" corresponds to days 141-168 (D141-D168), and "six months after the last dose" corresponds to days 197-224 (D197-D224). For those who received three administered doses,

"three months after the last dose" corresponds to days 141-168 (D141-D168), "four months after the last dose" corresponds to days 169-196 (D169-D196), and "six months after the last dose" corresponds to days 225-252 (D225-D252).

[1077] Patients treated with initial doses of 70 mg ASO-1 experienced substantial reductions in convulsive seizure frequency in as early as 3 months from baseline (**FIG. 47D**). ASO-1 was administered on Days 1, 29 and 57 in MONARCH, and on Days 1, 57 and 85 in ADMIRAL. MONARCH ended at Day 225 and ADMIRAL ended at Day 253. Phase 1/2a data-cut was December 12, 2023 (after End of Study). One 70 mg 1-dose patient who experienced <4 seizures during the Phase 1/2a baseline period was excluded. Patients were followed for 6 months after last dose of study drug. Data were censored if <50% diary data were available for a 28-day interval (D141 to D168 for 1 patient in 70 mg, 1 dose) and at time of ASM modification (1 patient in 70 mg, 2-dose; and 1 patient in 70 mg, 3-dose).

[1078] Two or three 70-mg loading doses were observed to provide similar levels of seizure reduction at three and four months after the last loading dose administration (**FIG. 47A-47B**, middle and right columns). Participants who were given a single ascending dose (SAD) of 70 mg of ASO experienced a reduction of about 43% in convulsive seizure frequency at three months (SAD, n=8) after the last loading dose (**FIG. 47A**, left column), a reduction of about 59% at four months (SAD, n=8) after the last loading dose (**FIG. 47B**, left column), and a reduction of about 57% at six months (SAD, n=7) after the last loading dose (**FIG. 47C**, left column). Participants who were given two doses of 70-mg of ASO experienced a reduction of about 82% in convulsive seizure frequency at three months (MAD, 2 doses, n=5) after the last loading dose (**FIG. 47A**, center column), a reduction of about 69% at four months (MAD, 2 doses, n=5) after the last loading dose (**FIG. 47B**, center column), and a reduction of about 68% at six months (MAD, 2 doses, n=5) after the last loading dose **FIG. 47C**, center column). Participants who were given three doses of 70-mg of ASO (MAD, 3 doses, n=5) experienced a reduction of about 89% in convulsive seizure frequency at three months after the last loading dose (**FIG. 47A**, right column), a reduction of about 75% at four months (MAD, 3 doses, n=4) after the last loading dose (**FIG. 47B**, right column), and a reduction of about 81% at six months (MAD, 3 doses, n=4) after the last loading dose (**FIG. 47C**, right column). In sum, generally, 2-dose administration induced about -69% to about 82% reduction by 3-4 months after the last loading dose, and 3-dose administration induced about 75% to about 89% reduction by 3-4 months after the last loading dose. The observed reduction in convulsive seizure frequency at four months in both MAD cohorts supports a maintenance dose administration interval of once every four months, which will be evaluated in Phase 3 trials.

[1079] ***Single 70-mg loading dose administration (MONARCH) induced meaningful reduction of convulsive seizures, while 2 or 3 doses of 70-mg loading doses (ADMIRAL) outperformed single 70-mg dose.***

[1080] Single (MONARCH) and multiple (ADMIRAL) 70-mg loading doses were evaluated three, four, and six months after the last loading dose **(FIG. 48A-48B)**. Data for patients with changes in their anti-seizure medications were excluded from this study. 70 mg were administered in each dose of the one-loading-dose, two-loading-dose, and three-loading-dose cohorts (*e.g.*, the two-loading-dose cohort

received one dose of 70 mg, followed by a later second dose of 70 mg). For those who were administered a single dose, "three months after the last dose" corresponds to days 57-84 (D57-D84), "four months after the last dose" corresponds to days 85-112 (D85-D112), and "six months after the last dose" corresponds to days 141-168 (D141-168). For those who received two administered doses, "three months after the last dose" corresponds to days 113-140 (D113-D140), "four months after the last dose" corresponds to days 141-168 (D141-D168), and "six months after the last dose" corresponds to days 197-224 (D197-D224). For those who received three administered doses, "three months after the last dose" corresponds to days 141-168 (D141-D168), "four months after the last dose" corresponds to days 169-196 (D169-D196), and "six months after the last dose" correspond to days 225-252 (D225-D252).

[1081] Study participants who were given a single ascending dose of 70 mg of ASO experienced a reduction of about 43% in convulsive seizure frequency at three months after the last loading dose (**FIG. 48A**, left column, n=8), a reduction of about 59% at four months after the last loading dose (**FIG. 48A**, center column, n=8), and a reduction of about 57% at six months after the last loading dose (**FIG. 48A**, right column, n=7). Study participants who were given multiple ascending doses comprising either two or three doses of 70-mg of ASO experienced a reduction of about 85% in convulsive seizure frequency at three months after the last loading dose (**FIG. 48B**, left column, n=10), a reduction of about 74% at four months after the last loading dose (**FIG. 48B**, center column, n=9), and maintained about a 74% reduction at six months after the last loading dose (**FIG. 48B**, right column, n=9). Single 70-mg loading dose administration resulted in meaningful convulsive seizure reduction; however, multiple 70-mg loading doses (2 or 3 doses) outperformed single 70-mg loading dose administration in reducing convulsive seizures.

[1082] ***Approximately 80% of patients experienced ≥50% reduction in seizures at 3 and 6 months after receiving the last loading dose.***

[1083] The majority of patients across varying ages who received multiple doses of 70 mg ASO-1 in the ADMIRAL Phase 1/2a study experienced ≥50% reduction in convulsive seizure frequency at 3 and 6 months after their final dose, respectively. The 50% responder rate (*i.e.*, those patients with ≥50% reduction in convulsive seizure frequency, CSF, from baseline) was evaluated at 3 months (**FIG. 49A**) and 6 months (**FIG. 49B**) after the last 70-mg dose when multiple 70-mg ASO-1 doses or a single 70-mg dose of ASO-1 were administered. Eight patients between the ages of 3 and 16 had more than a 50% reduction in seizures three months after the last of either two or three 70-mg doses. Two 4-year-old patients had more than a 50% reduction in seizures three months after a single 70-mg dose. Seven patients between the ages of 4 and 16 had more than a 50% reduction in seizures six months after the last of either two or three 70-mg doses. Four patients between the ages of 4 and 9 had more than a 50% reduction in seizures six months after a single 70-mg dose. Three months after last dose refers to D57 to D84 (1 dose SAD), D113 to D140 (2 dose MAD) and D141 to D168 (3 dose MAD); 6 months after last dose refers to D141 to D168 (1 dose SAD), D197 to D224 (2 dose MAD) and D225 to D252 (3 dose MAD). Phase 1/2a data-cut was December 12, 2023 (after End of Study).

[1084] ***Improvement in overall clinical status and quality of life 6 months after last dose***

[1085] Clinical Global Impression of Change (CGI-C) (**FIG. 49C**) and Caregiver Global Impression of Change (CaGI-C) (**FIG. 49D**) scales indicate improvements in the overall clinical status of patients who received single (MONARCH) or multiple (ADMIRAL) doses of 70 mg ASO-1 6 months after their last dose. *CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), or 7 (Very much worse). Sample size, N=63 for both assessments. Phase 1/2a data-cut was December 12, 2023 (after End of Study). †Mixed-effects model for repeated measures constructed with data from Phase 1/2a studies. One patient who received incorrect dose and 3 patients with <4 seizures during baseline were excluded. Patients' quality of life (QoL) was improved as demonstrated by model outcomes for the EQ-VAS component of the EQ-5D-Y assessment.

Example 27. Substantial improvements in cognition and behavior were observed within first 9 months of treatment for all doses in the UK Phase 1/2 ADMIRAL study.

[1086] Non-seizure comorbidities that are important in assessing improvement in Dravet Syndrome patients include communication skills, intellectual ability, motor balance, and sleep. As such, improvements in these arenas were assessed in multiple domains of cognition and behavior by Vineland Adaptive Behavior Scales, Third Edition (Vineland-3 or VABS-III) (*see*, Sparrow, S. *et al.*, Vineland Adaptive Behavior Scales, third edition (Vineland-3), Pearson, Bloomington, MN, 2016), which is a standardized assessment tool for measuring personal and social skills, or how a person performs in daily situations (**FIG. 51**). Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV.

[1087] Cognitive and behavioral domains such as receptive communication, expressive communication, personal skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills were evaluated at week 36 of the ADMIRAL study (**FIG. 52**). Nearly all cognitive and behavioral domains improved at week 36. A change of 2–3 points in GSV scores was considered meaningful by at least 50% of caregivers. Receptive communication showed the greatest positive change in GSV with a value of 5.778. Expressive communication had a change in GSV of 3.272. Personal skills had a change in GSV of 2.030. Interpersonal relationships had a change in GSV of 3.096. Play and leisure was the only instance of a negative change in GSV with a value of -1.644. Coping skills had a change in GSV of 0.700. Gross motor skills had a change in GSV of 3.517. Fine motor skills had a change in GSV of 1.993. Repeated and longitudinal assessments on patients from the ADMIRAL Phase 1/2 study (all dose cohorts) through Visit 2 (week 16) in the LONGWING OLE study were used to establish a pre-treatment/naïve baseline, and these data were further compared and analyzed with week 36 assessments via Machine Learning algorithms. The ADMIRAL study included 18 patients at screening (sample size: n=18) and 17 patients at week 36 (n=17).

Example 28. Data indicated substantial improvements in the overall condition of patients within the first 9 months of treatment in Phase 1/2 (MONARCH and ADMIRAL studies) compared to patient condition assessed during the BUTTERFLY natural history study.

[1088] ***Clinical Global Impression of Change (CGI-C) and Caregiver Global Impression of Change (CaGI-C) indicate overall improvement in patient condition.***

[1089] Patient condition was assessed in the natural history study ("BUTTERFLY" as described in Example 22) and used as the baseline for comparison to patient condition in the "MONARCH" and "ADMIRAL" Phase 1/2a studies in which at least 30-mg doses of ASO were administered to the patients. Clinical Global Impression of Change (CGI-C) (**FIG. 53A**) and Caregiver Global Impression of Change (CaGI-C) (**FIG. 53B**) were evaluated for all studies. CGI is scored on a 7-point scale and lower values (*e.g.,* a score of "1") correspond to improved conditions, while higher values (*e.g.,* a score of "7") correspond to worsened conditions. The baseline established during the natural history study was a score of 3.914 in the Clinical Global Impression of Change (**FIG. 53A**, left column) and a score of 4.133 in the Caregiver Global Impression of Change (**FIG. 53B**, left column); Least-Squares (LS) means are shown with a 95% confidence interval (CI). The Clinical Global Impression of Change for the MONARCH/ADMIRAL studies scored 2.911 (**FIG. 53A**, right column) by week 36, indicating improved patient condition, and a score of 2.866 in the Caregiver Global Impression of Change (**FIG. 53B**, right column) by week 36, also indicating improved patient condition; Least-Squares (LS) means are shown with a 95% confidence interval (CI).

[1090] A mixed-effects model (Mixed Model for Repeated Measures (MMRM), *see,* Bell, M. et al., "The mixed model for repeated measures for cluster randomized trials: a simulation study investigating bias and type I error with missing continuous data," BMC Methodology, February 2020) was used for repeated measures with a first-order autoregressive covariance structure. Baseline covariates in BUTTERFLY, including baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency, were matched to MONARCH/ADMIRAL patient population means. For CGI-C, the BUTTERFLY sample size was n=31 at month 3 and n=27 at month 12. For CaGI-C, the BUTTERFLY sample size was n=34 at month 3 and n=29 at month 12. The MONARCH/ADMIRAL sample size was n=59 at week 20/week 24, and n=40 at week 32/week 36 for both CGI-C and CaGI-C. Clinicians and caregivers rated overall aspects of Dravet Syndrome (DS) in both the MONARCH and ADMIRAL studies, and cognition-specific domains of DS in the BUTTERFLY study.

[1091] Data indicated substantial improvements in communication in ADMIRAL study participants for all dose cohorts within the first 9 months of the Phase 1/2 study compared to participants in the BUTTERFLY natural history study.

[1092] Expressive (**FIG. 54A**) and receptive (**FIG. 54B**) communication were evaluated by Vineland-3 in ADMIRAL study participants at week 36, or at the end of 9 months from the start of the study. Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV. Participants in the no-treatment BUTTERFLY natural history study were observed to experience no change in expressive communication and worsening in receptive

communication as indicated by a change in GSV of -3.148 by the end of the study at week 36. Participants in the ADMIRAL Phase 1/2 study were observed to demonstrate improvement in both expressive and receptive communication as indicated by the positive changes in GSV (3.222 for expressive communication and 6.250 for receptive communication). A mixed-effects model for repeated measures was used with a first-order autoregressive covariance structure constructed with data from the ADMIRAL study from the pre-treatment/naïve baseline to Visit 2 (week 16) in the LONGWING OLE study. Data from the BUTTERFLY study from the start of the study baseline to month 24 were analyzed with machine learning. Baseline covariates in BUTTERFLY (*e.g.,* baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency) were matched to ADMIRAL patient population means. For expressive and receptive communication, the ADMIRAL sample size was n=18 at screening and n=17 at week 36; the BUTTERFLY sample size was n=36 at screen and n=25 at month 12.

[1093] ***Data indicated substantial improvements in personal and interpersonal skills in ADMIRAL study participants for all dose cohorts within the first 9 months of Phase 1/2 compared to participants in the BUTTERFLY natural history study.***

[1094] Personal (**FIG. 55A**) and interpersonal relationships (**FIG. 55B**) skills were evaluated by Vineland-3 in ADMIRAL study participants at week 36, or at the end of 9 months from the start of the study. Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV. Participants in the no-treatment BUTTERFLY natural history study were observed to experience little change in personal skills, as indicated by a change in GSV of 0.484, and worsening in interpersonal relationships skills as indicated by a change in GSV of -1.434 by the end of the study at week 36. Participants in the ADMIRAL Phase 1/2 study were observed to demonstrate improvement in both personal skills and interpersonal skills as indicated by the positive changes in GSV (1.855 in personal skills and 4.407 in interpersonal skills). A mixed-effects model for repeated measures was used with a first-order autoregressive covariance structure constructed with data from ADMIRAL from pre-treatment/naïve baseline to Visit 2 (week 16) in the LONGWING OLE study. Data from the BUTTERFLY natural history study from the start-of-study baseline to month 24 were analyzed with machine learning. Baseline covariates in the BUTTERFLY study (*e.g.,* baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency) were matched to ADMIRAL patient population means. For personal skills and interpersonal relationships, the ADMIRAL sample size was n=18 at screening and n=17 at week 36; the BUTTERFLY study sample size was n=36 at screening, n=25 for personal skills, and n=24 for interpersonal relationships at month 12.

[1095] Results from these MONARCH/ADMIRAL Phase 1/2a studies support the potential of ASO-1 to be the first disease-modifying medicine for Dravet Syndrome. Treatment with ASO-1 resulted in seizure reduction, in addition to improvements in cognition and behavior, overall clinical status, and quality of life within the first 9 months of ASO-1 administration. The most substantial improvements were observed in study participants treated with 70 mg of ASO-1. Treatment with ASO-1 was generally well-tolerated.

Example 29. SWALLOWTAIL/LONGWING Open-Label Extension (OLE) studies for children and adolescents with Dravet Syndrome who previously participated in a study of Antisense Oligonucleotide (ASO-1).

[1096] The SWALLOWTAIL/LONGWING open-label extensions (OLEs) expand upon the MONARCH/ADMIRAL Phase 1/2a data on the effects of ASO-1 on seizures and non-seizure comorbidities to provide further insights into its long-term effects.

[1097] SWALLOWTAIL and LONGWING are ongoing OLEs of the MONARCH and ADMIRAL studies conducted in the USA and UK, respectively (**FIG. 69**). Patients who received at least 30 mg ASO-1 in the Phase 1/2a studies continued treatment in the SWALLOWTAIL and LONGWING OLEs in which they were administered either 30 mg or 45 mg of ASO-1 per dose as an intrathecal, slow bolus injection every 16 weeks (every 4 months). Phase 1/2a participants treated with a single dose of 70-mg ASO-1 in the MONARCH study received 30-mg maintenance doses at the start of the SWALLOWTAIL OLE study and every four months thereafter. Phase 1/2a participants treated with two or three doses of 70-mg ASO-1 in the ADMIRAL study received 45-mg maintenance doses at the start of the LONGWING OLE study and every four months thereafter.

[1098] Study Design

[1099] Eligibility criteria - Participants of SWALLOWTAIL/LONGWING open-label extensions must have completed MONARCH or ADMIRAL with an acceptable safety profile and were not treated with maintenance ASMs that primarily act as sodium channel blockers.

[1100] The study's primary objective was to determine long-term safety and tolerability of repeated doses of ASO-1 administered every 16 weeks (every four months). The study's secondary objectives were to measure the effects of ASO-1 as a percentage of change from baseline in convulsive seizure frequency, cognition, and behavior (Vineland-3), overall clinical status (CGI-C/CaGI-C, with a focus on symptoms of DS), and QoL (EQ-VAS component of EuroQol-5D Youth).

[1101] Baseline characteristics

[1102] Study statistics at the initial phase (as of 24 weeks after last dose in Phase ½ study) were as follows: 54 of 57 (94.7%) participants who completed the MONARCH study and 14 of 17 (84.2%) participants who completed the ADMIRAL study were enrolled in SWALLOWTAIL and LONGWING, respectively (**Table 16A**).

Table 16A. Summary of baseline characteristics and patient demographics in the SWALLOWTAIL and LONGWING studies at the initial phase.

Parameter	SWALLOWTAIL (n=54)	LONGWING (n=14)	All enrolled (N=68)
Age at screening, years			
Median (min, max)	12 (2, 19)	7.5 (4, 17)	10 (2, 18)
Age group, n (%)			
2–12 years	27 (50.0)	9 (64.3)	38 (55.9)
≥13 years	27 (50.0)	5 (35.7)	30 (44.1)
Gender, n (%)			
Female	29 (53.7)	7 (50.0)	36 (52.9)

Parameter	SWALLOWTAIL (n=54)	LONGWING (n=14)	All enrolled (N=68)
Race*, n (%)			
Asian	4 (7.4)	0 (0.0)	4 (5.9)
Black or African American	5 (9.3)	0 (0.0)	5 (7.4)
White	45 (83.3)	14 (100.0)	60 (88.2)
Prefer not to answer	4 (7.4)	0 (0.0)	3 (4.4)

[1103] As of June 28, 2024, 58 of 61 (95.1%) MONARCH completers were enrolled in SWALLOWTAIL, with 47 of 58 (81.0%) remaining in study, and 16 of 19 (84.2%) ADMIRAL completers enrolled in LONGWING, with 14/16 (87.5%) remaining in study. Patient demographics were generally comparable across both SWALLOWTAIL and LONGWING OLE studies (**Table 16B**). Overall, about 52.7% (39/74) patients were concomitantly taking fenfluamine.

Table 16B. Summary of baseline characteristics and patient demographics in the SWALLOWTAIL and LONGWING studies at the initial phase.

Parameter	SWALLOWTAIL (n=58)	LONGWING (n=16)	All enrolled (N=74)
Age at screening, years			
Median (range)	11 (2, 19)	7 (4, 17)	11 (2, 19)
Age group, n (%)			
2–12 years	31 (53.4)	11 (68.8)	42 (56.8)
≥13 years	27 (46.6)	5 (31.3)	32 (43.2)
Gender, n (%)			
Female	29 (50.0)	8 (50.0)	37 (50.0)
Male	29 (50.0)	8 (50.0)	37 (50.0)
Race*, n (%)			
Asian	5 (8.6)	0	5 (6.8)
Black or African American	5 (8.6)	0	5 (6.8)
White	48 (82.8)	16 (100.0)	65 (87.8)
Prefer not to answer	4 (6.9)	0	3 (4.1)

*Multiple selections for race could be entered.

[1104] Safety and tolerability

[1105] ASO-1 was generally well-tolerated across patients in both SWALLOWTAIL and LONGWING OLEs at the initial phase (**Table 17A**), with the top 3 treatment-emergent adverse events (TEAEs) reported by >10% of patients being cerebrospinal fluid (CSF) protein increased, pyrexia, and COVID-19. All drug-related TEAEs were non-serious and mild or moderate. CSF protein elevation was observed in 74% (n/n) of patients, was the only drug-related TEAE reported in >1 patient and resulted in one study withdrawal; no patients experienced any associated clinical manifestations.

Table 17A. Summary of TEAEs in OLE studies at the initial phase.

TEAE* Category Number of patients (%)	SWALLOWTAIL (n=54)	LONGWING (n=14)	All enrolled (N=68)
Any TEAE	47 (87.0)	10 (71.4)	57 (83.8)
Drug-related TEAEs	21 (38.9)	2 (14.3)	23 (33.8)
Study procedure-related TEAEs	23 (42.6)	4 (28.6)	27 (39.7)
≥Grade 3 TEAE	3 (5.6)	1 (7.1)	4 (5.9)
Serious TEAE	8 (14.8)	2 (14.3)	10 (14.7)
Drug-related serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Potential dose limiting toxicity	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to study withdrawal	1 (1.9)	0 (0.0)	1 (1.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)

*TEAE is defined in this study as an adverse event first identified, or identified to worsen in intensity, at a time occurring after first dose of study drug.

[1106] As of June 28, 2024, ASO-1 was generally well-tolerated across patients in both SWALLOWTAIL and LONGWING OLEs (**Table 17B**), with the most commonly reported treatment-emergent adverse events (TEAEs) being cerebrospinal fluid (CSF) protein increased (n=23, 31.1%), pyrexia (n=22, 29.7%), and COVID-19 (n=19, 25.7%). All drug-related and procedure-related TEAEs were non-serious and mild or moderate in severity; drug-related TEAEs reported in >1 patient were CSF protein increase (n=20, 27.0%) and proteinuria (n=2, 2.7%). About 79% of patients had CSF protein elevations (*>1 CSF protein value >50 mg/dL. This percentage is based on 71/74 patients who had ≥1 post-baseline CSF protein value in SWALLOWTAIL or LONGWING). No patients experienced clinical manifestations associated with increased CSF protein; one patient withdrew due to laboratory findings of elevated CSF protein. Of the 71/74 patients with ≥1 post-baseline CSF value, about 78.9% patients had at least 1 value >50 mg/dL, and about 7.0% had a value >250 mg/dL.

Table 17B. Summary of TEAEs in OLE studies as of June 28, 2024.

TEAE Category Number of patients (%)	SWALLOWTAIL (n=58)	LONGWING (n=16)	All enrolled (N=74)
Any TEAE	58 (100)	15 (93.8)	73 (98.6)
Drug-related TEAEs	25 (43.1)	2 (12.5)	27 (36.5)
Procedure-related TEAEs	30 (51.7)	8 (50.0)	38 (51.4)
≥Grade 3 TEAE	5 (8.6)	1 (6.3)	6 (8.1)
TESAE	12 (20.7)	2 (12.5)	14 (18.9)
Drug-related TESAE	0	0	0
Potential DLT	0	0	0
TEAE leading to study withdrawal	1 (1.7)	0	1 (1.4)
TEAE leading to death	0	0	0†

*TEAE is defined as an adverse event first identified, or is identified to worsen in intensity, at a time occurring after the first dose of study drug. †Following the data cut, 1 patient in SWALLOWTAIL died

due to sudden unexpected death in epilepsy (SUDEP) that was assessed as unrelated to ASO-1. DLT, dose limiting toxicity; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

[1107] ***SWALLOWTAIL and LONGWING study participants experienced sustained reductions in convulsive seizure frequency when administered with 30- and 45-mg maintenance doses at regular time intervals.***

[1108] Reductions in convulsive seizure frequency were sustained throughout Month 12 (**FIG. 50A**). Participants who received either 30 or 45 mg ASO at regular intervals (about once every four months) maintained a reduction of convulsive seizure frequencies at about 26% to about 52% below baseline (**FIG. 50A**). These patients were administered with ASO three times over the course of the open-label extension study (at weeks 1-4, weeks 17-20, and weeks 33-36), corresponding to once every four months (**FIG. 50A**, square data points). Patients (n=3) who had received three 70-mg doses during the Phase 1/2 study were administered 45 mg of a maintenance dose approximately 24 weeks after the last dose in the Phase 1/2 study and were observed to have a median reduction between about 80% and 90% in convulsive seizure frequency over the course of 16 weeks (**FIG. 50A**, triangular data points). These seizure suppression effects observed with treatment with 30 and 45 mg ASO at regular intervals support the concept of a treatment schedule comprising the administration of a maintenance dose every four months. More substantial reductions were observed in the initial three patients who received multiple doses of 70 mg ASO-1 in the Phase 1/2a studies followed by a single dose of 45 mg in the OLE study.

[1109] SWALLOWTAIL and LONGWING participants experienced durable reductions in convulsive seizure frequency sustained through Month 24 of the OLEs relative to Phase 1/2a baseline values. Patients who received doses of 70 mg ASO-1 in the Phase 1/2a studies, followed by maintenance doses of ≥30 mg every four months in the OLEs experienced greater magnitudes of reduction (**FIG. 50B**, triangular data points) relative to participants who had received either 30- or 45-mg doses of ASO-1 in the Phase 1/2a studies followed by maintenance doses of ≥30 mg every four months in the OLEs (**FIG. 50B**, square points). Data in **FIG. 50B** have no exclusion for ASM modification. Phase 1/2a data exclude patients who did not enter the OLE studies. Of the patients enrolled in the OLEs, one patient was excluded due to receiving an incorrect dose during the Phase 1/2a study, and three patients were excluded for not meeting the minimum convulsive seizure frequency threshold at the Phase 1/2a baseline. Phase 1/2a data-cut: December 12, 2023 (after End of Study); OLE data-cut: June 28, 2024. ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open-label extension; "Ph1/2a" = Phase 1/2a.

[1110] Substantial and durable reductions in convulsive seizure frequency from Phase 1/2a baseline were observed in patients who received 70 mg ASO-1 in Phase 1/2a. In patients treated with 1, 2, or 3 doses of 70 mg ASO-1 in the Phase 1/2a studies, ≥50% reductions in median convulsive seizure frequency were observed in the OLEs through Month 8 (**FIG. 50C**). Phase 1/2a participants who received 70 mg ASO-1 included those who (1) were treated with a single dose of 70-mg ASO-1 in the MONARCH study and 30-mg maintenance doses at the start of the SWALLOWTAIL OLE study and every four months thereafter; (2) were treated with two doses of 70-mg ASO-1 in the ADMIRAL study

and received 45-mg maintenance doses at the start of the LONGWING OLE study and every four months thereafter; and (3) were treated with three doses of 70-mg ASO-1 in the ADMIRAL study and received 45-mg maintenance doses at the start of the LONGWING OLE study and every four months thereafter. The data in **FIG. 50C** had no exclusion for ASM modification. Phase 1/2a data exclude patients who did not enter the OLE studies. Phase 1/2a data-cut: December 12, 2023 (after End of Study); OLE data-cut: June 28, 2024. ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open-label extension; "Ph1/2a" = Phase 1/2a.

[1111] ***SWALLOWTAIL and LONGWING study participants experienced substantial overall improvement when treated at regular time intervals with 30- and 45-mg doses.***

[1112] SWALLOWTAIL and LONGWING study participants experienced substantial improvements in cognition and behavior when treated at regular time intervals (every four months, or 16-week, dosing) with 30- and 45-mg maintenance doses in the ongoing OLE study. Data from the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) indicate participants had clinically meaningful improvements in cognition and behavior by Month 12 and up to Month 24. Similarly, data from the Clinical and Caregiver Global Impression of Change for Cognition (CGI-C and CaGI-C) indicate clinically meaningful improvements in overall clinical status. These improvements were in stark contrast to estimated change based on BUTTERFLY natural history study data (**FIGS. 70A-70C**).

[1113] Improvements were observed in multiple domains of cognition and behavior as assessed by the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3, or VABS-III) at 12 months (**FIG. 56A**) and at 24 months (**FIG. 56B**) of the SWALLOWTAIL and LONGWING studies in which patients were administered with 30- or 45- mg ASO-1 maintenance doses at regular time intervals. Change in GSV for SWALLOWTAIL/LONGWING is from the OLE baseline. Changes in cognition and behavior were also assessed at month 12 of the BUTTERFLY natural history study in which the participants had received no treatment (**FIG. 65**) and as described in Example 22. Data from the BUTTERFLY natural history study indicated that participants who do not receive treatment experience little to no change over the course of 12 months in the cognition and behavioral domains observed in the SWALLOWTAIL and LONGWING studies. Improvement corresponds to a positive change in Growth Scale Value (GSV), and worsening corresponds to a negative change in GSV.

[1114] All cognitive and behavioral domains improved at month 12 as demonstrated by the positive GSV values shown in **FIG. 56A**. Receptive communication had a change in GSV of 3.231; expressive communication had a change in GSV of 2.490; personal skills had a change in GSV of 2.970; interpersonal relationships had a change in GSV of 3.780; and fine motor skills had a change in GSV of 0.864. A mixed-effects model for repeated measures was used with an unconstructed covariance structure constructed with data from SWALLOWTAIL and LONGWING for all patients who received ≥30 mg for all doses. For the data shown in **FIG. 56A**, the sample size was n=48 at screening, n=28 at week 48, and n=15 at week 64, except for those evaluated for Fine Motor skills, in which the sample size was n=45 at screening, n=28 at week 48, and n=14 at week 64. The change in GSV is measured from the OLE study baseline.

[1115] All cognitive and behavioral domains remain improved at month 24 as demonstrated by the positive GSV values shown in **FIG. 56B**. Receptive communication had a change in GSV of 5.22; expressive communication had a change in GSV of 3.79; personal skills had a change in GSV of 3.88; interpersonal relationships had a change in GSV of 5.9; play and leisure had a change in GSV of 8.14; coping skills had a change in GSV of 5.17; gross motor skills had a change in GSV of 6.28; and fine motor skills had a change in GSV of 4.63. Phase 1/2a data-cut: December 12, 2023 (after End of Study); OLE data-cut: June 28, 2024. A change of 2–3 points in GSV scores was considered meaningful by at least 50% of caregivers. Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies. One patient who received an incorrect dose in the Phase 1/2 study was excluded; One patient had multiple results classified as extreme outliers in fine motor subdomain. For the data shown in **FIGS. 56B-56C**, sample sizes were n=72 at OLE baseline, n=45-50 at Month 12, and n=18-22 at Month 24. These data show the continuing improvements in cognition and behavior as evaluated by Vineland-3 subdomain growth scale values from OLE baseline with interval improvements across Vineland-3 subdomains between Months 12 and 24 (**FIG. 56C**).

[1116] ***SWALLOWTAIL and LONGWING study participants experienced substantial improvement in communication when treated at regular time intervals with 30- and 45-mg doses in the ongoing OLE study.***

[1117] Participants who received either 30 mg or 45 mg ASO at regular intervals (about once every four months) showed substantial improvements in expressive communication (**FIG. 57A**) and receptive communication (**FIG. 57B**) across 4, 8, and 12 months. These patients were administered with ASO three times over the course of the open-label extension study (at weeks 1-4, weeks 17-20, and weeks 33-36) as described in Example 2, and assessed with Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) as described in Example 3. Improvement corresponds to a positive change in Growth Scale Value (GSV) (above the line demarcated by 0), and worsening corresponds to a negative change in GSV (below the line demarcated by 0). Change in GSV from the BUTTERFLY natural history study was used as the baseline for comparison.

[1118] Participants in the SWALLOWTAIL/LONGWING studies were observed to experience greater positive change in GSV indicative of improvement in behavior for both expressive and receptive communication. The change in GSV for expressive communication in SWALLOWTAIL/LONGWING participants was 0.185 at month 4, which increased to 1.209 by month 8, and increased to 2.490 by month 12. The change in GSV for receptive communication in SWALLOWTAIL/LONGWING participants was 1.623 at month 4, which increased to 2.337 by month 8, and increased to 3.231 by month 12. While expressive communication remained nearly unchanged for natural history study participants (0.053 at month 4, 0.105 at month 8, and 0.171 at month 12), receptive communication appeared to worsen for these same natural history participants, such that the change in GSV was -2.166 at month 4, -2.951 at month 8, and -3.934 at month 12.

[1119] A mixed-effects model for repeated measures (MMRM) was used with an unconstructed covariance structure constructed with data from SWALLOWTAIL and LONGWING for all patients who

received ≥30 mg for all doses. Data from BUTTERFLY from the start of the study to month 24 were analyzed with machine learning. Baseline covariates in the BUTTERFLY study, including baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency, were matched to SWALLOWTAIL/LONGWING patient population means. For expressive and receptive communication, the BUTTERFLY sample size was n=36 at the initial screen and n=25 at month 12; the SWALLOWTAIL/LONGWING sample size was n=48 at the initial screen, n=28 at week 48, and n=15 at week 64. Change in GSV for SWALLOWTAIL/LONGWING is measured from the OLE study baseline.

[1120] ***SWALLOWTAIL and LONGWING study participants experienced substantial improvement in personal and interpersonal relationship skills when treated at regular time intervals with 30- and 45-mg doses in the ongoing OLE study.***

[1121] Participants who received either 30 mg or 45 mg ASO at regular intervals (about once every four months) showed substantial improvements in personal **(FIG. 58A)** and interpersonal relationship skills **(FIG. 58B)** across 4, 8, and 12 months. These patients were administered with ASO three times over the course of the open-label extension study (at weeks 1-4, weeks 17-20, and weeks 33-36) as described in Example 2, and assessed Vineland-3 as described in Example 3. Improvement corresponds to a positive change in Growth Scale Value (GSV) (above the line demarcated by 0), and worsening corresponds to a negative change in GSV (below the line demarcated by 0). Change in GSV from the BUTTERFLY natural history study was used as the baseline for comparison.

[1122] Participants in the SWALLOWTAIL/LONGWING studies were observed to experience greater positive change in GSV indicative of improvement in behavior for both personal skills and interpersonal relationship skills. The change in GSV for personal skills from baseline in SWALLOWTAIL/LONGWING participants was 1.687 by month 8 and increased to 2.970 by month 12. The change in GSV for interpersonal relationship skills from baseline in SWALLOWTAIL/LONGWING participants was 1.276 at month 4, which increased to 2.389 by month 8, and increased to 3.780 by month 12. While personal skills remained nearly unchanged for natural history study participants (0.408 at month 4, 0.469 at month 8, and 0.530 at month 12), interpersonal relationship skills appeared to slightly improve as observed by the reduction in the absolute value for the change in GSV for these same natural history participants, such that the change in GSV was -2.629 at month 4, -1.673 at month 8, and -0.478 at month 12.

[1123] A mixed-effects model for repeated measures (MMRM) was used with an unconstructed covariance structure constructed with data from SWALLOWTAIL and LONGWING for all patients who received ≥30 mg for all doses. Data from BUTTERFLY from the start of the study to month 24 were analyzed with machine learning. Baseline covariates in the BUTTERFLY study, including baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency, were matched to SWALLOWTAIL/LONGWING patient population means. For personal skills and interpersonal relationships, the BUTTERFLY study sample size was n=36 at screening, n=25 at month 12 for personal skills, and n=24 for interpersonal relationships; the SWALLOWTAIL/LONGWING sample size was

n=48 at screening, n=28 at week 48 and n=15 at week 64. Change in GSV for SWALLOWTAIL/LONGWING is measured from the OLE baseline.

[1124] ***SWALLOWTAIL and LONGWING study participants experienced substantial improvement in overall condition when treated at regular time intervals with 30- and 45-mg doses in the ongoing OLE study.***

[1125] Participants who received either 30 mg or 45 mg of ASO at regular intervals (about once every four months) showed substantial improvement in overall condition as assessed by Clinical Global Impression of Change (CGI-C) at month 12 (**FIG. 59A**) and at month 24 (**FIG. 59C**), and Caregiver Global Impression of Change (CaGI-C) at month 12 (**FIG. 59B**) and at month 24 (**FIG. 59D**). CGI is scored on a 7-point scale and lower values (*e.g.,* a score of "1") correspond to improved conditions, while higher values (*e.g.,* a score of "7") correspond to worsened conditions. The baseline established during the natural history study was a score of approximately 4, with 4.360 in the Clinical Global Impression of Change and a score of 3.860 in the Caregiver Global Impression of Change; Least-Squares (LS) means are shown with a 95% confidence interval (CI) in **FIGS 59A-59B**.

[1126] The CGI-C for the SWALLOWTAIL/LONGWING studies indicate improved patient condition as seen in a score of 3.047 at month 4, 2.389 at month 8, and 1.567 at month 12 (**FIG. 59A**). Assessments using the CGI-C for the BUTTERFLY natural history study show that there was moderate change in overall condition over time when participants were not administered any ASO, as seen in a score of 4.360 at month 4, 3.769 at month 8, and 3.179 at month 12, but these improvements were not as clear as those observed in the participants of the SWALLOWTAIL/LONGWING studies.

[1127] Assessments using the CaGI-C for the SWALLOWTAIL/LONGWING show corresponding improvement in patient condition as seen in a score of 2.920 by month 4, 2.630 by month 8, and 2.270 by month 12 (**FIG. 59B**). Assessments using the CaGI-C for the BUTTERFLY natural history study show that there was very little change in overall condition over time when participants were not administered any ASO, as seen in a score of 3.860 at month 4, 3.795 at month 8, and 3.731 at month 12.

[1128] A mixed-effects model (MMRM) was used for repeated measures with an unconstructed covariance structure constructed with data from SWALLOWTAIL and LONGWING for all patients who received ≥30 mg for all doses. Data from BUTTERFLY from the start of study to month 24 were analyzed with machine learning. Baseline covariates in the BUTTERFLY study included the baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency matched to SWALLOWTAIL/LONGWING patient population means. For CGI-C, the BUTTERFLY study sample size was n=31 at month 3 and n=27 at month 12; the SWALLOWTAIL/LONGWING sample size was n=46 at screening, n=28 at week 48, and n=14 at week 64. For CaGI-C, the BUTTERFLY study sample size was n=34 at month 3, and n=29 at month 12; the SWALLOWTAIL/LONGWING sample size was n=46 at screening, n=29 at week 48, and n=14 at week 64. Clinicians and caregivers rated overall aspects of Dravet Syndrome (DS) in SWALLOWTAIL and LONGWING.

[1129] Clinical and Caregiver Global Impression of Change (CGI-C and CaGI-C) scales indicate substantial and ongoing improvements in overall clinical status through month 24 of the

SWALLOWTAIL and LONGWING OLEs (**FIGS. 59C-59D**). CGI-C data evaluated at month 24 indicate that about 13.6% of participants were very much improved, about 50.0% of participants were much improved, and about 36.5% of patients were at least minimally improved. 100% of these participants were found to be at least "minimally improved" to "very much improved" as evaluated by CGI-C (**FIG. 59A**). CaGI-C data evaluated at month 24 indicate that about 22.7% of participants were very much improved, about 45.5% of participants were much improved, about 27.3% of patients were at least minimally improved, and about 4.5% of participants experienced no change in CaGI-C scores. About 95.5% of these participants were found to be at least "minimally improved" to "very much improved" as evaluated by CaGI-C (**FIG. 59B**). †Mixed-effects model for repeated measures constructed using data through Month 24 (Week 96) from enrolled patients in OLE studies. One patient who received an incorrect dose in Phase 1/2a study was excluded. SWALLOWTAIL/LONGWING sample sizes: n=70 at Week 16, n=50 (CGI-C) and 51 (CaGI-C) at Week 48, n=22 at Week 96. OLE data-cut: June 28, 2024. LS, least squares; OLE, open-label extension.

[1130] ***Model outcomes from the EQ-VAS component of the EuroQol-5D Youth indicate ongoing improvements in quality of life through Month 24 of the SWALLOWTAIL/LONGWING OLEs.***

[1131] The EuroQol-5D-Y (EQ-5D-Y) is a health-related quality of life (HRQoL) assessment for children and adolescents ages 8-15. The EuroQol visual analogue scale (EQ-VAS) component records the young person's overall current health on a vertical visual analog scale ranging between 0 at the lower point of the scale (labeled "The worst health you can imagine") and 100 at the top of the scale ("The best health you can imagine"). The EQ-VAS is used as a quantitative measure of self-rated overall health. EQ VAS results collected in the SWALLOWTAIL/LONGWING studies indicate improvement from OLE baseline to Month 24. EQ-VAS scores at month 4 had a least-squares (LS) mean increase to about 1.65 from baseline, at month 12 had an LS mean increase to about 3.84 from baseline, and at month 24 had an LS mean increase to about 6.51 from baseline (**FIG. 72**). A mixed-effects model was used for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies. One patient who received an incorrect dose in Phase 1/2a study was excluded. OLE data-cut: June 28, 2024. SWALLOWTAIL/LONGWING sample sizes at OLE baseline: n=62. SWALLOWTAIL/LONGWING sample sizes at OLE baseline: n=62. Data had about a 95% confidence interval (CI).

[1132] ***Clinical Status Within First 9 Months of Phase 1/2a Treatment, Continuing Through Ongoing Treatment in SWALLOWTAIL and LONGWING OLE Studies***

[1133] Clinical and Caregiver Global Impression of Change (CGI-C and CaGI-C) scales indicate substantial and ongoing improvements in overall clinical status within the first 9 months of Phase 1/2a treatment continuing through month 24 of the SWALLOWTAIL and LONGWING OLEs (**FIGS. 71A-71B**). CGI-C data indicate that about 16.7% of participants were very much improved, about 33.3% of participants were much improved, and about 50.0% of patients were at least minimally improved. 100% of these participants were found to be at least "minimally improved" to "very much improved" as evaluated by CGI-C (**FIG. 71A**). CaGI-C data indicate that about 25.0% of participants were very much improved, about 33.3% of participants were much improved, and about 41.7% of patients were at least

minimally improved. About 100% of these participants were found to be at least "minimally improved" to "very much improved" as evaluated by CaGI-C (**FIG. 71B**). Data cutoff was December 12, 2023, for MONARCH/ADMIRAL. †Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies.

[1134] The studies described herein in Examples 25-29 show that loading doses comprising 70 mg of ASO-1 confirm findings from earlier studies. Maintenance dosing of either 30 mg or 45 mg ASO-1 can sustain reductions in convulsive seizure frequency. Maintenance dosing of either 30 mg or 45 mg ASO-1 can also sustains improvements in behavior and cognition. Long-term OLE data support the potential for ASO-1 to be the first disease-modifying medicine for Dravet Syndrome. Substantial and durable reductions in convulsive seizure frequency were observed through Month 24 in patients already receiving best available ASMs, with the largest reductions in patients who received doses of 70 mg in Phase 1/2a followed by 30 or 45 mg in the OLEs. Patients treated with ASO-1 experienced durable improvements in multiple measures of cognition, behavior, quality of life, and overall clinical status, which continued to improve through 24 months of the OLEs with ongoing maintenance dosing. Multiple maintenance doses of ASO-1 up to 45 mg were generally well tolerated.

[1135] ***Favorable safety and tolerability of ASO-1.***

[1136] Furthermore, no new safety concerns related to ASO-1 drug emerged during the studies. Single and multiple doses of ASO-1 comprising up to 70 mg of ASO have been generally well-tolerated. Patients have been treated for up to 3 years and 10 patients have received 9 or 10 total doses of ASO-1. At the 70-mg ASO dose level, the observed safety profile is similar to those of other dosing levels. One patient who received three 70-mg ASO doses experienced related Suspected Unexpected Serious Adverse Reactions (SUSAR) (previously disclosed). The most common treatment-emergent adverse events (TEAEs) related to this study drug were elevated levels of cerebrospinal fluid (CSF) proteins (CSF protein elevation) and procedural vomiting. 30% (24 out of 81) of patients in Phase 1/2a studies had elevated CSF protein levels and/or vomiting. 22% (18 out of 81) of patients had a TEAE, which were assessed as unrelated to the study drug except for the previously reported case of one patient who experienced SUSAR. Safety findings from patients who continued treatment in the OLEs were consistent with these findings, with the exception of a greater incidence of CSF protein elevation. In the OLE studies, 74% (50 out of 68) of study participants had cerebral spinal fluid (CSF) protein concentrations exceeding 50 mg/dL. No clinical manifestations have been observed in patients who developed CSF protein elevations, although one patient discontinued treatment in OLE due to protein levels.

[1137] These 12-month OLE data support the potential for ASO-1 being administered concomitantly with multiple ASMs as the first disease-modifying medicine for DS. Multiple doses of ASO-1 up to 45 mg per dose every 4 months were generally well-tolerated. Significant and durable reductions in seizure frequency were observed on top of best-available ASMs. Clinically meaningful improvements were detected in multiple measures of cognition, behavior, and overall clinical status. The improvements reported in the OLEs are in stark contrast to the lack of improvement reported in the BUTTERFLY natural history study.

[1138] Pharmacokinetics (PK) models, exposure-response models, patient burden, regulatory feasibility, and product profile are additional considerations that will be evaluated in determining progression to Phase 3 trials.

Example 30. Phase 3 Design.

[1139] Exposure-Response (ER) seizure model predicts that two or three loading doses of 70-mg ASO would reduce seizure frequency.

[1140] ER seizure model predicts that two loading doses of 70 mg ASO followed by 70-mg maintenance doses administered at regular time intervals (**FIG. 60A**) would offer similar, predicted long-term effects as three loading doses of 70 mg followed by 70-mg maintenance doses administered at regular intervals (**FIG. 60B**). When two 70-mg loading doses were used for simulation based on the ER seizure model, an estimated 65% reduction in seizure frequency was predicted to be attainable at four months after the fourth 70-mg maintenance dose, while when three 70-mg loading doses were used, an estimated 67% reduction in seizure frequency was predicted to be attainable at four months after the fourth 70-mg maintenance dose. Population Pharmacokinetic-Pharmacodynamic (PK/PD) models were used to generate simulations based on 10,000 subjects stratified by age group using a sampling of the subjects from an omega matrix obtained from the PK/PD analysis (ER Model #1.5). For the simulations, the age parameter was fixed at between about 2 and about 18 years of age, inclusive; weight was set to be between about 12.9 and 67.9 kg; baseline set at [1,1393]; mixture = direct depot: 50%; transient compartment: 50%.

[1141] A semi-mechanistic population pharmacokinetic (PK) model in non-human primates (NHP) was developed using ASO-1 concentration data collected in CSF, plasma, brain, and spinal cord tissues from 95 NHPs following single or multiple IT injections of ASO-1 in the dose range of 2 to 30 mg/dose in five nonclinical studies. The NHP model was adjusted after including interim PK data from a 45-week chronic study (up to main necropsy) and interim PK data from 9- and 12-month necropsy time points from a 52-week tissue half-life study. In the final NHP model (total 141 NHPs), a 15th compartment named “deep brain” was added to account for a slower distribution phase, translating into a longer terminal half-life in the brain compartment. This model demonstrated goodness of fit; mostly all observed levels of ASO-1 were within the 2.5th and 97.5th percentiles of the model simulations from 6 studies in NHPs.

[1142] The population PK model in NHP served as the basis to support a human model that described the available PK dataset from 81 pediatric patients with DS after single IT administration of 10 mg to 70 mg ASO-1 and multiple IT administrations of 20 mg to 70 mg ASO-1 (2290 and 341 observations in plasma and in CSF samples with detectable levels of ASO-1, respectively).

[1143] Compared to the NHP model alone, the structural human PK model was modified by adding a transit compartment in the absorption phase to explain lower Cmax and longer time to achieve Cmax (Tmax) observed in plasma in some patients. A mixture model was implemented to identify patients who would benefit from the transit compartment and those who would not benefit from the transit compartment. From the 81 patients with PK data, 38.3% were modelled with dose administration in a

transit compartment before CSF (Mixture #2) and 61.7% using a direct dose administration into CSF (Mixture #1).

[1144] ***Two 70-mg loading doses are predicted to offer improved safety margin compared to three 70-mg loading doses based on the PK model and estimated total dose.***

[1145] Predicted safety margins were calculated from the PK model based on the total Cmax and cumulative systemic exposure represented by the area-under-the curve (AUC) in the brain using Lowest-observed-adverse-effect level (LOAEL). For two 70-mg loading doses and one 70-mg maintenance dose, safety margins are greater than 1. For three 70-mg loading doses and one 70-mg maintenance dose, safety margins are not greater than 1.

[1146] Using total dose administered for a 45-week chronic study, predicted safety margins in humans for both two and three 70-mg loading doses are estimated to be greater than 1 (**Table 18**).

Table 18. Predicted safety margins estimated based on total dose administered.

Juvenile NHP				**Total HED (mg)**	**Human**		
Study type	**No. of doses**	**LOAEL (mg/dose)**	**Cumulative dose (mg)**		**Loading regimen**	**Yearly total human dose (mg)**	**Safety margins (ratio)**
45-week chronic study	7	5.25	36.75	367.5	2 x 70 mg	3 x 70 = 210	**1.75**
					3 x 70 mg	4 x 70 = 280	**1.31**

[1147] ***Two 70-mg loading doses are predicted to achieve a steady state five months sooner and reduce the duration of a Phase 3 study.***

[1148] When modeling two 70-mg loading doses followed by four 70-mg maintenance doses, the concentration in the brain was estimated to reach a steady state of 26.0 μg ASO per gram of brain weight calculated without the thalamus (26.0 μg/g) (**FIG. 61A**) at 2 months calculated from the start of the first loading dose administration. When modeling three 70-mg loading doses followed by four 70-mg maintenance doses, the concentration in the brain was estimated to reach a steady state of 26.0 μg/g (**FIG. 61B**) at 7 months calculated from the start of the first loading dose administration. The two 70-mg loading dose regiment was predicted to achieve the 26.0 μg/g steady state about five months sooner than the three 70-mg loading dose regimen. The arrows at the top of each graph indicate the projected steady-state brain exposure maximum concentration (Cmax), and the Cmax reference is 26.0 μg/g in mean brain without thalamus.

[1149] ***ER model predicts robust reduction in convulsive seizure frequency after administration with either 70- or 45-mg maintenance doses at regular time intervals.***

[1150] The most robust long-term effect was predicted to occur with the administration of 70-mg maintenance doses, but 45-mg maintenance doses also appear to provide substantial benefit. When modeling what would occur with two 70-mg loading doses followed by four 70-mg maintenance doses, a 65% reduction in convulsive seizures was predicted to occur by four months after the fourth maintenance dose (**FIG. 62A**). When modeling what would occur with two 70-mg loading doses followed by four 45-

mg maintenance doses, a 55% reduction in convulsive seizures was predicted to occur by four months after the fourth maintenance dose (**FIG. 62B**). For the simulations, the age parameter was fixed at between about 2 and about 18 years of age, inclusive; weight was set to be between about 12.9 and 67.9 kg; baseline set at [1,1393]; mixture = direct depot: 50%; transient compartment: 50%.

[1151] ***Pharmacokinetic model predicts that a steady state would be achieved eight months sooner with 70-mg maintenance doses administered at regular time intervals than with 45-mg maintenance doses.***

[1152] When modeling two 70-mg loading doses followed by four 70-mg maintenance doses, the concentration in the brain was estimated to reach a steady state of 26.0 μg ASO per gram of brain weight calculated without the thalamus (26.0 μg/g) (**FIG. 63A**) at 2 months calculated from the start of the first loading dose administration. When modeling two 70-mg loading doses followed by four 45-mg maintenance doses, the concentration in the brain was estimated to reach a steady state of 16.7 μg/g (**FIG. 63B**) at 10 months calculated from the start of the first loading dose administration. The two 70-mg loading dose regiment was predicted to achieve the 26.0 μg/g steady state about eight months sooner than the 45-mg maintenance dose regimen. The arrows at the top of each graph indicate the projected steady-state brain exposure maximum concentration (Cmax), and the Cmax reference is either 16.7 or 26.0 μg/g in mean brain without thalamus.

[1153] Screening of patients for the proposal comprised of two 70-mg loading doses, followed by 70-mg maintenance doses every 4 months, occur at day -42, or week 6 of a six-week observation period prior to dosing (**FIG. 64**). During the initial 24-week treatment period, either a placebo or the ASO drug is randomly assigned to participants at (1) day 1, or week 0, and (2) day 57, or week 8. A maintenance dose is administered at day 169, or week 24 of the 16-week ongoing treatment period. Change in anti-seizure therapies are allowed at the beginning of week 24 if there is a lack of improvement or the participant has ongoing seizures. The end of the study occurs on day 281, or week 40, and the total study period comprises 46 weeks of time. On day 281, or week 40, all patients are given the option to enter the open-label extension study.

[1154] Another proposal for the study comprises of three 70-mg loading doses, followed by 70-mg maintenance doses every 4 months, which is predicted to have a safety margin of 1.75 and a patient burden of 3 total doses. The three 70-mg loading doses are administered 8 weeks apart, and the first 70-mg maintenance dose is administered 16 weeks after the third loading dose.

[1155] Screening of patients for the proposal comprised of three 70-mg loading doses, followed by 70-mg maintenance doses, occur at day 42, or week 6 of a six-week observation period. During the initial 32-week treatment period, either a placebo or the ASO drug is randomly assigned to participants at (1) day 1, or week 0, (2) day 57, or week 8, and (3) day 113, or week 16. A maintenance dose is administered at day 225, or week 32 of the 24-week ongoing treatment period.

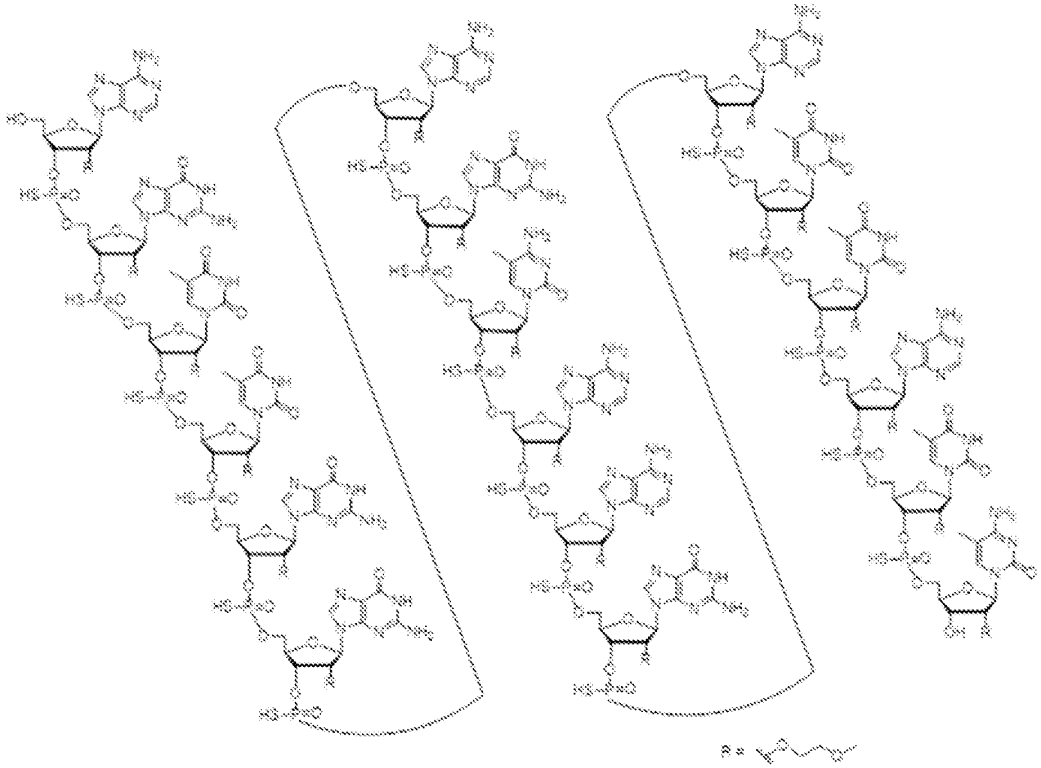
[1156] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without

departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

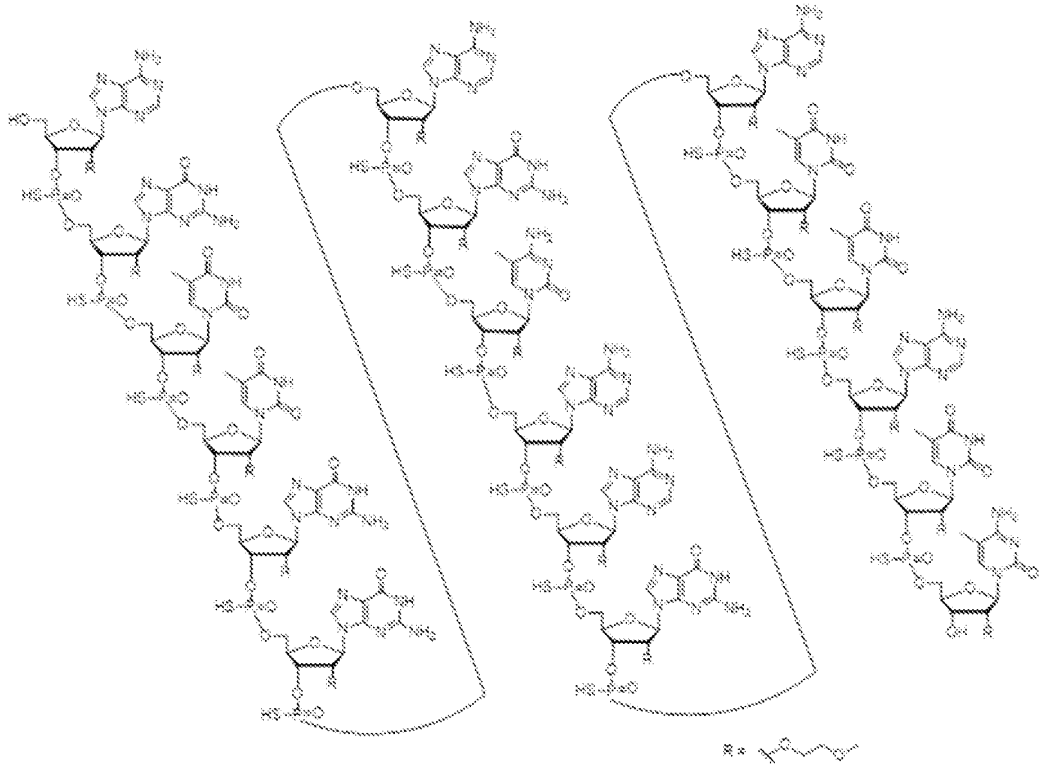
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and a first maintenance dose following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the first maintenance dose independently contains the compound at an amount of from about 25 mg to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and the first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose.

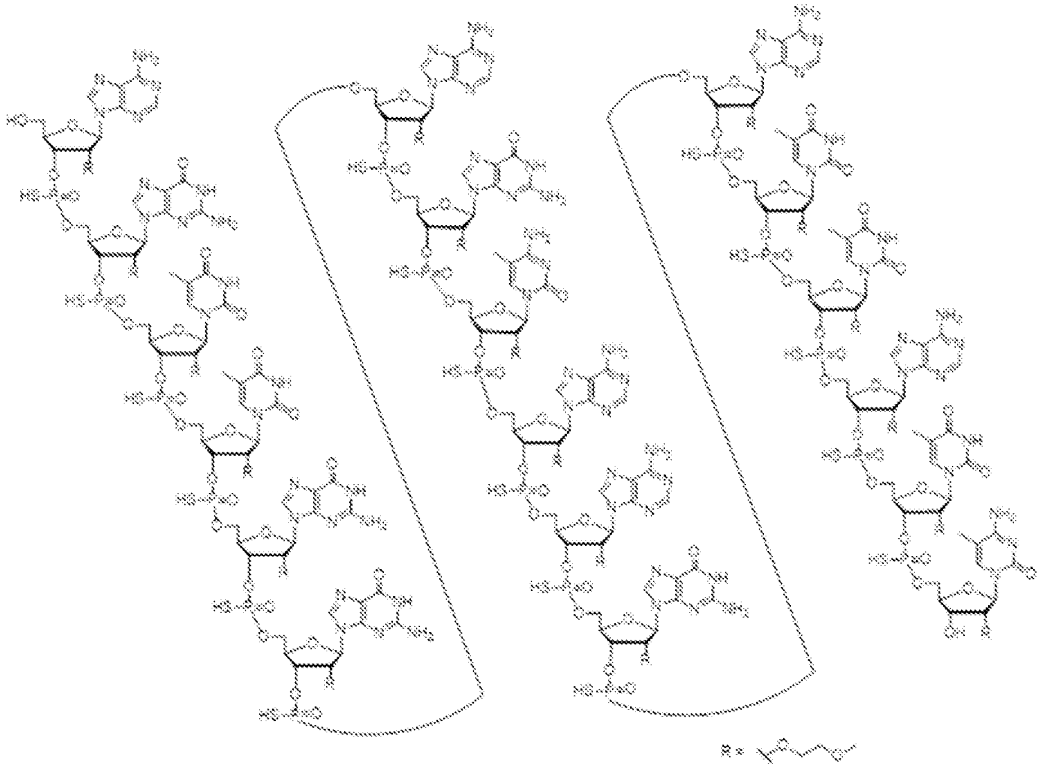
2. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I), or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and a first maintenance dose following the third loading dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the first maintenance dose independently contains the compound at an amount of from about 25 mg to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose, and the first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose.

3. A dosing regimen for administering a compound according to the following chemical structure:



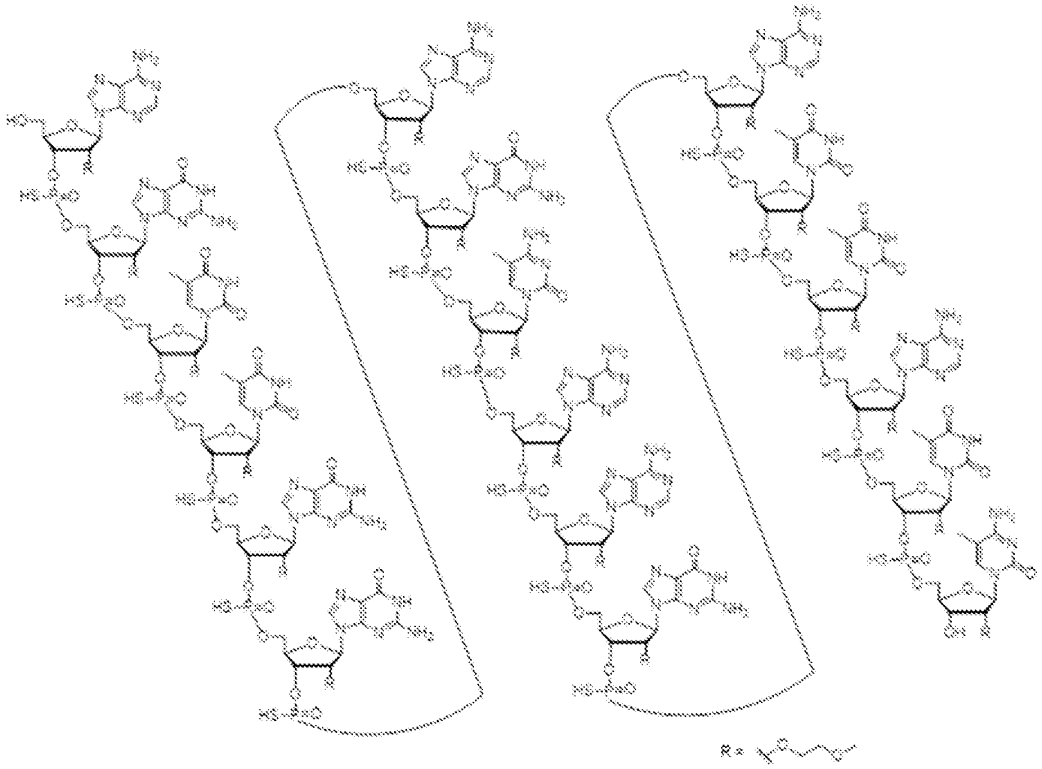
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day of treatment, (b) 4 months after the second loading dose, or (c) 16 weeks after the second loading dose.

4. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

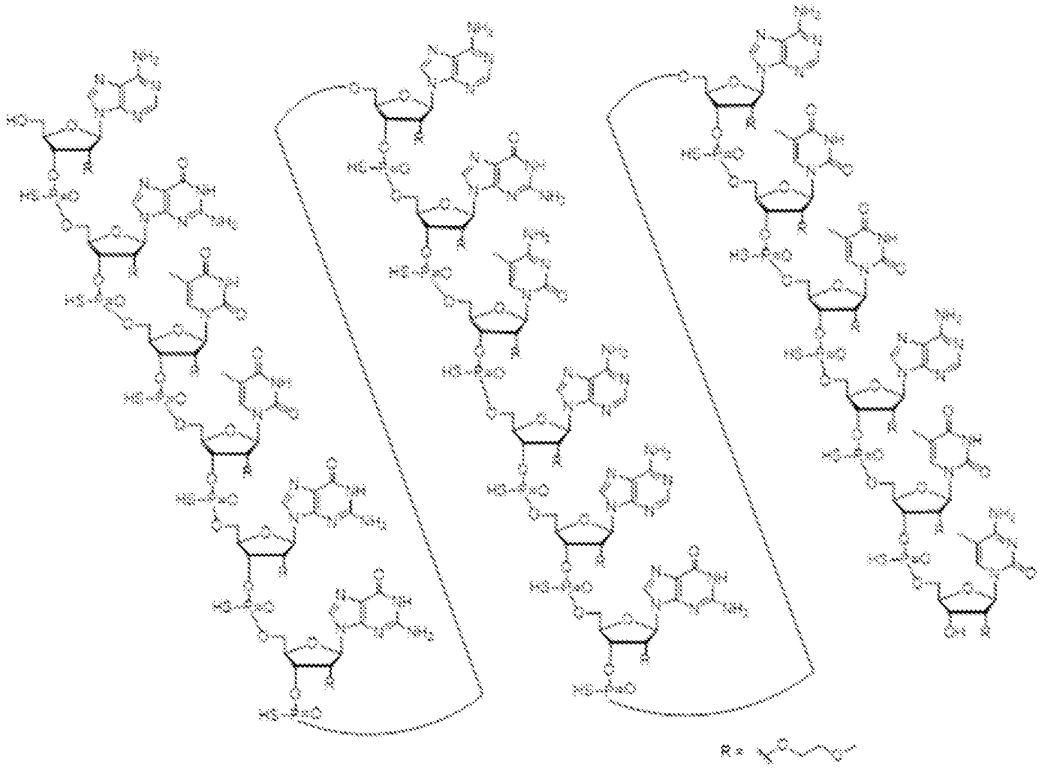
administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day of treatment, (b) 1 month after the second loading dose, or (c) 4 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

5. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

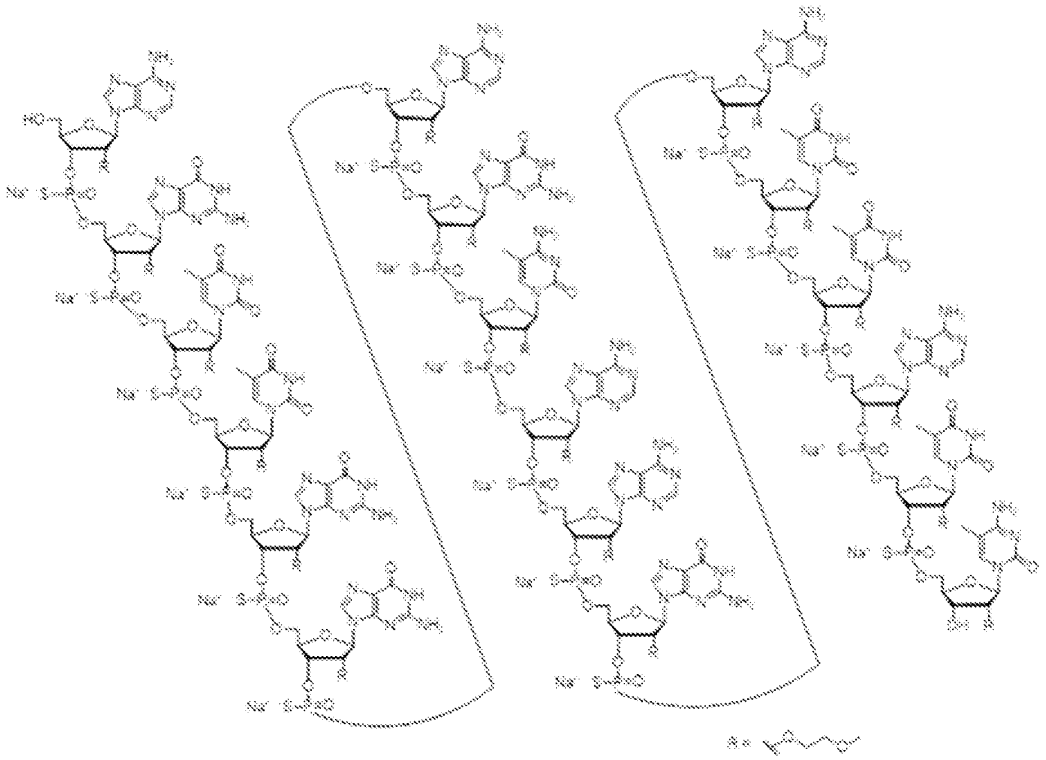
administering to the human subject a second loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day of treatment, (b) 2 months after the second loading dose, or (c) 8 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 25 mg to about 100 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

6. The dosing regimen of any one of claims 3-5, wherein the dosing regimen further comprises administering to the human subject one or more maintenance doses after the first maintenance dose is administered.

7. The dosing regimen of claim 6, wherein each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of from about 25 mg to about 100 mg.
8. The dosing regimen of claim 7, wherein each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of about 45 mg.
9. The dosing regimen of claim 7, wherein each of the one or more maintenance doses after the first maintenance dose independently contains the compound at an amount of about 70 mg.
10. The method of claim 1 or 2 or the dosing regimen of any one of claims 3-9, wherein the compound has the following structure:



(II).

11. The method of any one of claims 1, 2, and 10 or the dosing regimen of any one of claims 3-10, wherein the first loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.
12. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of about 30 mg.
13. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of about 70 mg.

14. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of about 45 mg.
15. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of about 50 mg.
16. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 25 mg to about 35 mg.
17. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 35 mg to about 50 mg.
18. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 45 mg to about 70 mg.
19. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 50 mg to about 70 mg.
20. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 60 mg to about 80 mg.
21. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 30 mg to about 45 mg.
22. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 25 mg to about 40 mg.
23. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 35 mg to about 45 mg.
24. The method of any one of claims 1, 2, 10, and 11 or the dosing regimen of any one of claims 3-11, wherein the first loading dose contains the compound at an amount of from about 40 mg to about 55 mg.
25. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.

26. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of about 30 mg.
27. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of about 70 mg.
28. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of about 45 mg.
29. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of about 50 mg.
30. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 25 mg to about 35 mg.
31. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 35 mg to about 50 mg.
32. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 45 mg to about 70 mg.
33. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 50 mg to about 70 mg.
34. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 60 mg to about 80 mg.
35. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 30 mg to about 45 mg.
36. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 25 mg to about 40 mg.
37. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 35 mg to about 45 mg.
38. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains the compound at an amount of from about 40 mg to about 55 mg.
39. The method of any one of claims 1, 2, and 10-24 or the dosing regimen of any one of claims 3-24, wherein the second loading dose contains same amount of the compound as the first loading dose.

40. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.
41. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of about 30 mg.
42. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of about 70 mg.
43. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of about 45 mg.
44. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of about 50 mg.
45. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 25 mg to about 35 mg.
46. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 35 mg to about 50 mg.
47. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 45 mg to about 70 mg.
48. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 50 mg to about 70 mg.
49. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 60 mg to about 80 mg.
50. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 30 mg to about 45 mg.
51. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 25 mg to about 40 mg.
52. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 35 mg to about 45 mg.

53. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains the compound at an amount of from about 40 mg to about 55 mg.
54. The method of any one of claims 2 and 10-39 or the dosing regimen of any one of claims 3-39, wherein the third loading dose contains same amount of the compound as the first loading dose.
55. The method of any one of claims 1, 2, and 10-54 or the dosing regimen of any one of claims 3-54, wherein the first maintenance dose contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.
56. The method of any one of claims 1, 2, and 10-55 or the dosing regimen of any one of claims 3-55, further comprising administering one or more maintenance doses after the first maintenance dose.
57. The method or dosing regimen of claim 56, wherein each maintenance dose of the one or more maintenance doses independently contains the compound at an amount of about 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, or 80 mg, or at least 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, or 90 mg.
58. The method or dosing regimen of claim 56 or 57, wherein each maintenance dose of the one or more maintenance doses is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.
59. The method of any one of claims 1, 2, and 10-58 or the dosing regimen of any one of claims 3-58, wherein each maintenance dose of the one or more maintenance doses contains same amount of the compound.
60. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 30 mg.
61. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 45 mg.
62. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of about 70 mg.
63. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 55 mg to about 70 mg.

64. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 55 mg to about 75 mg.
65. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 55 mg to about 80 mg.
66. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 40 mg to about 70 mg.
67. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 40 mg to about 75 mg.
68. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 40 mg to about 80 mg.
69. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 65 mg to about 90 mg.
70. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 65 mg to about 95 mg.
71. The method or the dosing regimen of claim 59, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount of from about 65 mg to about 100 mg.
72. The method of any one of claims 1, 2, and 10-71 or the dosing regimen of any one of claims 3-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains same amount of the compound as the first loading dose or the second loading dose.
73. The method of any one of claims 2 and 10-71 or the dosing regimen of any one of claims 4-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains same amount of the compound as the first loading dose, the second loading dose, or the third loading dose.
74. The method of any one of claims 1, 2, and 10-71 or the dosing regimen of any one of claims 3-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a higher amount of the compound than the first loading dose or the second loading dose.
75. The method or the dosing regimen of claim 74, wherein the first maintenance dose or each maintenance dose of the one and more maintenance doses contains the compound at an amount that

is at least about 10%, 20%, or 30% higher than the amount in the first loading dose or the second loading dose.

76. The method or the dosing regimen of claim 74, wherein the first maintenance dose or each maintenance dose of the one and more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg higher than the amount in the first loading dose or the second loading dose.
77. The method of any one of claims 2 and 10-71 or the dosing regimen of any one of claims 4-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a higher amount of the compound than the first loading dose, the second loading dose, or the third loading dose.
78. The method or the dosing regimen of claim 77, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% higher than the amount in the first loading dose, the second loading dose, or the third loading dose.
79. The method or the dosing regimen of claim 77, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg higher than the amount in the first loading dose, the second loading dose, or the third loading dose.
80. The method of any one of claims 1, 2, and 10-71 or the dosing regimen of any one of claims 3-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a lower amount of the compound than the first loading dose or the second loading dose.
81. The method or the dosing regimen of claim 80, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% lower than the amount in the first loading dose or the second loading dose.
82. The method or the dosing regimen of claim 80, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg lower than the amount in the first loading dose or the second loading dose.
83. The method of any one of claims 2 and 10-71 or the dosing regimen of any one of claims 4-71, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contain a lower amount of the compound than the first loading dose, the second loading dose, or the third loading dose.
84. The method or the dosing regimen of claim 83, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 10%, 20%, or 30% lower than the amount in the first loading dose, the second loading dose, or the third loading dose.

85. The method or the dosing regimen of claim 83, wherein the first maintenance dose and each maintenance dose of the one or more maintenance doses contains the compound at an amount that is at least about 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg lower than the amount in the first loading dose, the second loading dose, or the third loading dose.
86. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5 weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks, from 6 weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the first loading dose.
87. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks after the first loading dose.
88. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 6 weeks after the administration of the first loading dose.
89. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 7 weeks after the administration of the first loading dose.
90. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 8 weeks after the administration of the first loading dose.
91. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 9 weeks after the administration of the first loading dose.
92. The method of any one of claims 1, 2, and 10-85 or the dosing regimen of any one of claims 3-85, wherein the second loading dose is administered about 10 weeks after the administration of the first loading dose.
93. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered from 4 weeks to 11 weeks, from 4 weeks to 10 weeks, from 4 weeks to 9 weeks, from 4 weeks to 8 weeks, from 4 weeks to 7 weeks, from 4 weeks to 6 weeks, from 4 weeks to 5 weeks, from 5 weeks to 12 weeks, from 5 weeks to 11 weeks, from 5

weeks to 10 weeks, from 5 weeks to 9 weeks, from 5 weeks to 8 weeks, from 5 weeks to 7 weeks, from 5 weeks to 6 weeks, from 6 weeks to 12 weeks, from 6 weeks to 11 weeks, from 6 weeks to 10 weeks, from 6 weeks to 9 weeks, from 6 weeks to 8 weeks, from 6 weeks to 7 weeks, from 7 weeks to 12 weeks, from 7 weeks to 11 weeks, from 7 weeks to 10 weeks, from 7 weeks to 9 weeks, from 7 weeks to 8 weeks, from 8 weeks to 12 weeks, from 8 weeks to 11 weeks, from 8 weeks to 10 weeks, from 8 weeks to 9 weeks, from 9 weeks to 12 weeks, from 9 weeks to 11 weeks, from 9 weeks to 10 weeks, from 10 weeks to 12 weeks, from 10 weeks to 11 weeks, or from 11 weeks to 12 weeks after the second loading dose.

94. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks after the second loading dose.
95. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 4 weeks after the administration of the second loading dose.
96. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 5 weeks after the administration of the second loading dose.
97. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 6 weeks after the administration of the second loading dose.
98. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 7 weeks after the administration of the second loading dose.
99. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 8 weeks after the administration of the second loading dose.
100. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 9 weeks after the administration of the second loading dose.
101. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the third loading dose is administered about 10 weeks after the administration of the second loading dose.
102. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks apart from each other.

103. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 6 weeks apart from each other.

104. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 7 weeks apart from each other.

105. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 8 weeks apart from each other.

106. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 9 weeks apart from each other.

107. The method of any one of claims 2 and 10-92 or the dosing regimen of any one of claims 4-92, wherein the first loading dose, the second loading dose, and the third loading dose are administered about 10 weeks apart from each other.

108. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the second loading dose.

109. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the second loading dose.

110. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 8 weeks after the second loading dose.
111. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 12 weeks after the second loading dose.
112. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 16 weeks after the second loading dose.
113. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 20 weeks after the second loading dose.
114. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 4 months after the second loading dose.
115. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 6 months after the second loading dose.
116. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 9 months after the second loading dose.
117. The method of any one of claims 1 and 10-107 or the dosing regimen of any one of claims 3 and 6-107, wherein the first maintenance dose is administered about 12 months after the second loading dose.
118. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months, from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12

months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the third loading dose.

119. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the third loading dose.

120. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 8 weeks after the third loading dose.

121. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 12 weeks after the third loading dose.

122. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 16 weeks after the third loading dose.

123. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 20 weeks after the third loading dose.

124. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 4 months after the third loading dose.

125. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 6 months after the third loading dose.

126. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 9 months after the third loading dose.

127. The method of any one of claims 2 and 10-107 or the dosing regimen of any one of claims 4-107, wherein the first maintenance dose is administered about 12 months after the third loading dose.

128. The method of any one of claims 1, 2, and 10-107 or the dosing regimen of any one of claims 3-107, wherein the one or more maintenance doses consist of one maintenance dose.

129. The method of any one of claims 1, 2, and 10-107 or the dosing regimen of any one of claims 3-107, wherein the one or more maintenance doses comprise at least two maintenance doses, and wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently from 8 weeks to 11 months, from 8 weeks to 10 months, from 8 weeks to 8 months, from 8 weeks to 6 months, from 8 weeks to 20 weeks, from 8 weeks to 16 weeks, from 8 weeks to 14 weeks, from 8 weeks to 12 weeks, from 8 weeks to 10 weeks, from 10 weeks to 12 weeks, from 12 weeks to 16 weeks, from 12 weeks to 12 months, from 12 weeks to 11 months, from 12 weeks to 12 months, from 12 weeks to 8 months, from 12 weeks to 6 months, from 12 weeks to 20 weeks, from 12 weeks to 16 weeks, from 12 weeks to 14 weeks, from 16 weeks to 12 months, from 16 weeks to 11 months, from 16 weeks to 10 months, from 16 weeks to 8 months, from 16 weeks to 6 months, from 16 weeks to 20 weeks, from 20 weeks to 12 months, from 20 weeks to 11 months, from 20 weeks to 10 months, from 20 weeks to 8 months, from 20 weeks to 6 months, from 6 months to 12 months, from 6 months to 11 months, from 6 months to 10 months,

from 6 months to 9 months, from 6 months to 8 months, from 6 months to 7 months, from 7 months to 12 months, from 7 months to 11 months, from 7 months to 10 months, from 7 months to 9 months, from 7 months to 8 months, from 8 months to 12 months, from 8 months to 11 months, from 8 months to 10 months, from 8 months to 9 months, from 9 months to 12 months, from 9 months to 11 months, from 9 months to 10 months, from 10 months to 12 months, from 10 months to 11 months, or from 11 months to 12 months after the dose immediately preceding the respective maintenance dose.

130. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered independently about 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 22 weeks, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the dose immediately preceding the respective maintenance dose.

131. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 8 weeks after the dose immediately preceding the respective maintenance dose.

132. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 12 weeks after the dose immediately preceding the respective maintenance dose.

133. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 16 weeks after the dose immediately preceding the respective maintenance dose.

134. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 20 weeks after the dose immediately preceding the respective maintenance dose.

135. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 4 months after the dose immediately preceding the respective maintenance dose.

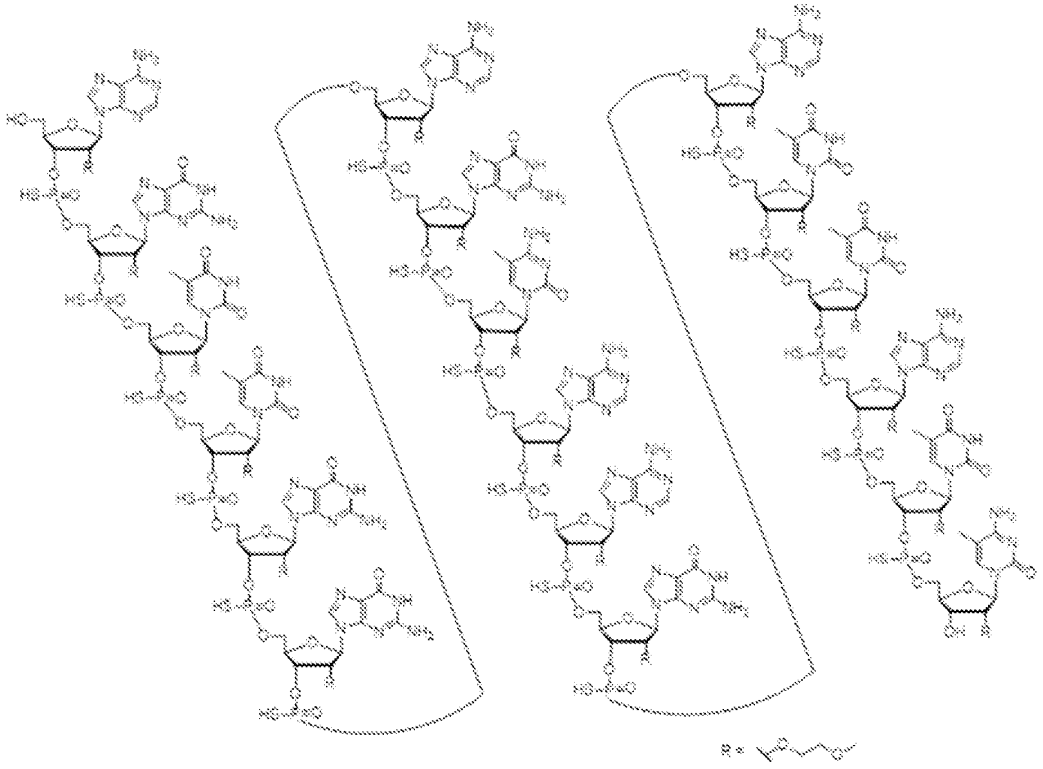
136. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 6 months after the dose immediately preceding the respective maintenance dose.

137. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 9 months after the dose immediately preceding the respective maintenance dose.

138. The method or the dosing regimen of claim 129, wherein each maintenance dose of the one or more maintenance doses other than the first maintenance dose is administered about 12 months after the dose immediately preceding the respective maintenance dose.

139. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses consist of two maintenance doses.
140. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses consist of three maintenance doses.
141. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses consist of four maintenance doses.
142. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses consist of five, six, seven, eight, or more maintenance doses.
143. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses comprise more than three maintenance doses.
144. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses are administered over a lifetime of the human subject.
145. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the method or the dosing regimen comprises administering the one or more maintenance doses to the human subject until an indication that a most recent maintenance dose is not tolerated by the human subject.
146. The method of any one of claims 1, 2, and 10-138 or the dosing regimen of any one of claims 3-138, wherein the one or more maintenance doses are administered to the human subject over a period of at least one year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35, years, 40 years, 45 years, 50 years, 55 years, or 60 years.
147. The method of any one of claims 1 and 10-146 or the dosing regimen of any one of claims 3 and 6-146, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg.
148. The method of any one of claims 1 and 10-146 or the dosing regimen of any one of claims 3 and 6-146, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 70 mg.
149. The method of any one of claims 2 and 10-146 or the dosing regimen of any one of claims 4-146, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 70 mg.
150. The method of any one of claims 2 and 10-146 or the dosing regimen of any one of claims 4-146, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg.

151. The method of any one of claims 1 and 10-146 or the dosing regimen of any one of claims 3 and 6-146, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose of the after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.
152. The method of any one of claims 2 and 10-146 or the dosing regimen of any one of claims 4-146, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.
153. The method or the dosing regimen of any one of claims 139-146, wherein the one or more maintenance doses are administered at a same dose frequency or a substantially same dose frequency.
154. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

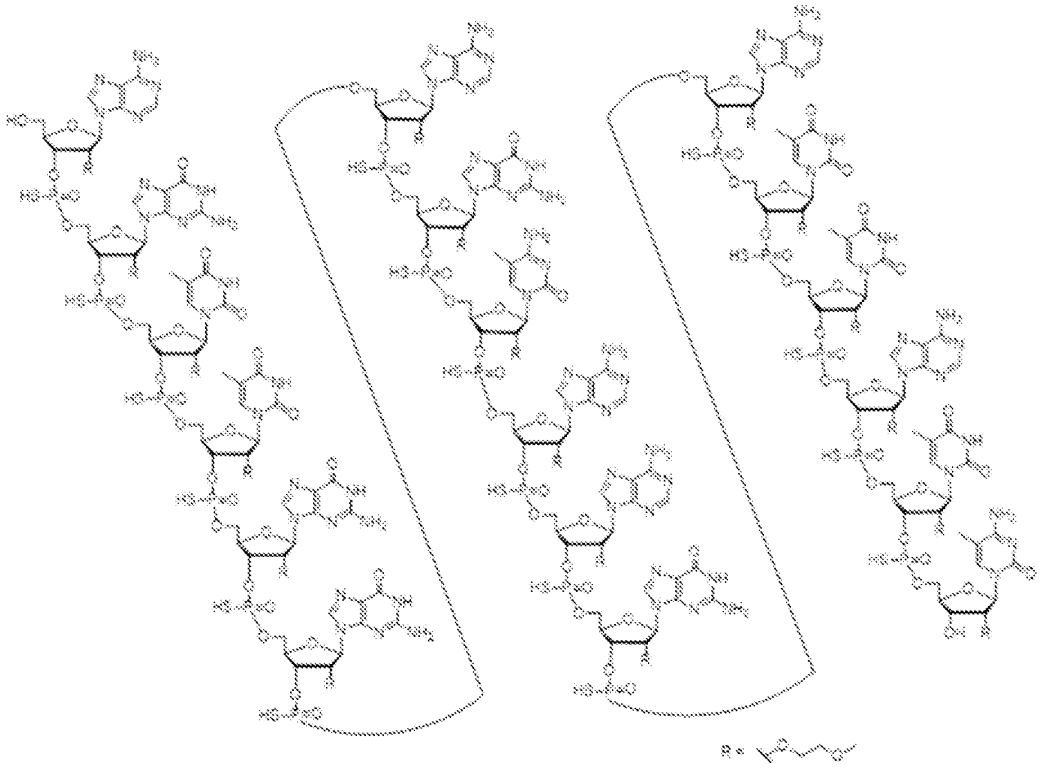
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

155. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

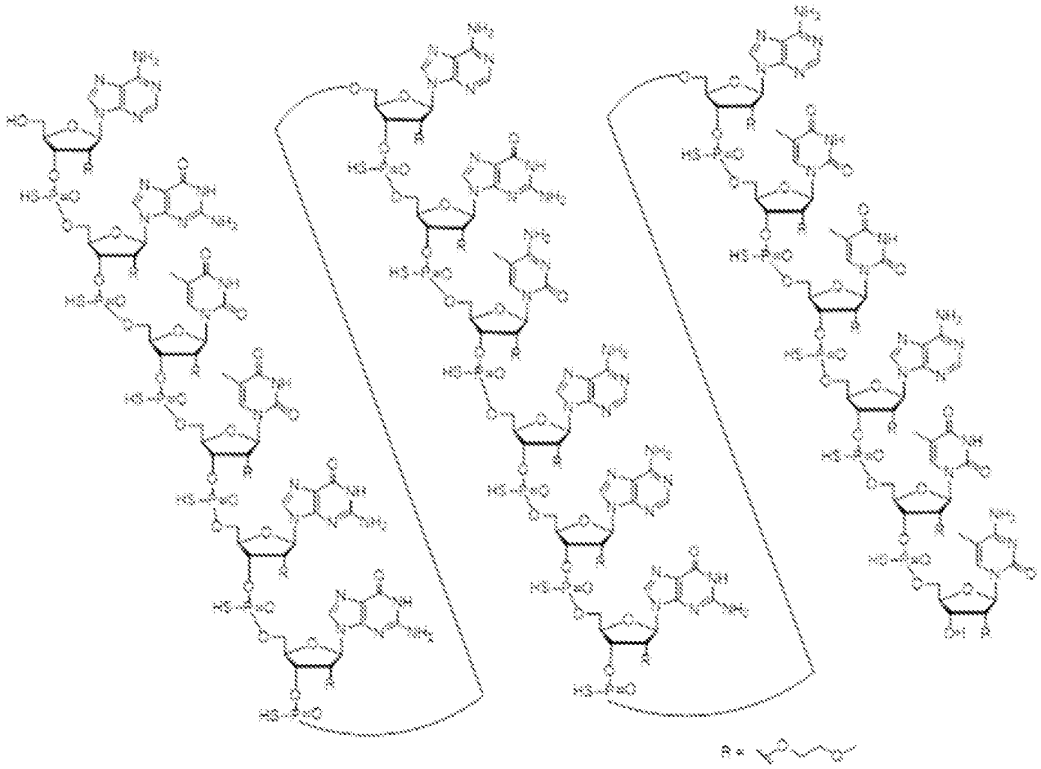
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

156. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

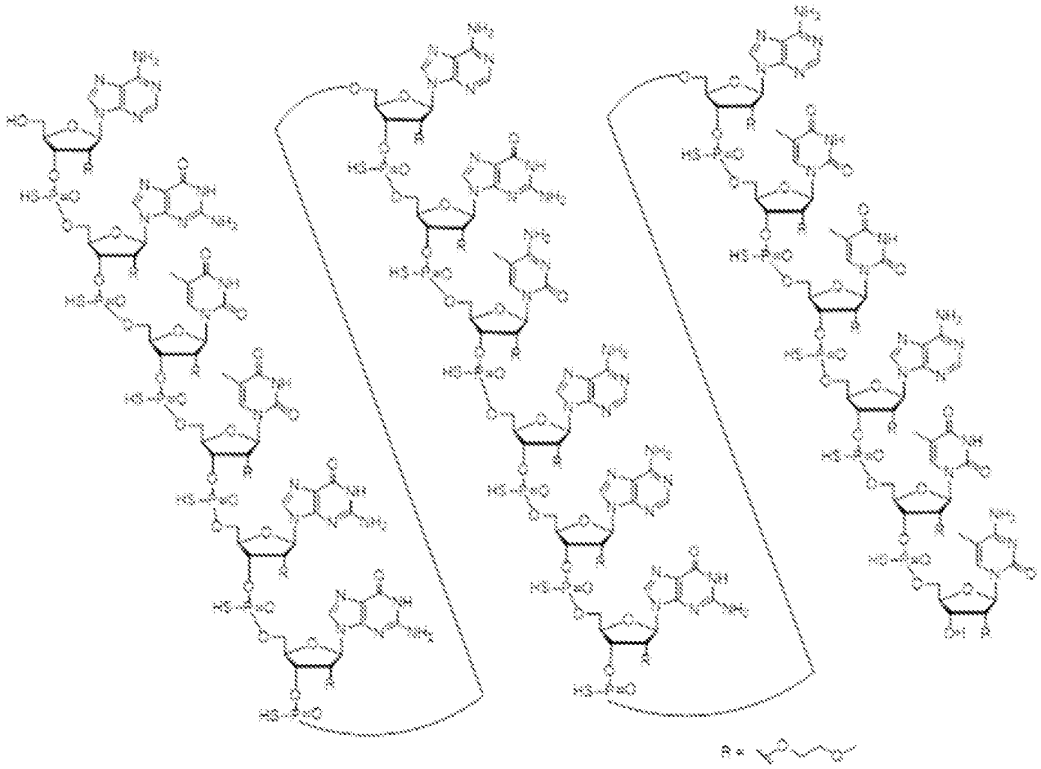
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

157. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, and each maintenance dose of the one or more maintenance doses is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

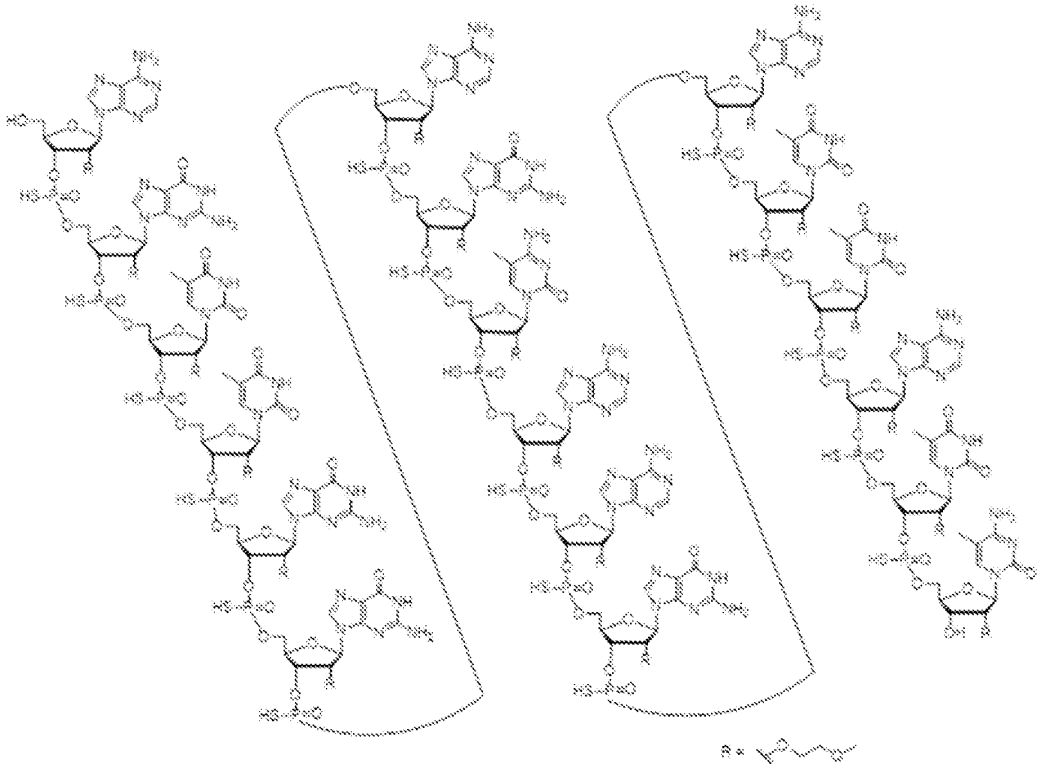
158. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 30 mg.

159. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 45 mg.

160. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 50 mg.

161. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 60 mg.

162. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the one or more maintenance doses is about 70 mg.
163. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose and the second loading dose is about 30 mg, and the amount of the compound in each of the one or more maintenance doses is about 25 mg.
164. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose and the second loading dose is about 45 mg, and the amount of the compound in each of the one or more maintenance doses is about 30 mg.
165. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose and the second loading dose is about 50 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.
166. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose and the second loading dose is about 60 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.
167. The method of any one of claims 154-157, wherein the amount of the compound in each dose of the first loading dose and the second loading dose is about 70 mg, and the amount of the compound in each of the one or more maintenance doses is about 45 mg.
168. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

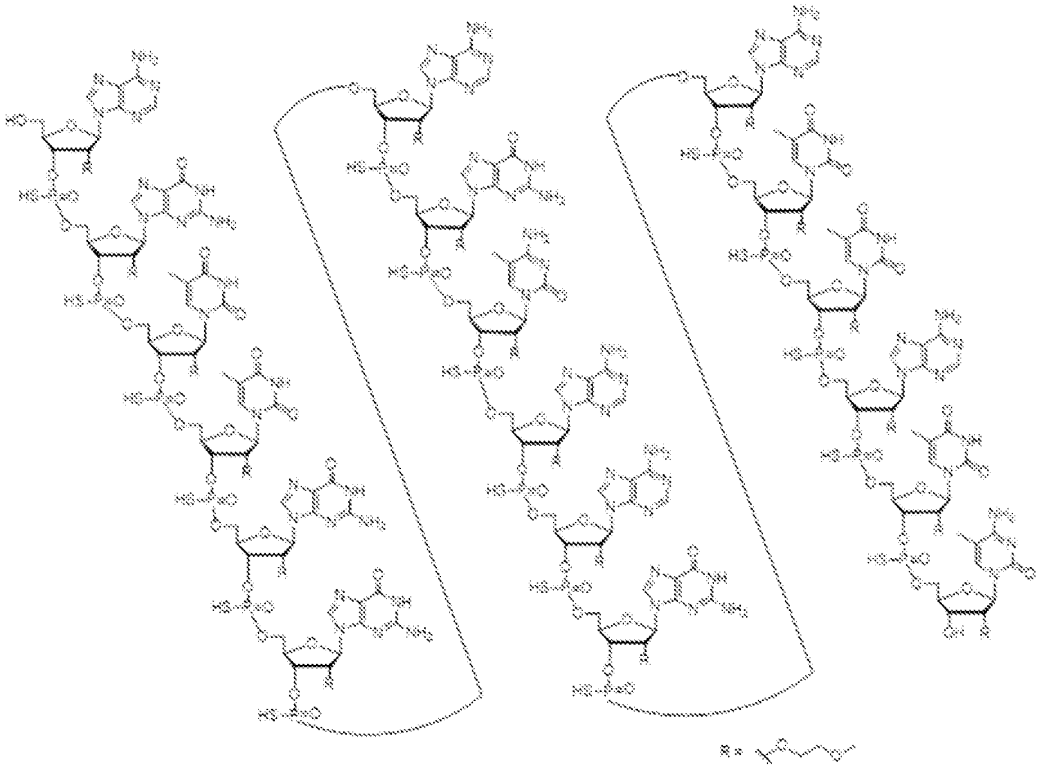
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

169. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

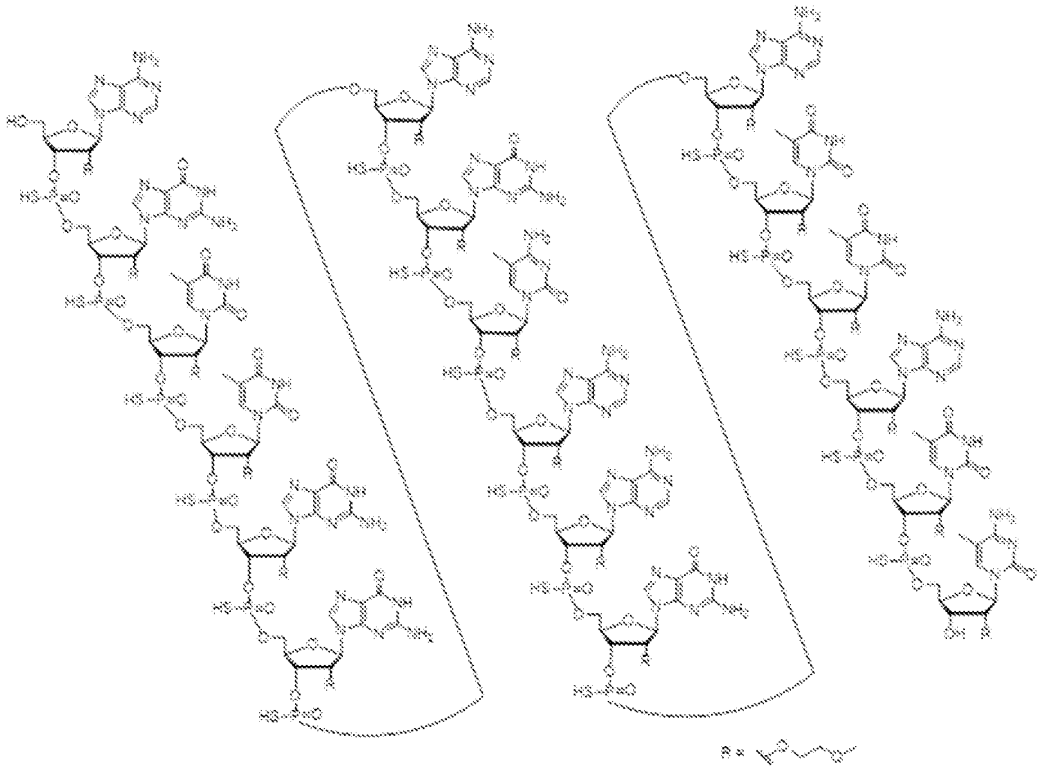
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

170. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

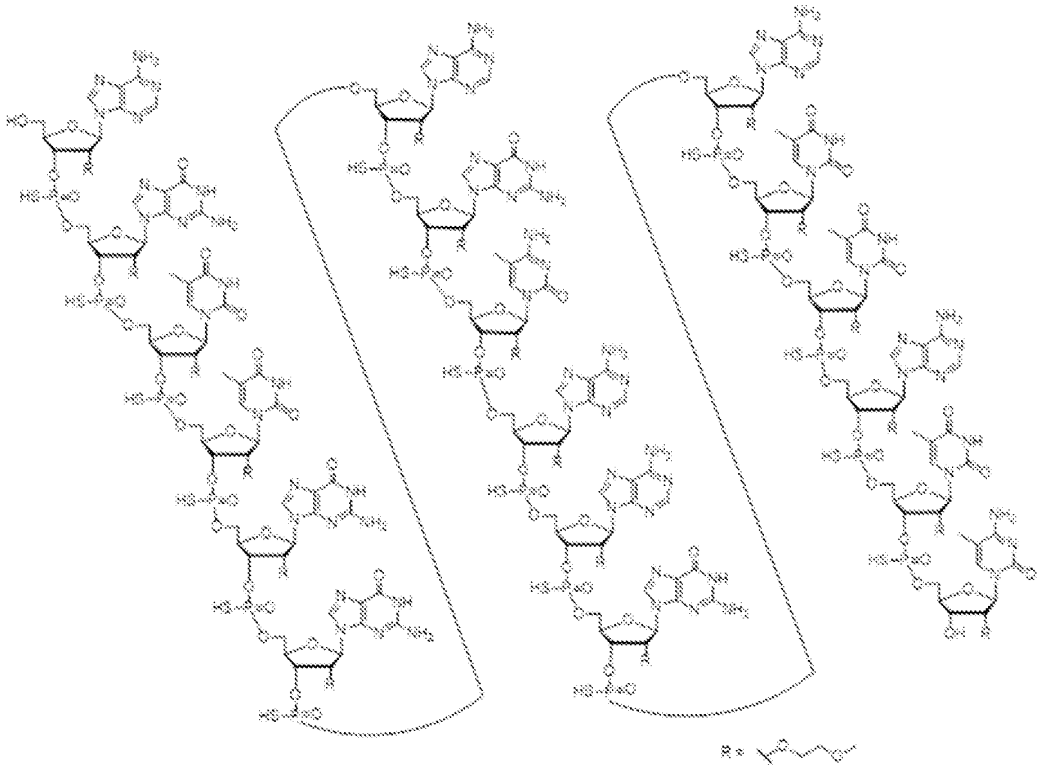
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

171. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

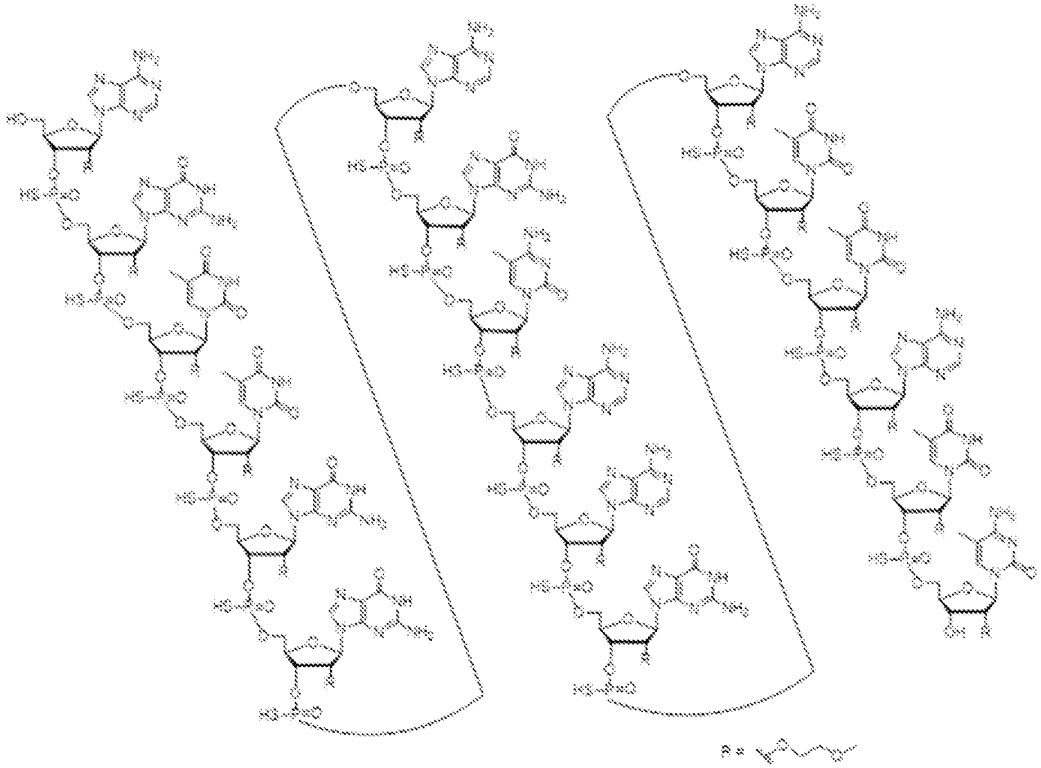
wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 6 months after the third loading dose, and each maintenance after the first maintenance dose is administered

independently about 6 months after a dose immediately preceding the respective maintenance dose.

172. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

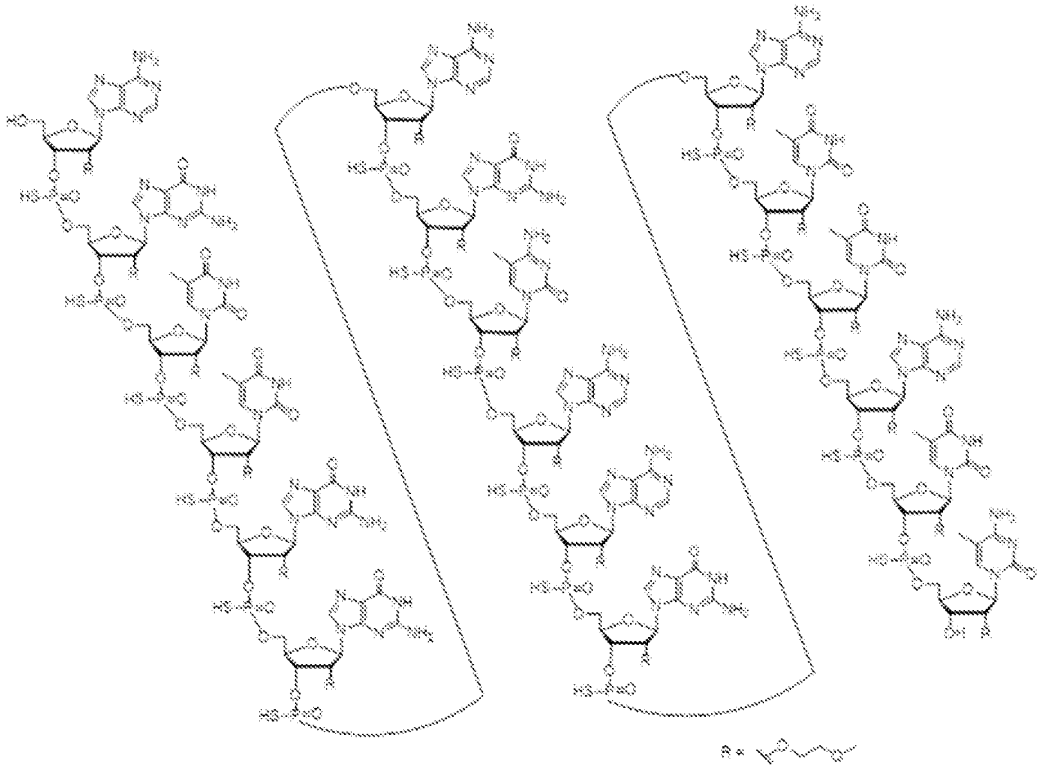
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

173. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

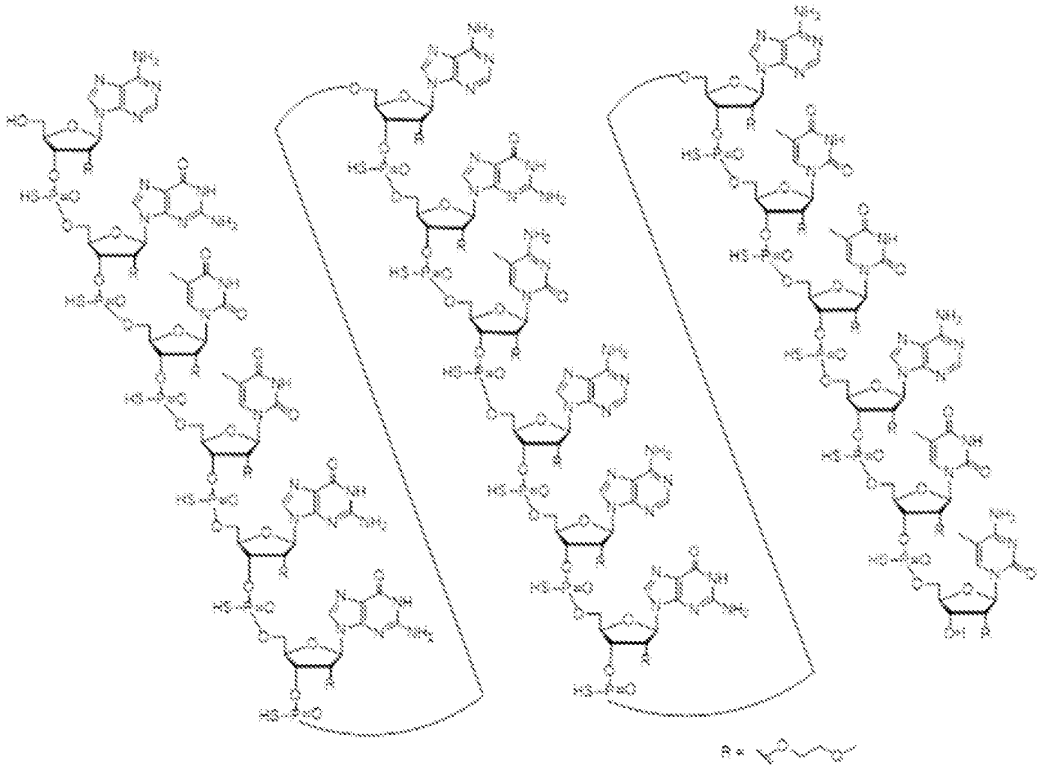
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

174. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

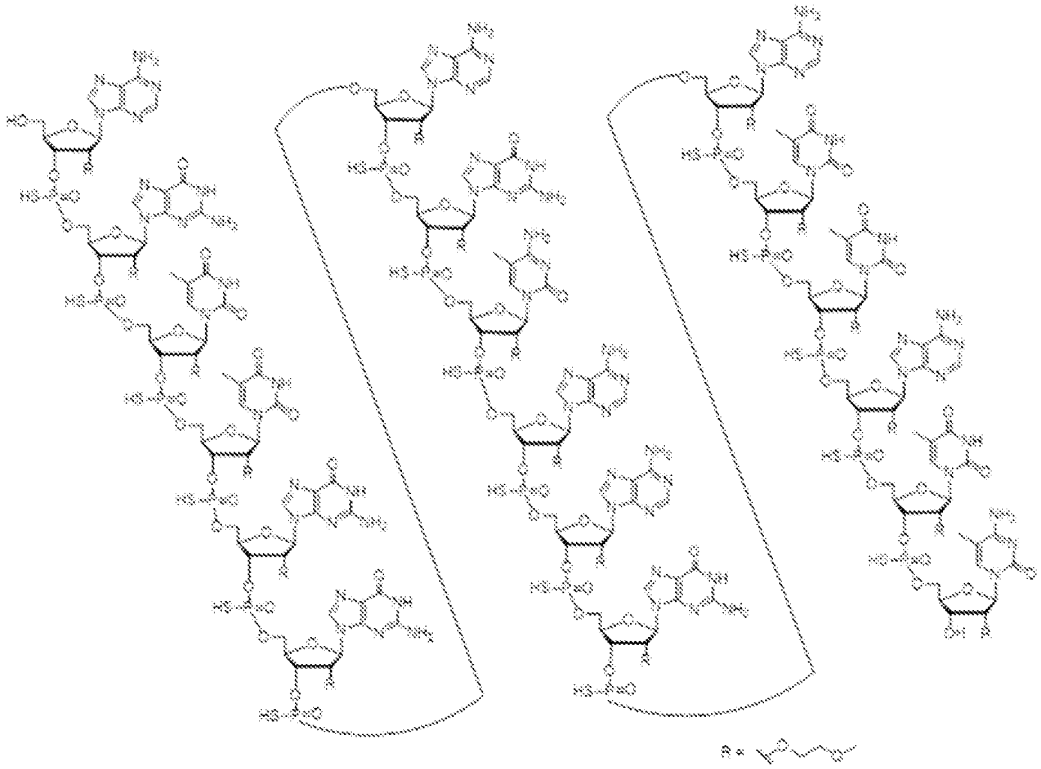
or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the third loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

175. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose,

wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses contains the compound at an amount of from about 30 mg to about 80 mg,

wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered about 6 months after the third loading dose, and each maintenance after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

176. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 30 mg.

177. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 45 mg.

178. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 50 mg.

179. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 60 mg.

180. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses is about 70 mg.

181. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 30 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 25 mg.

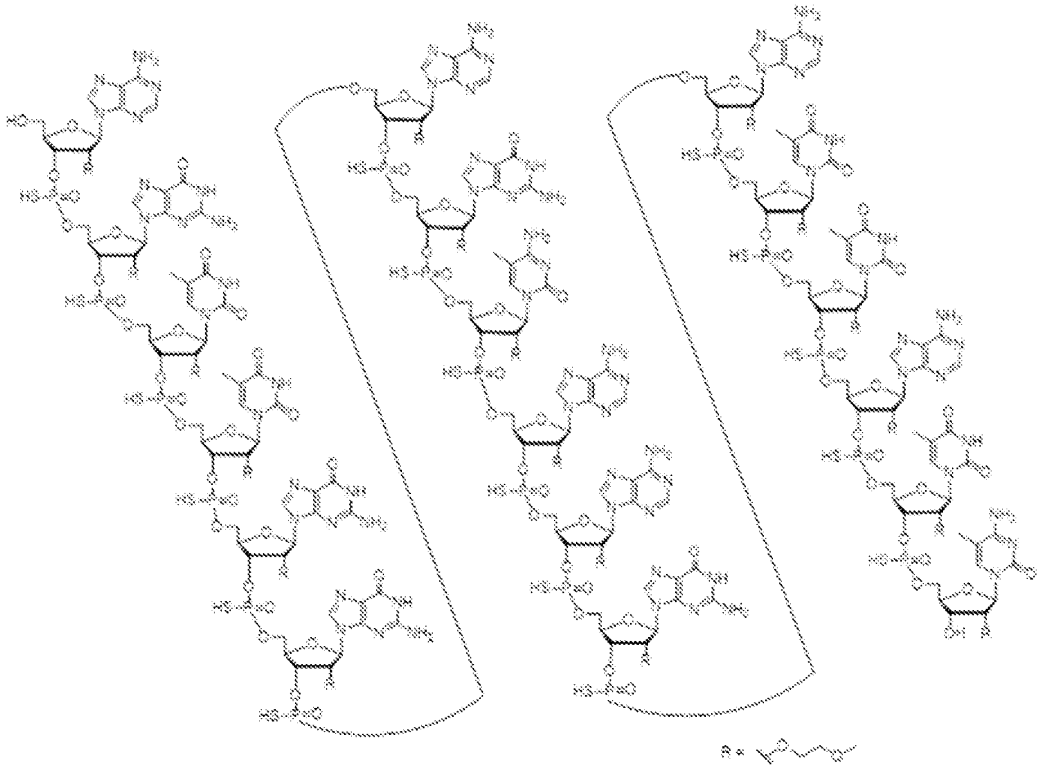
182. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the amount of the compound in each of the first loading dose, the second loading dose, and the third loading dose is about 45 mg, and the first maintenance dose and the one or more maintenance doses is about 40 mg.

183. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 50 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

184. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 60 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

185. The method of any one of claims 168-175, wherein the amount of the compound in each dose of the first loading dose, the second loading dose, and the third loading dose is about 70 mg, and the amount of the compound in each of the first maintenance dose and the one or more maintenance doses is about 45 mg.

186. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

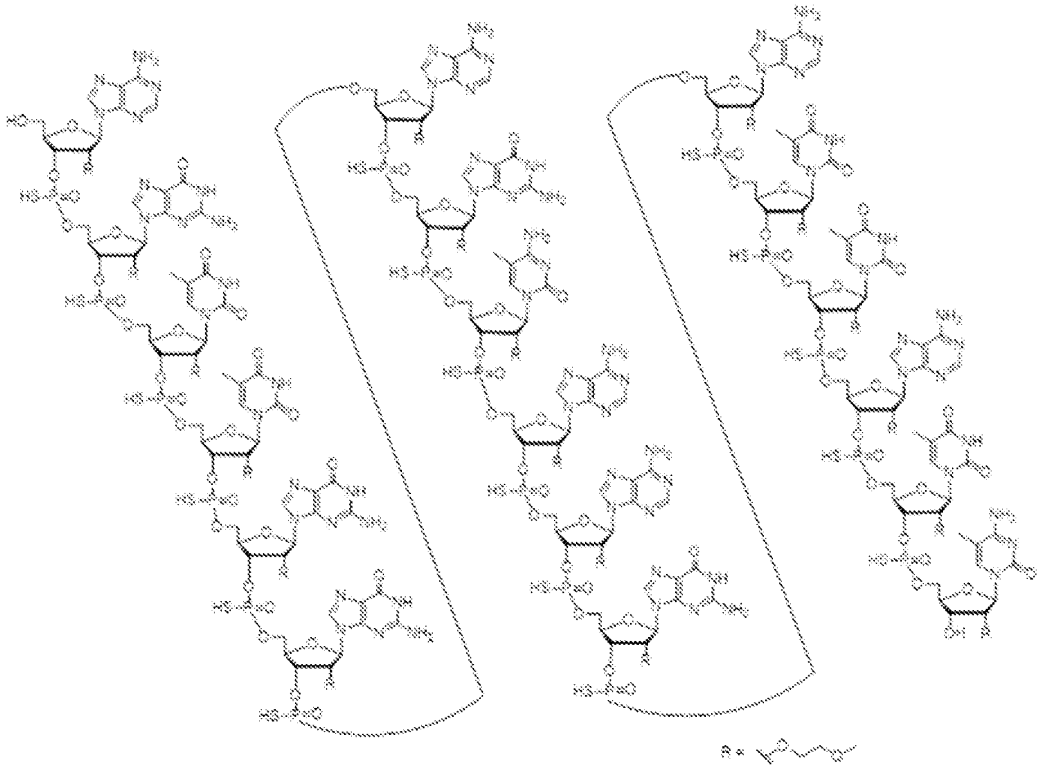


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

187. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

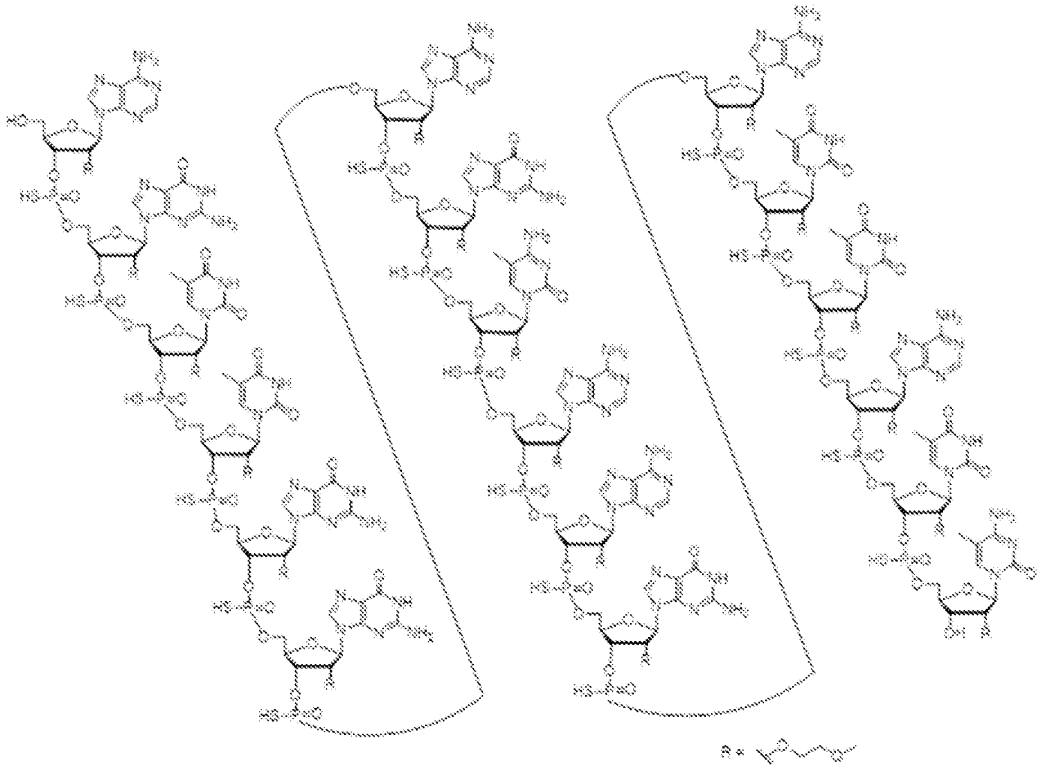


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

188. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

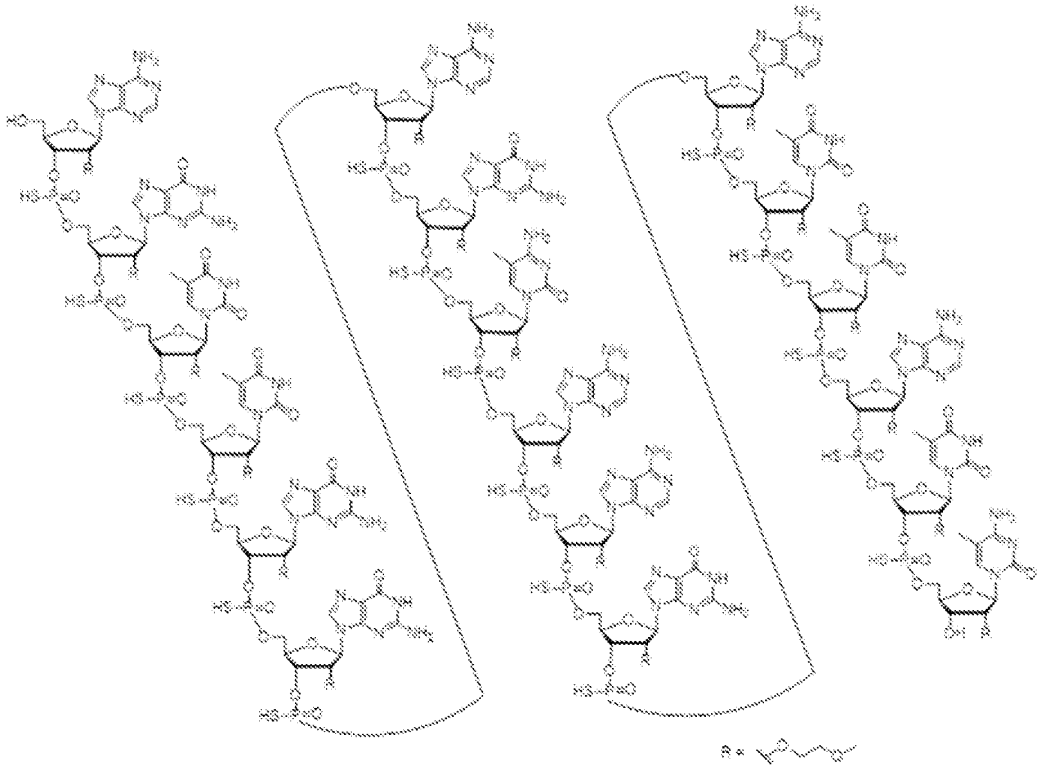


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

189. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

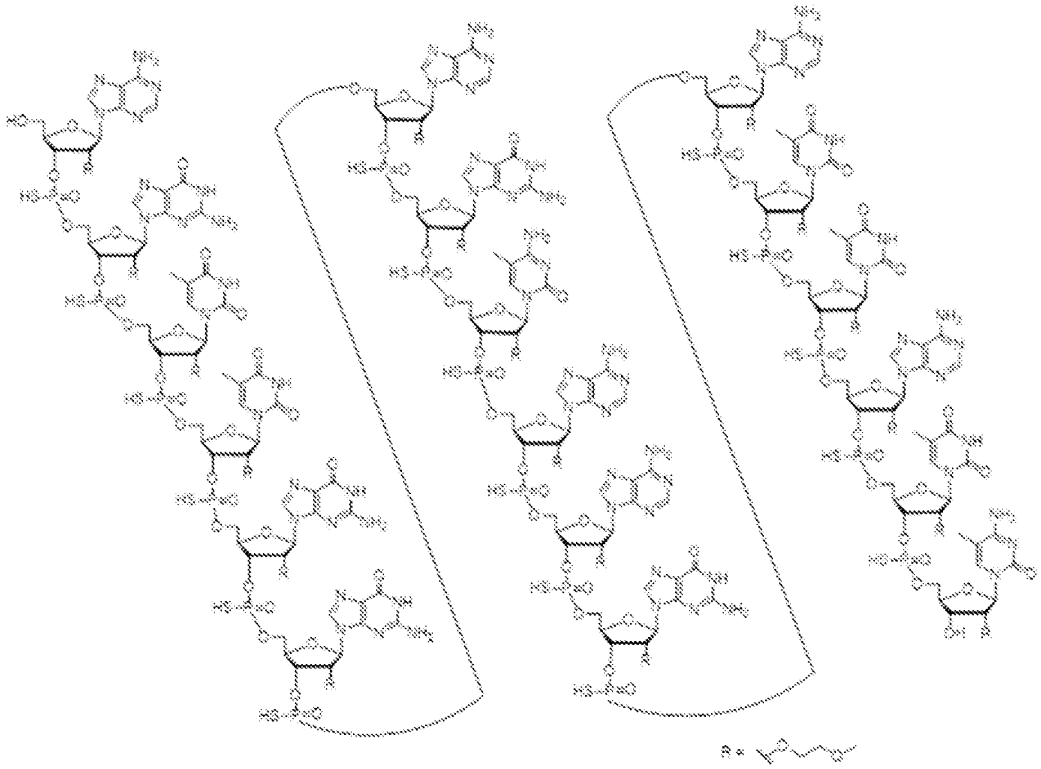


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 6 months after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

190. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

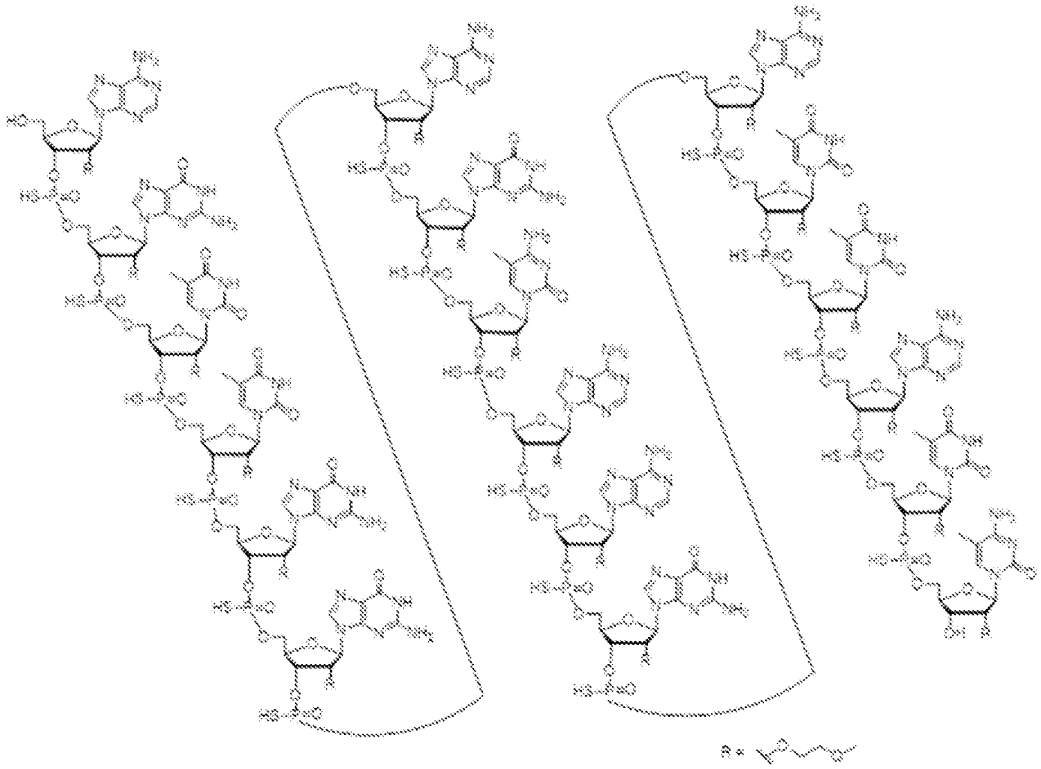


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

191. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

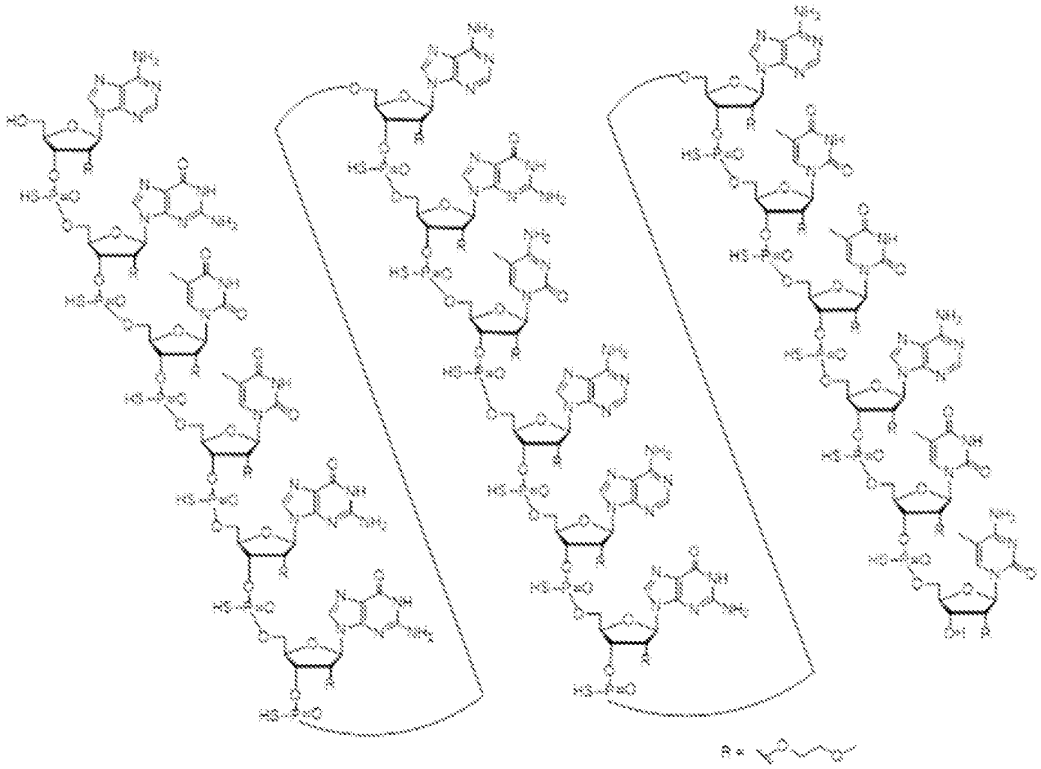


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

192. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

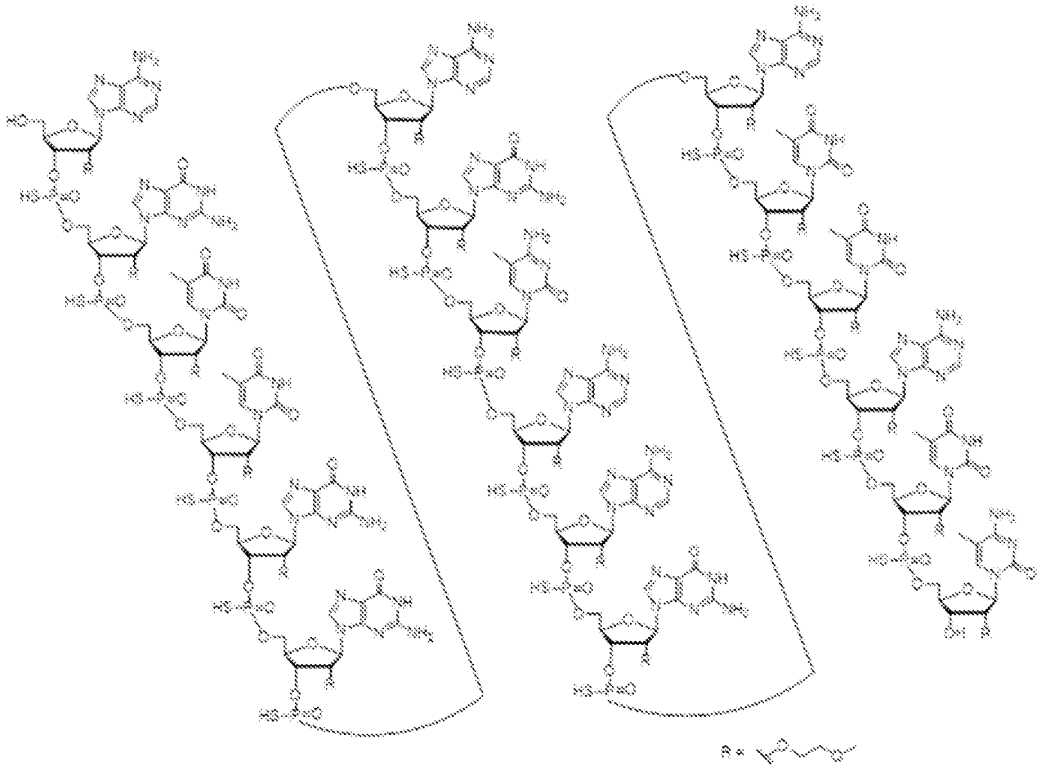


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

193. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

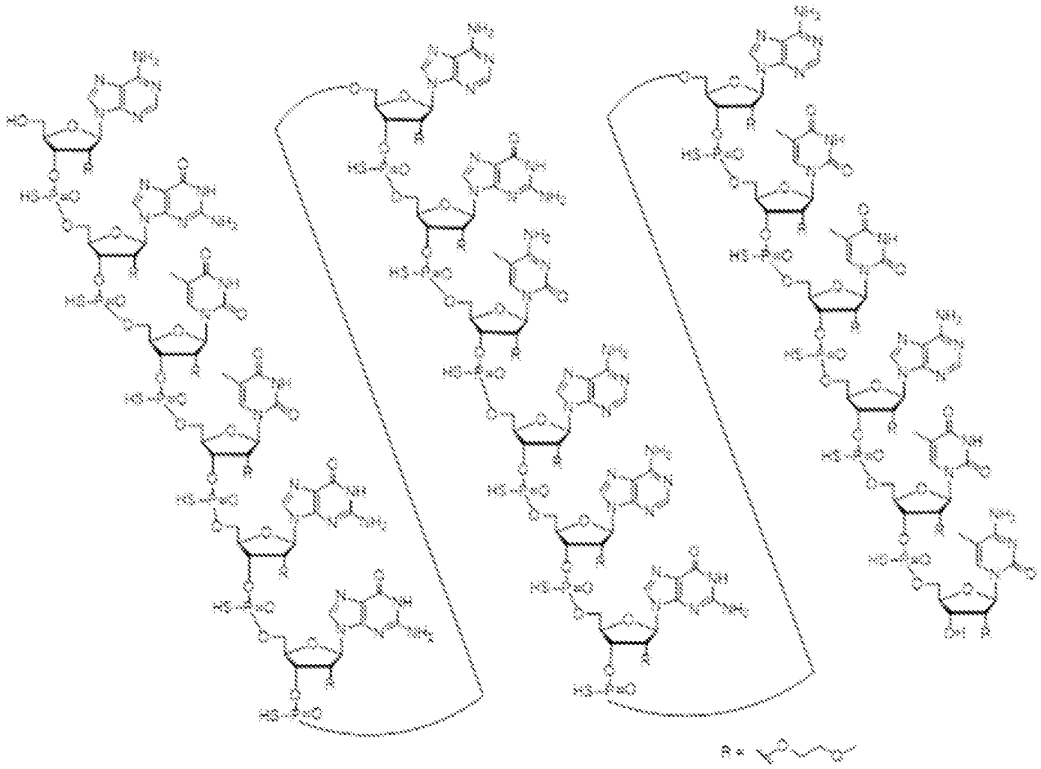


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

194. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

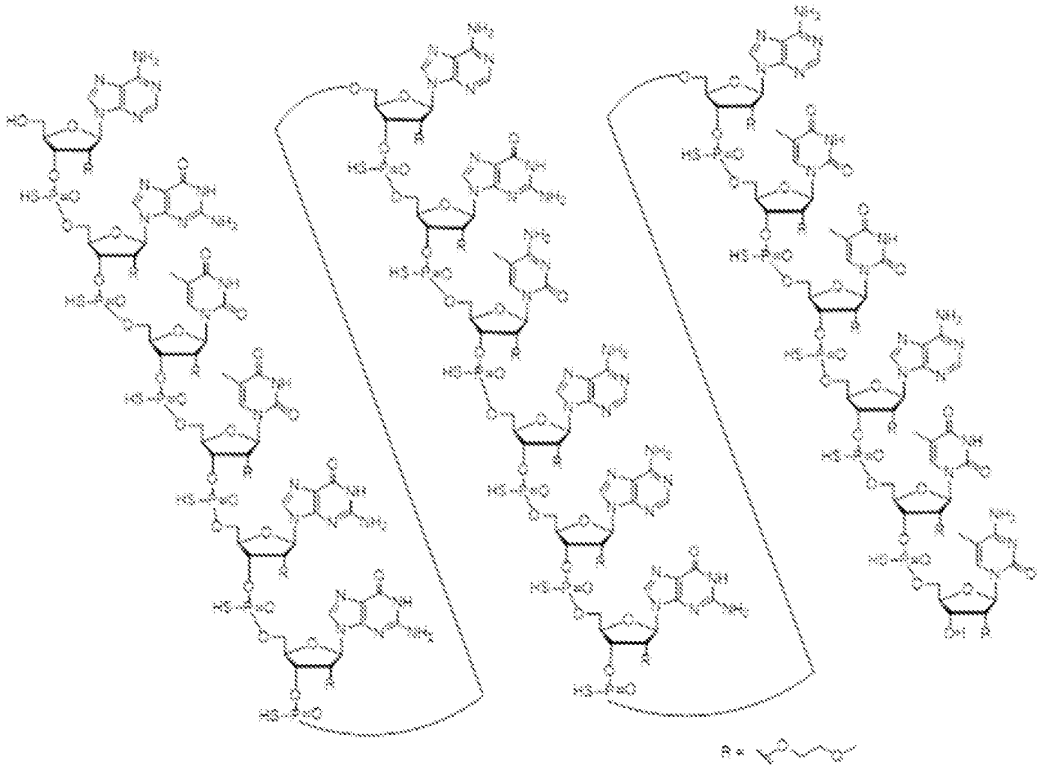


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

195. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

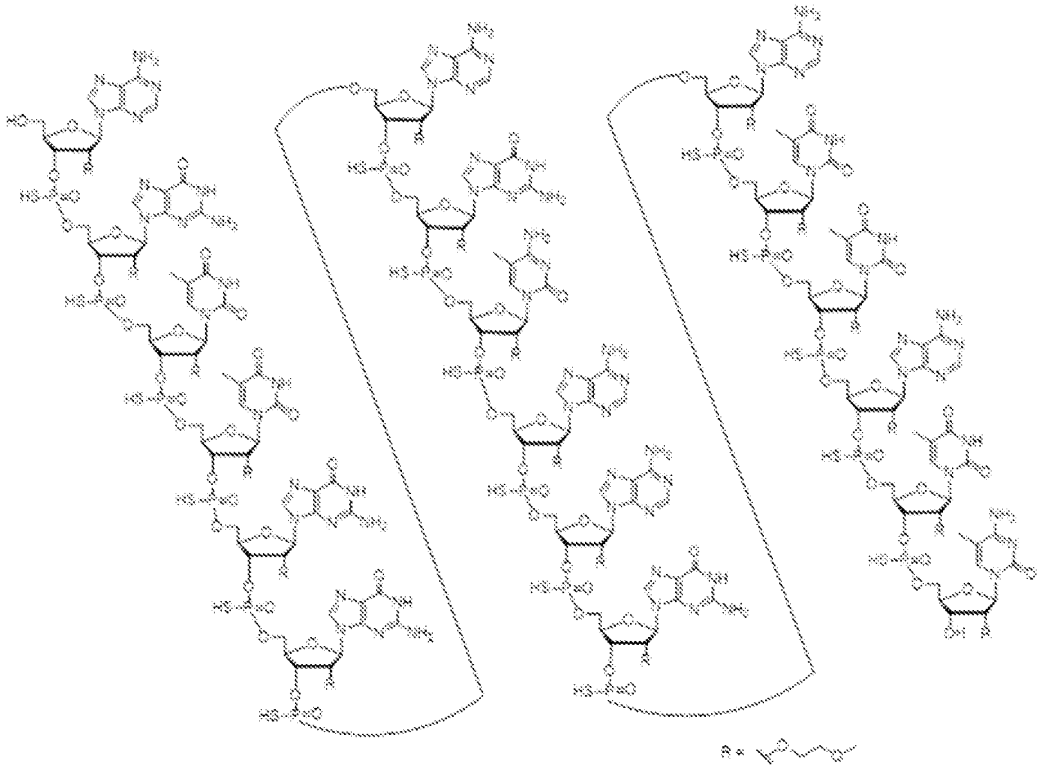


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

196. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

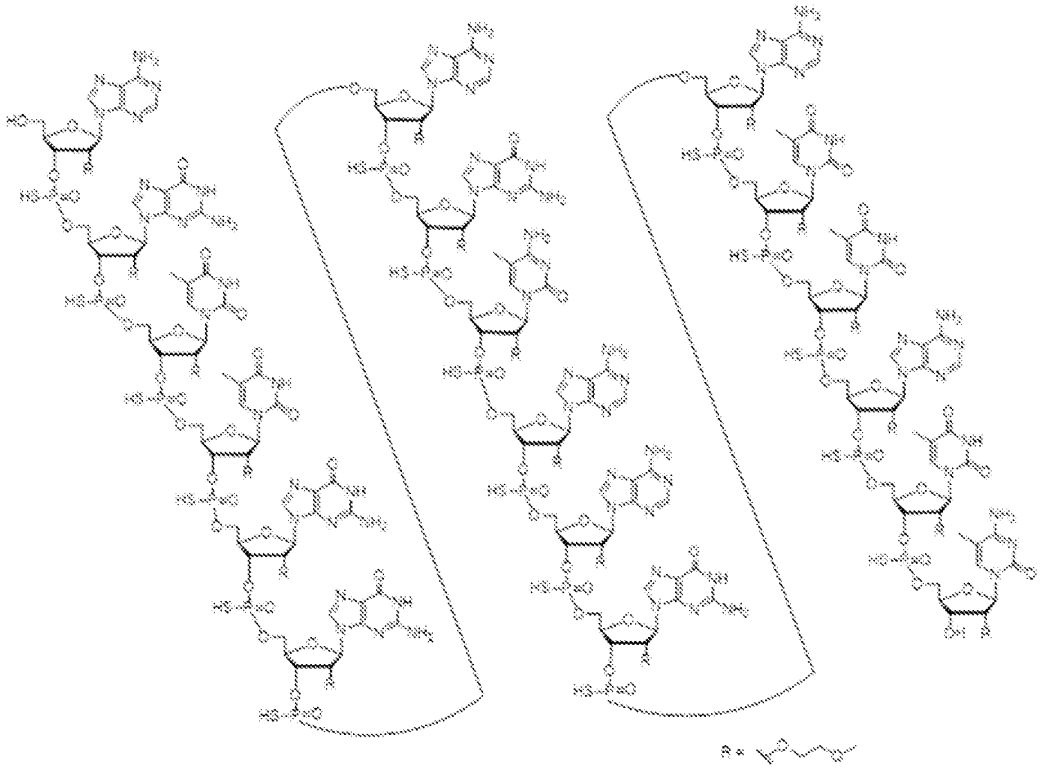


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

197. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

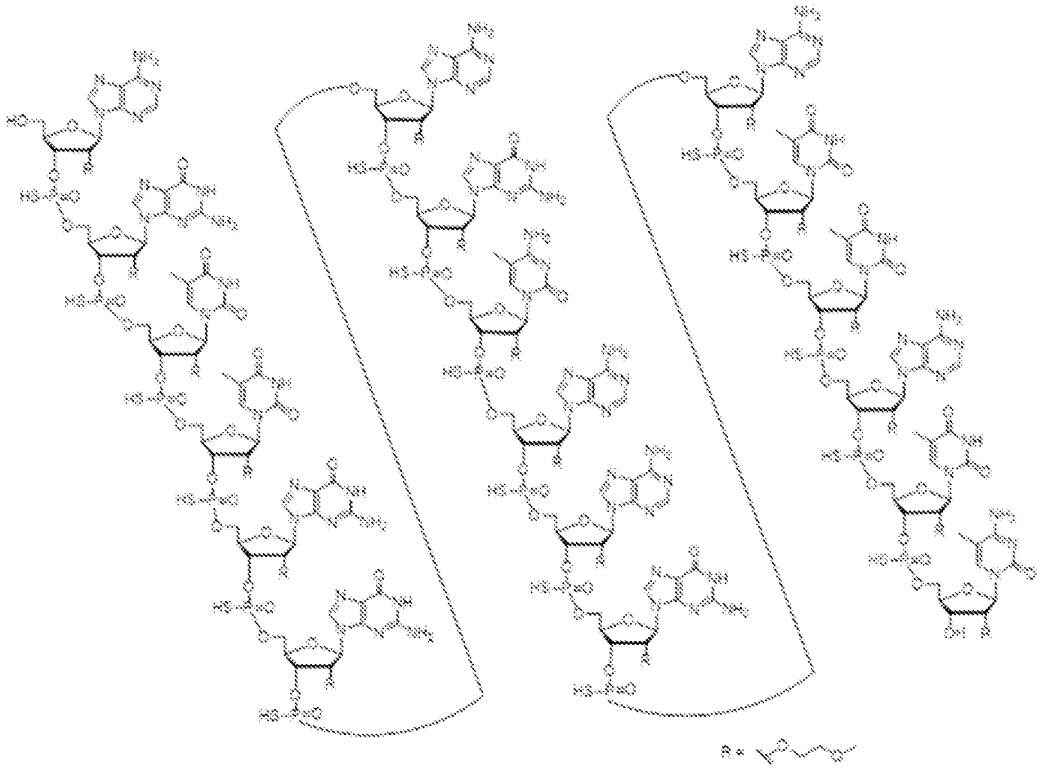


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, the first maintenance dose and the one or more maintenance doses contains the compound at an amount of about 70 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

198. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

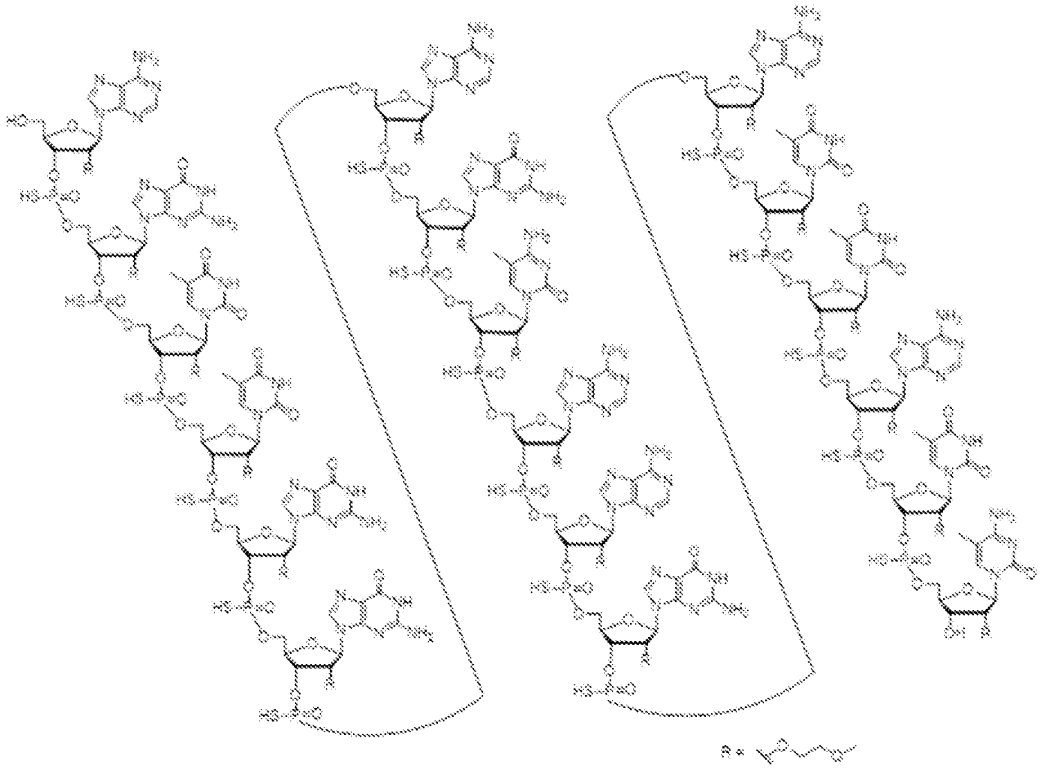


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 12 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

199. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

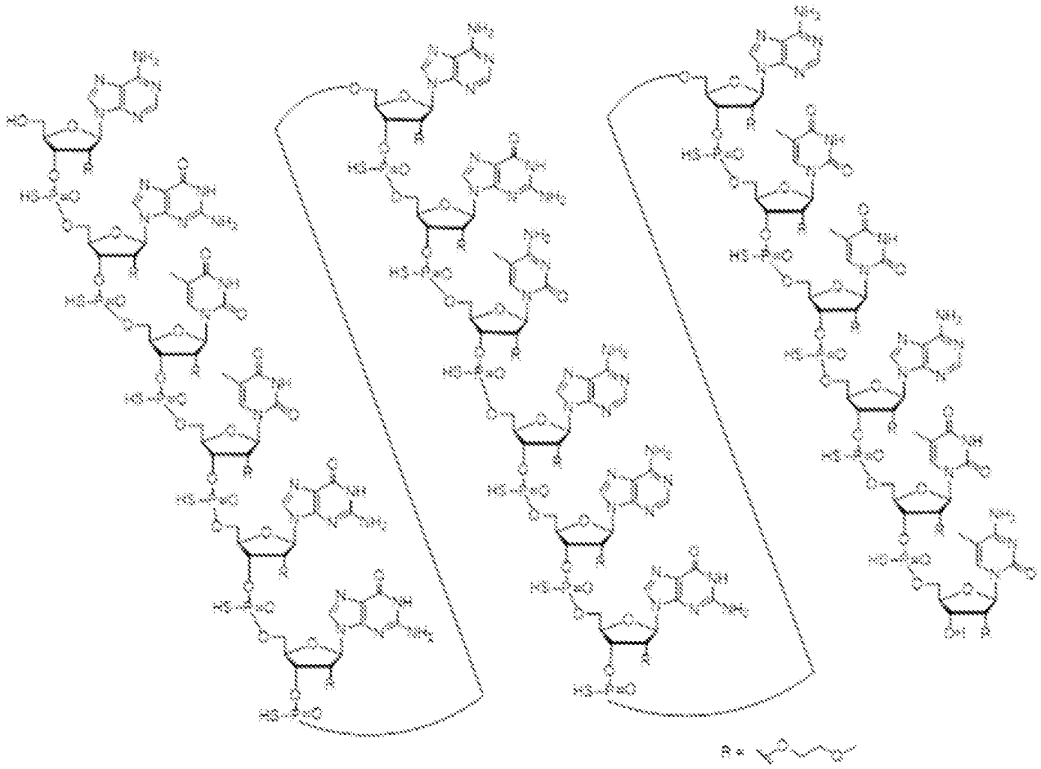


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

200. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

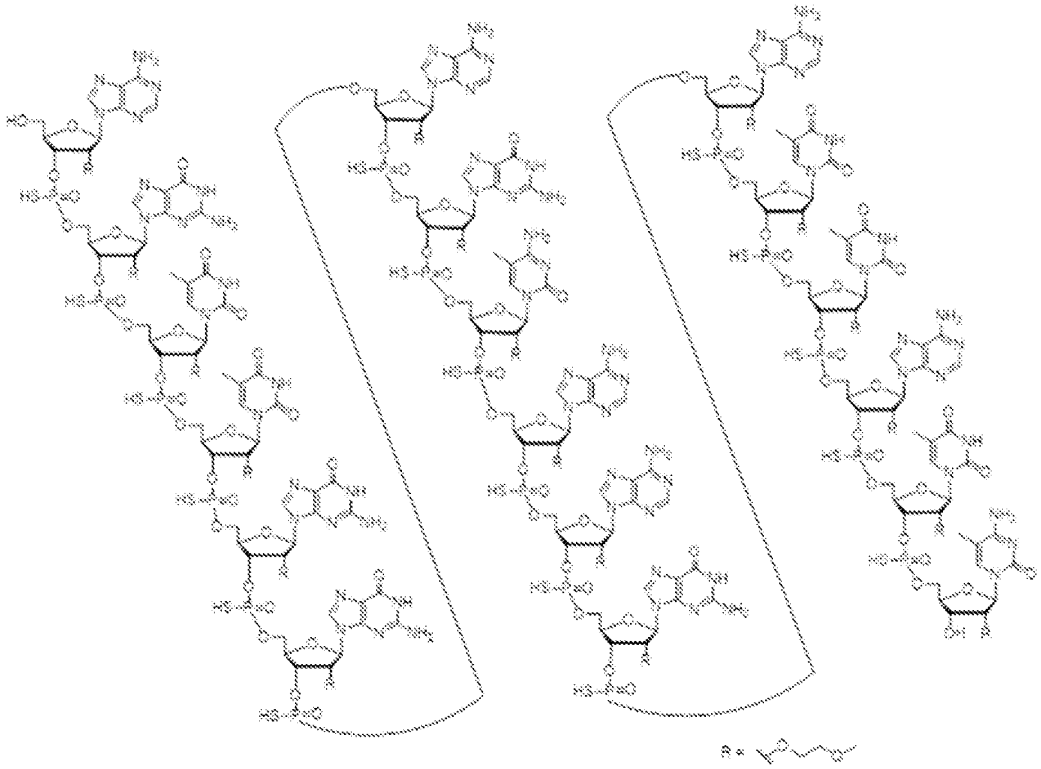


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 20 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

201. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

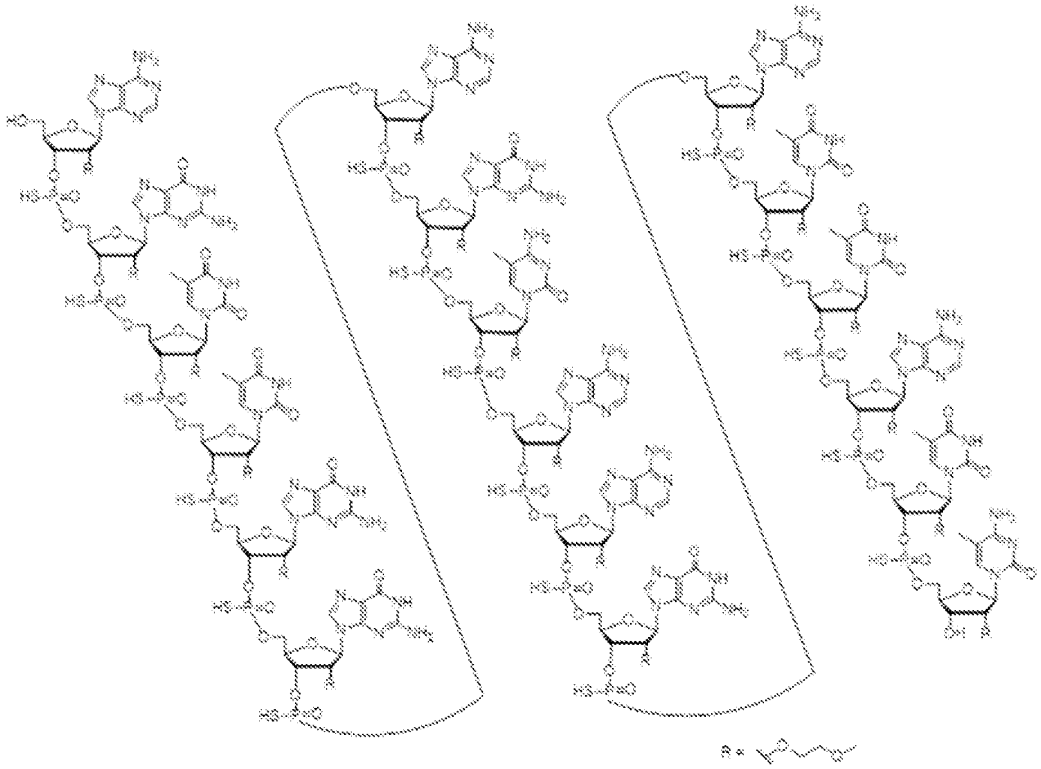


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 6 months after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

202. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

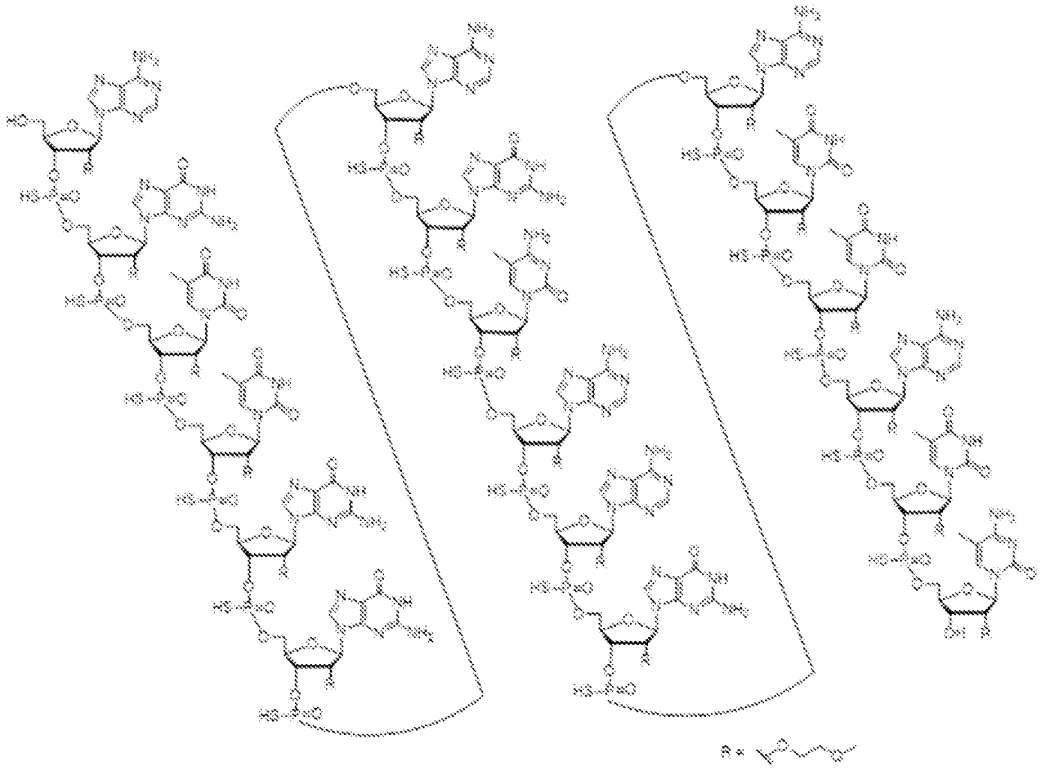


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

203. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

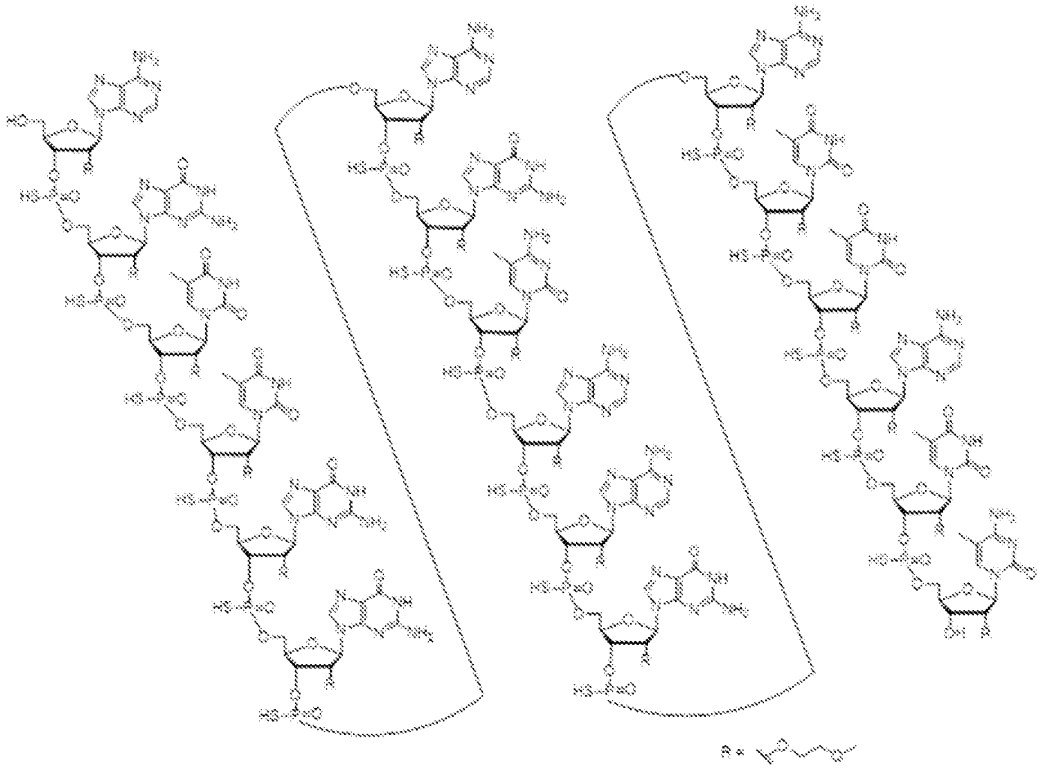


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 8 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

204. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

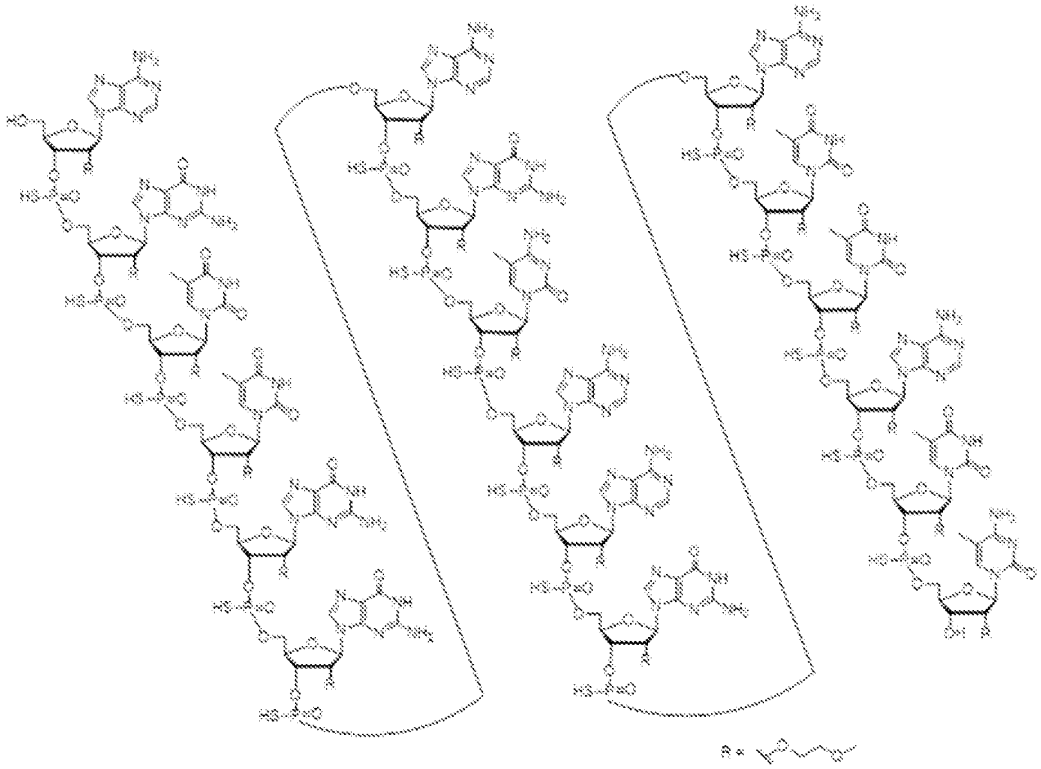


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 10 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

205. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

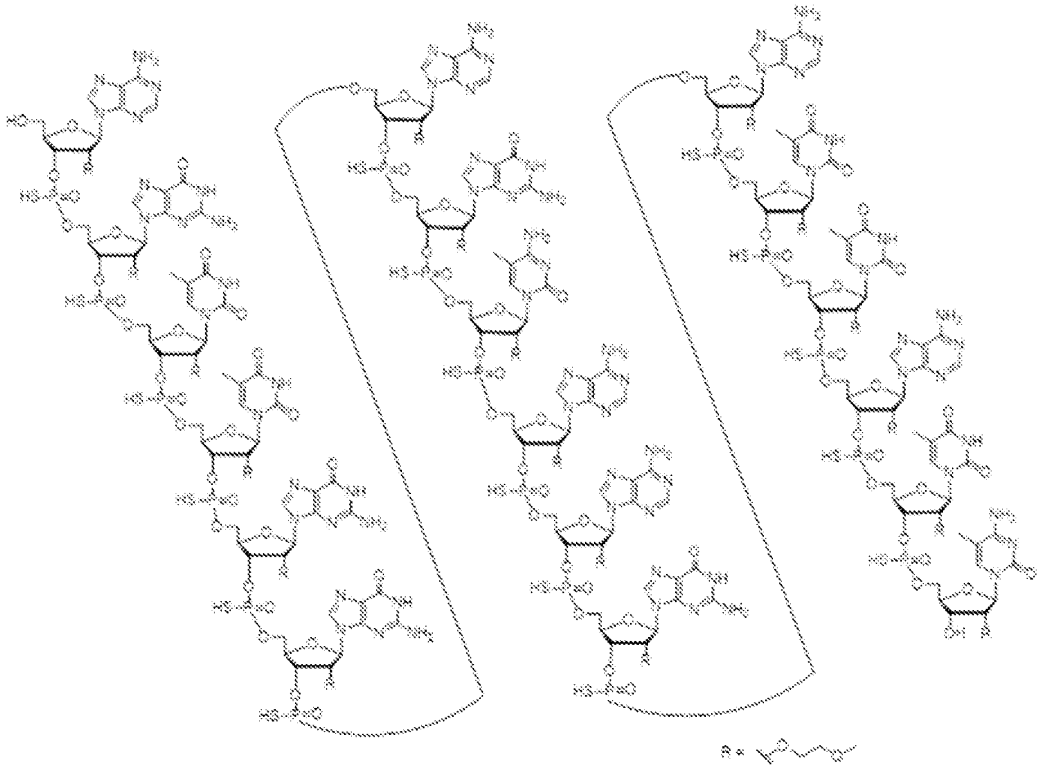


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 12 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

206. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

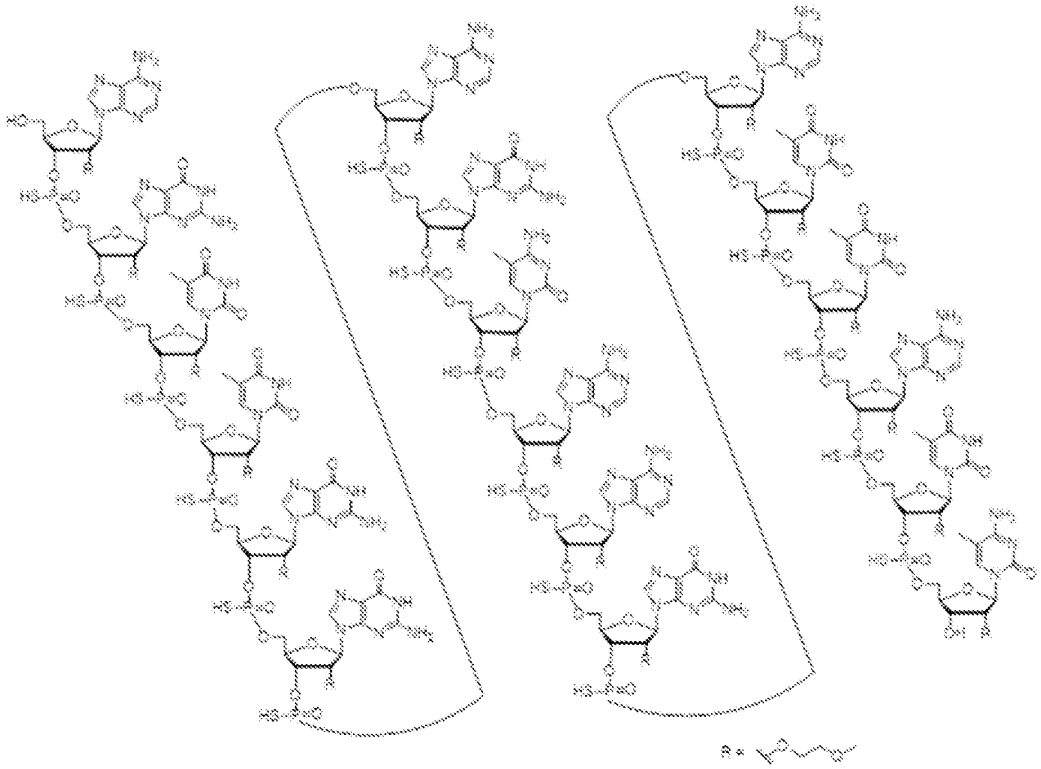


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 6 weeks after the first loading dose, the third loading dose is administered about 3 weeks after the second loading dose, the first maintenance dose is administered about 12 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 12 weeks after a dose immediately preceding the respective maintenance dose.

207. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

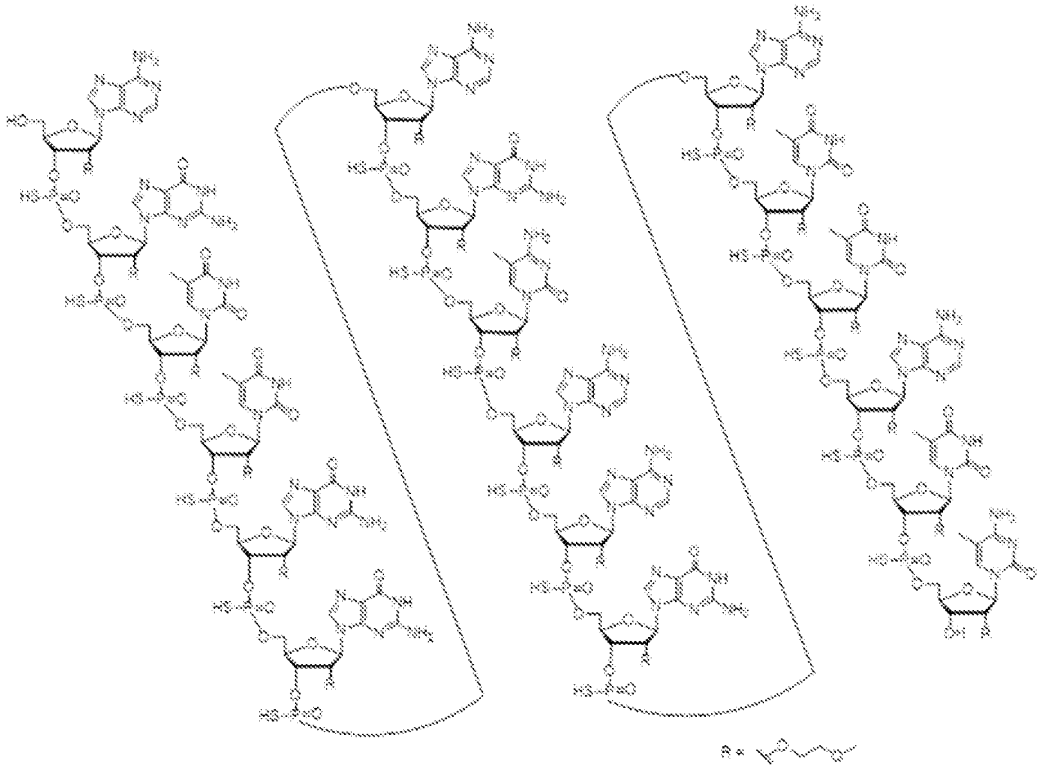


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the third loading dose is administered about 4 weeks after the second loading dose, the first maintenance dose is administered about 16 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

208. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

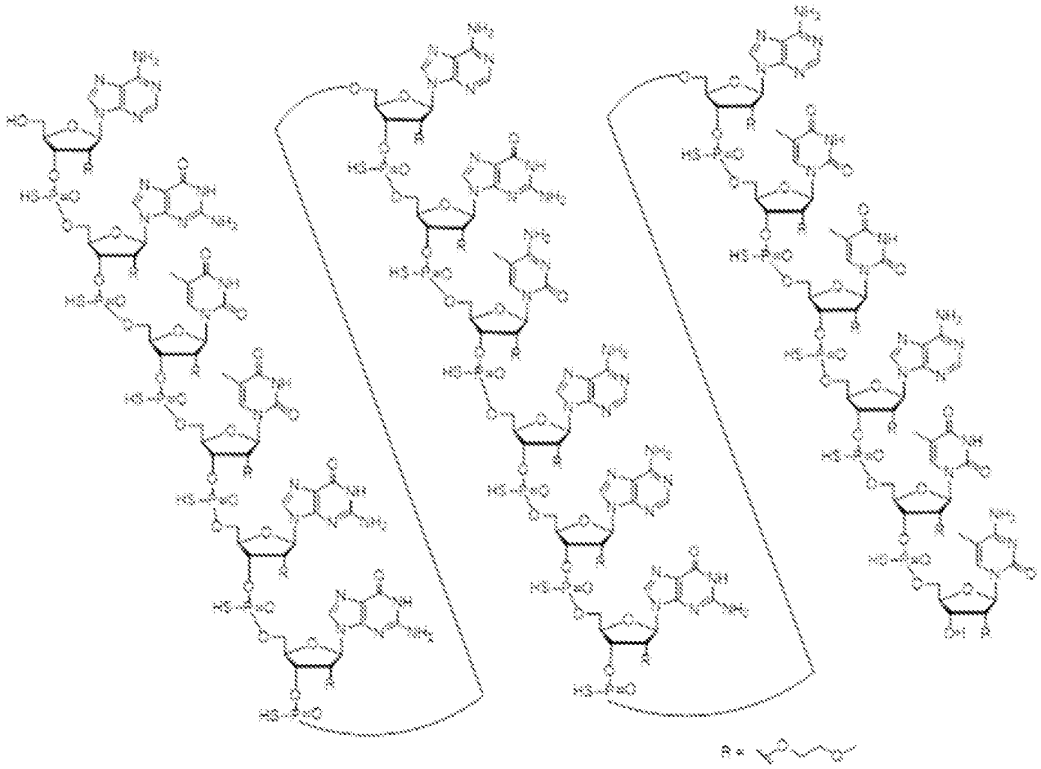


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 10 weeks after the first loading dose, the third loading dose is administered about 5 weeks after the second loading dose, the first maintenance dose is administered about 20 weeks after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 20 weeks after a dose immediately preceding the respective maintenance dose.

209. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:

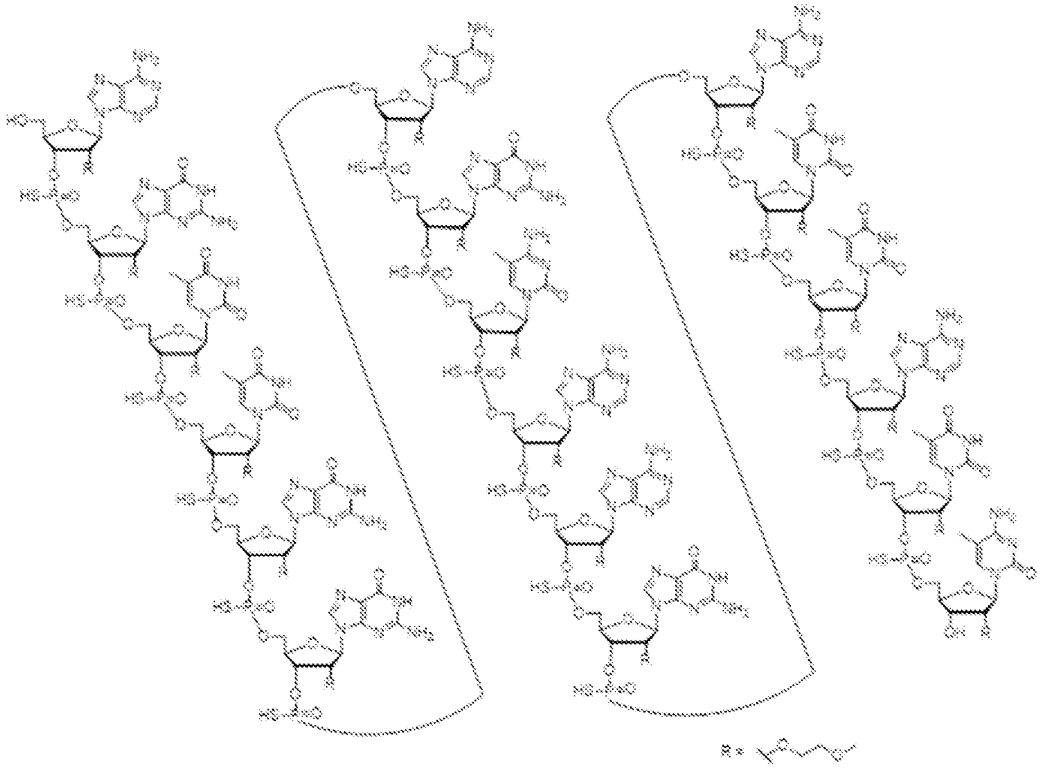


(I),

or a salt thereof,

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, a first maintenance dose following the third loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose, the second loading dose and the third loading dose contains the compound at an amount of about 70 mg, wherein the first maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 12 weeks after the first loading dose, the third loading dose is administered about 6 weeks after the second loading dose, the first maintenance dose is administered about 6 months after the third loading dose, and each maintenance dose of the one or more maintenance doses following the first maintenance dose is administered independently about 6 months after a dose immediately preceding the respective maintenance dose.

210. A dosing regimen for administering a compound according to the following chemical structure:



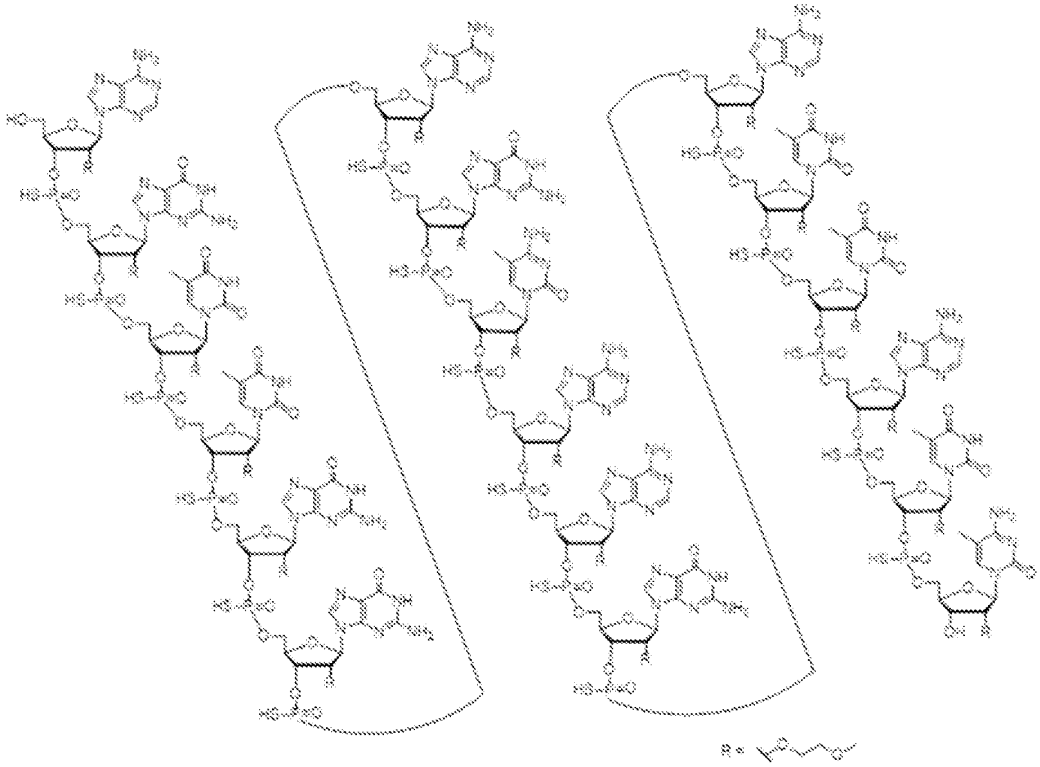
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day of treatment, (b) 4 months after the second loading dose, or (c) 16 weeks after the second loading dose.

211. A dosing regimen for administering a compound according to the following chemical structure:



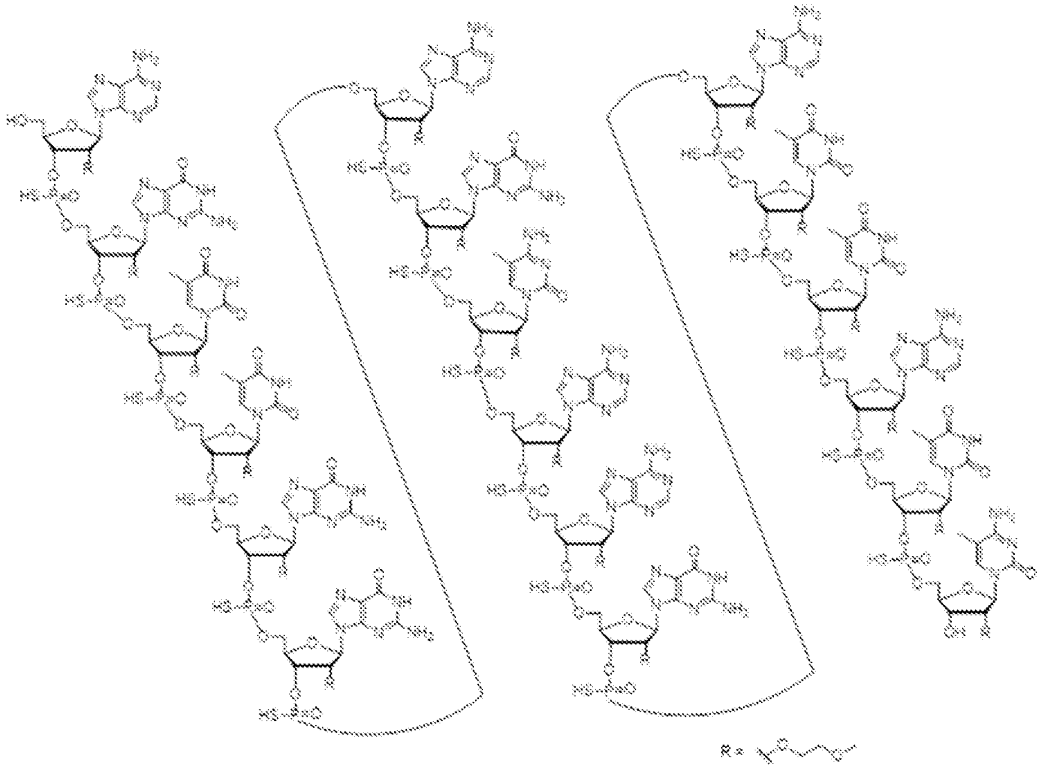
(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 169th day of treatment, (b) 4 months after the second loading dose, or (c) 16 weeks after the second loading dose.

212. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

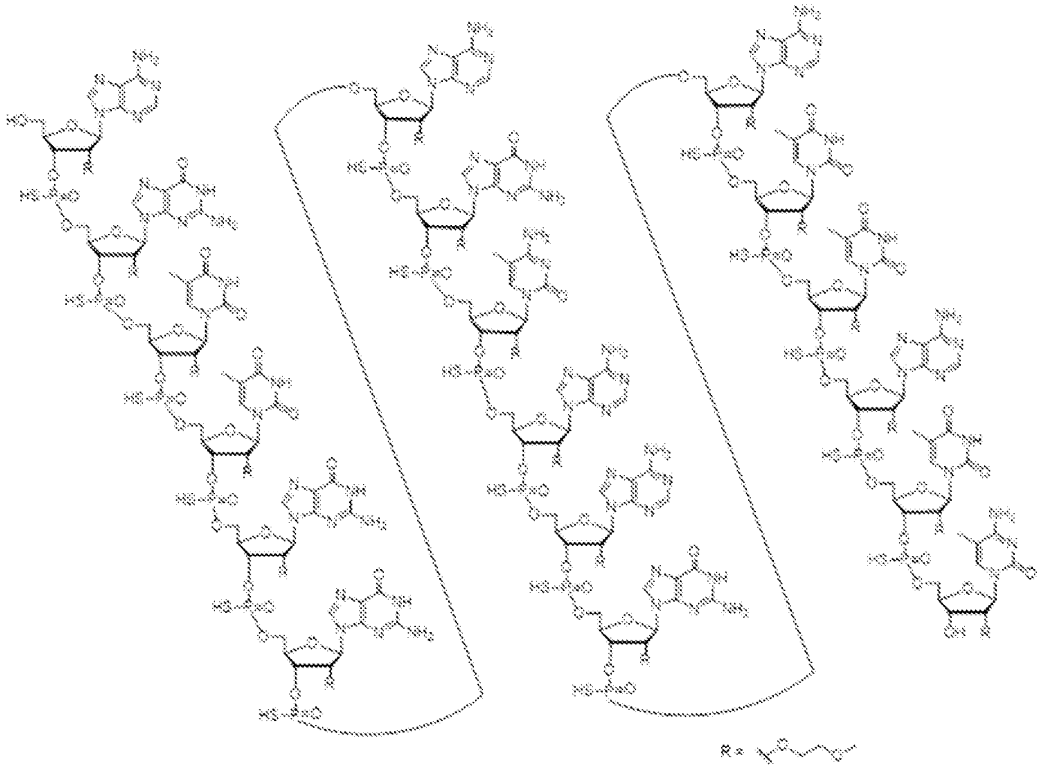
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day of treatment, (b) 1 month after the second loading dose, or (c) 4 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

213. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

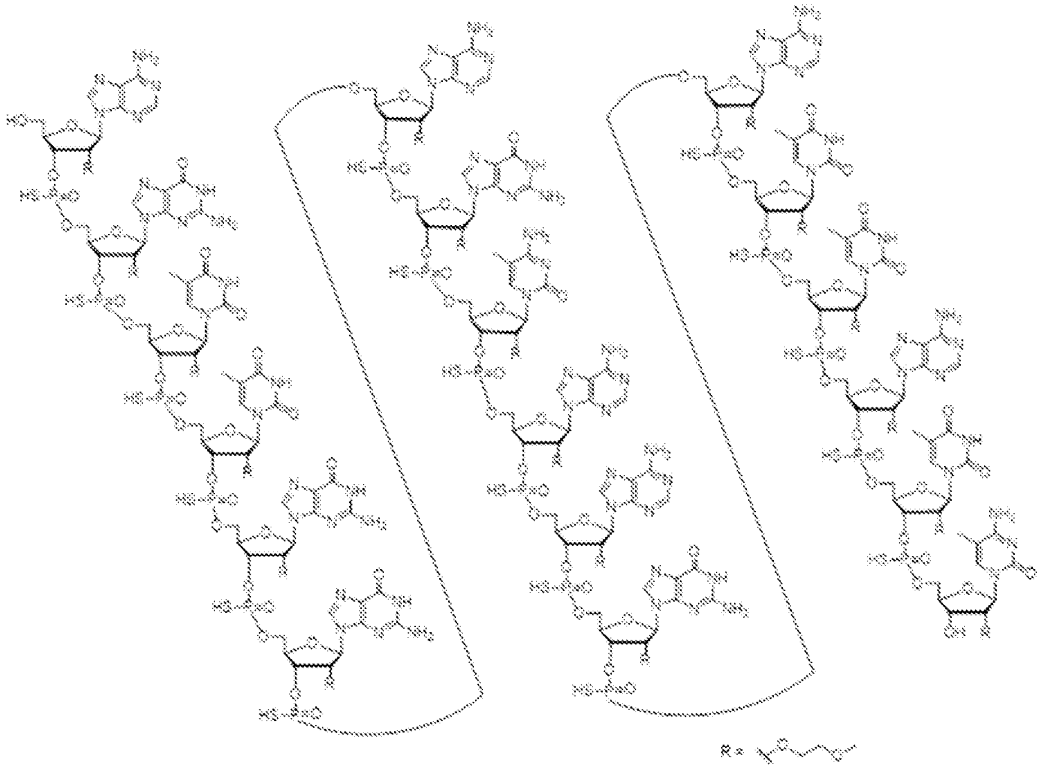
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 85th day of treatment, (b) 1 month after the second loading dose, or (c) 4 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 197th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

214. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

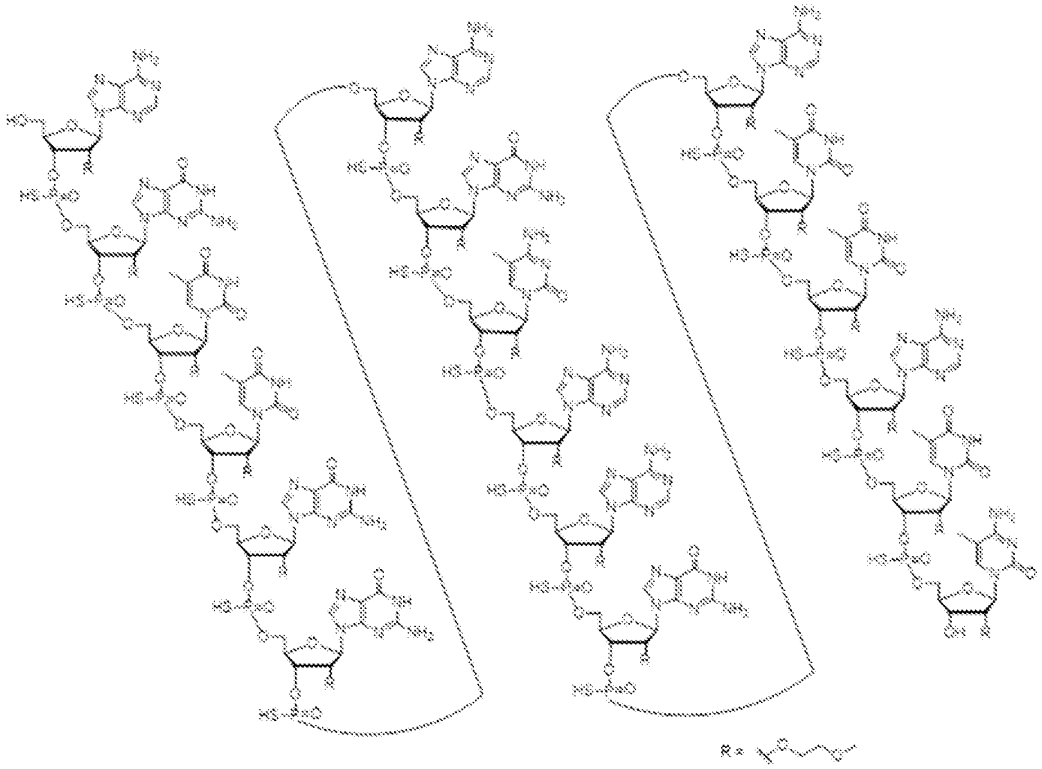
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day of treatment, (b) 2 months after the second loading dose, or (c) 8 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

215. A dosing regimen for administering a compound according to the following chemical structure:



(I), or a salt thereof to a human subject in need of treatment for a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein, wherein the dosing regimen comprises:

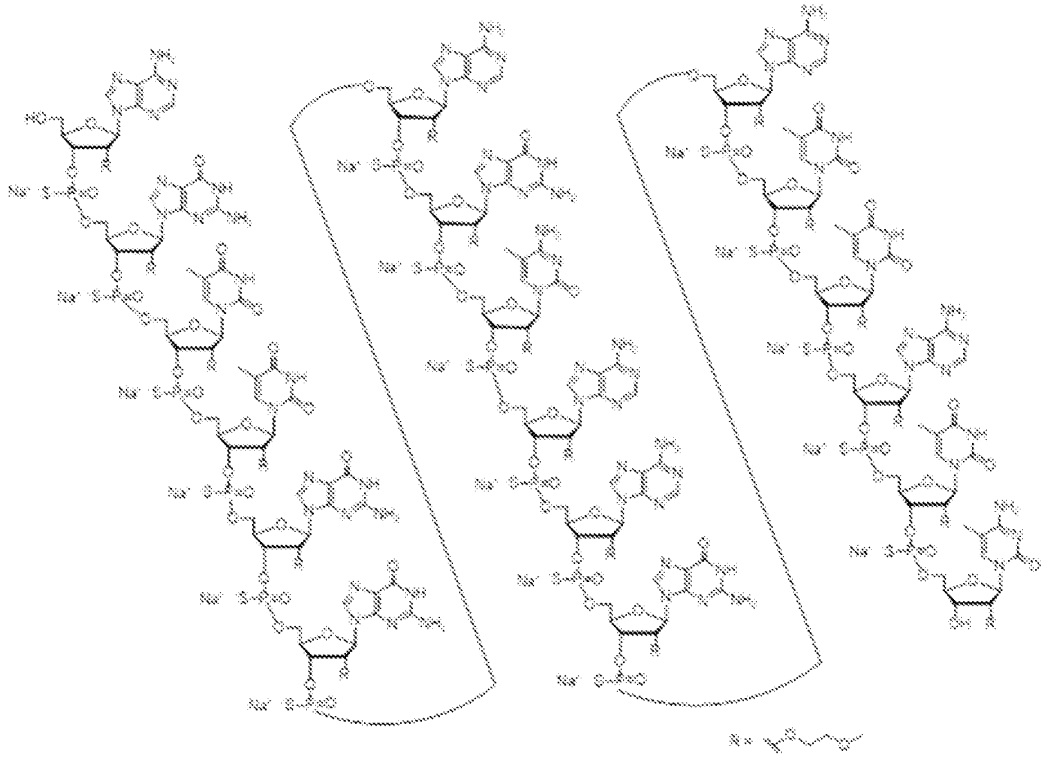
administering to the human subject a first loading dose of from about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition on the first day of treatment;

administering to the human subject a second loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 57th day of treatment, (b) 2 months after the first loading dose, or (c) 8 weeks after the first loading dose;

administering to the human subject a third loading dose of about 70 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 113th day of treatment, (b) 2 months after the second loading dose, or (c) 8 weeks after the second loading dose; and

administering to the human subject a first maintenance dose of about 45 mg of the compound of formula (I) or a salt thereof in a pharmaceutical composition (a) on the 225th day of treatment, (b) 4 months after the third loading dose, or (c) 16 weeks after the third loading dose.

216. The method of any one of claims 154-209 or the dosing regimen of any one of claims 210-215, wherein the compound has the following structure:



(II).

217. The method of any one of claims 1, 2, 10-209, and 216 or the dosing regimen of any one of claims 3-153 and 210-216, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient, carrier, or diluent.

218. The method of any one of claims 1, 2, 10-209, and 216 or the dosing regimen of any one of claims 3-153 and 210-217, wherein the pharmaceutical composition is a liquid composition.

219. The method or the dosing regimen of claim 218, wherein the pharmaceutical composition comprises from 0.1 mL to 50 mL of a diluent, and wherein the compound is solubilized or diluted in the diluent.

220. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 0.1 mL, 0.5 mL, 1 mL, 2 mL, 2.5 mL, 3 mL, 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, 10 mL, 11 mL, 12 mL, 13 mL, 14 mL, 15 mL, 16 mL, 17 mL, 18 mL, 19 mL, 20 mL, 25 mL, 30 mL, 35 mL, 40 mL, 45 mL, or 50 mL of the diluent.

221. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises 1 mL to 20 mL of the diluent, 2 mL to 10 mL of the diluent, or 1 mL to 5 mL of the diluent.

222. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises at least 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, or 10 mL of the diluent.

223. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, or 10 mL of the diluent.
224. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 4 mL of the diluent.
225. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 7 mL of the diluent.
226. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 9 mL of the diluent.
227. The method or the dosing regimen of any one of claims 217-219, wherein the pharmaceutical composition comprises about 10 mL of the diluent.
228. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of 10 mL or higher.
229. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of 5 mL or higher.
230. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 10 mL.
231. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 15 mL.
232. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 20 mL.
233. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 25 mL.
234. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and the first loading dose has volume of about 30 mL.
235. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of 5 mL or higher.
236. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of 10 mL or higher.
237. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 5 mL.
238. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 10 mL.

239. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 15 mL.
240. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 20 mL.
241. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 25 mL.
242. The method or the dosing regimen of any one of claims 217-219, wherein the compound is dissolved or diluted in the diluent and each maintenance dose of the one or more maintenance doses has a volume of about 30 mL.
243. The method or the dosing regimen of any one of claims 217-242, wherein the diluent comprises a cerebral spinal fluid (CSF) sample from the subject or an artificial cerebral spinal fluid (aCSF) solution.
244. The method or the dosing regimen of claim 243, wherein the diluent is the aCSF solution that lacks sodium phosphate.
245. The method or the dosing regimen of claim 243, wherein each dose of the pharmaceutical composition comprises 10 mL of the diluent.
246. The method or the dosing regimen of any one of claims 217-245, wherein the diluent is an isotonic solution.
247. The method or the dosing regimen of any one of claims 217-245, wherein the diluent is a solution with at least pH 5.8.
248. The method or the dosing regimen of any one of claims 217-245, wherein the diluent is a solution with pH 6.6 – 7.6.
249. The method or the dosing regimen of any one of claims 217-248, wherein the diluent is a buffer comprising 25-250 mM NaCl.
250. The method or the dosing regimen of any one of claims 217-249, wherein the diluent is a buffer comprising 0.1-20 mM KCl.
251. The method or the dosing regimen of any one of claims 217-243 and 245-250, wherein the diluent is a buffer comprising 0.1-50 mM Na_2HPO_4.
252. The method or the dosing regimen of any one of claims 217-243 and 245-250, wherein the diluent is a buffer comprising 0.1-50 mM NaH_2PO_4.
253. The method or the dosing regimen of any one of claims 217-252, wherein the diluent is a buffer comprising 0.1-50 mM $CaCl_2$.
254. The method or the dosing regimen of any one of claims 217-253, wherein the diluent is a buffer comprising 0.1-50 mM $MgCl_2$.

255. The method or the dosing regimen of any one of claims 217-243 and 245-254, wherein the diluent is a buffer comprising 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 0.79 mM $MgCl_2$, and 1.4 mM $CaCl_2$.

256. The method or the dosing regimen of any one of claims 217-255, wherein the diluent is a buffer further comprising 1-100 mM $NaHCO_3$, 1-100 mM $KHCO_3$, or a combination thereof.

257. The method or the dosing regimen of any one of claims 217-256, wherein the diluent further comprises carbohydrates.

258. The method or the dosing regimen of claim 257, wherein the carbohydrates comprise D-glucose.

259. The method or the dosing regimen of claim 257, wherein the diluent comprises 1-100 mM D-glucose.

260. The method of any one of claims 1, 2, 10-209, and 216-259 or the dosing regimen of any one of claims 3-153, and 210-259, wherein the pharmaceutical composition comprises 0.1-50 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

261. The method or the dosing regimen of claim 260, wherein the pharmaceutical composition comprises 1-2 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

262. The method or the dosing regimen of claim 260, wherein the pharmaceutical composition comprises about 1.4 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

263. The method of any one of claims 1, 2, 10-209, and 216-262 or the dosing regimen of any one of claims 3-153, and 210-262, wherein the pharmaceutical composition further comprises 0.1-50 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

264. The method or the dosing regimen of claim 263, wherein the pharmaceutical composition comprises 0.5-1.5 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

265. The method or the dosing regimen of claim 263, wherein the pharmaceutical composition comprises about 0.79 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

266. The method of any one of claims 1, 2, 10-209, and 216-265 or the dosing regimen of any one of claims 3-153 and 210-265, wherein the pharmaceutical composition comprises 5-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$, and 0.1-50 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

267. The method of any one of claims 1, 2, 10-209, and 216-265 or the dosing regimen of any one of claims 3-153 and 210-265, wherein the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL,

(a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM;

(b) magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM;

(c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM;

(d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and

(e) water.

268. The method or the dosing regimen of claim 267, wherein the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is 0.2 mM to 25 mM, 0.5 mM to 10 mM, 0.75 mM to 5 mM, or 1 mM to 2 mM.

269. The method or the dosing regimen of claim 267, wherein the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is from about 1 mM to about 2 mM.

270. The method or the dosing regimen of claim 267, wherein the concentration of calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) is about 1.4 mM.

271. The method or the dosing regimen of any one of claims 267-270, wherein the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is 0.2 mM to 25 mM, 0.3 mM to 15 mM, 0.4 mM to 5 mM, 0.5 mM to 1.5 mM, or 0.6 mM to 1 mM.

272. The method or the dosing regimen of any one of claims 267-270, wherein the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is from about 0.6 mM to about 1 mM.

273. The method or the dosing regimen of any one of claims 267-270, wherein the concentration of magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) is about 0.79 mM.

274. The method or the dosing regimen of any one of claims 267-273, wherein the concentration of potassium chloride is 0.5 mM to 10 mM, 1 mM to 7.5 mM, or 2 mM to 5 mM.

275. The method or the dosing regimen of any one of claims 267-273, wherein the concentration of potassium chloride is from about 2 mM to about 5 mM.

276. The method or the dosing regimen of any one of claims 267-273, wherein the concentration of potassium chloride is about 3 mM.

277. The method or the dosing regimen of any one of claims 267-276, wherein the concentration of sodium chloride is 25 mM to 250 mM, 100 mM to 160 mM, 110 mM to 140 mM, or 130 mM to 160 mM.

278. The method or the dosing regimen of any one of claims 267-276, wherein the concentration of sodium chloride is from about 125 mM to 145 mM.

279. The method or the dosing regimen of any one of claims 267-276, wherein the concentration of sodium chloride is about 130 mM.

280. The method or the dosing regimen of any one of claims 267-276, wherein the concentration of sodium chloride is from about 140 mM to 160 mM.

281. The method or the dosing regimen of any one of claims 267-276, wherein the concentration of sodium chloride is about 150 mM.

282. The method or the dosing regimen of any one of claims 267-281, wherein:

the concentration of the compound is about 3 mg/mL, about 4.5 mg/mL, about 7 mg/mL, or about 33 mg/mL;

(i) the concentration of calcium chloride dihydrate is about 1.4 mM;

(ii) the concentration of magnesium chloride hexahydrate is about 0.79 mM;

(iii) the concentration of potassium chloride is about 3 mM; and

(iv) the concentration of sodium chloride is about 150 mM.

283. The method of any one of claims 1, 2, 10-209, and 216-265 or the dosing regimen of any one of claims 3-153 and 210-265, wherein the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL,

(a) calcium ion (Ca^{2+}) at a concentration of about 0.1 mM to about 50 mM;

(b) magnesium ion (Mg^{2+}) at a concentration of about 0.1 mM to about 50 mM;

(c) potassium ion (K^{+}) at a concentration of about 0.1 mM to about 20 mM;

(d) sodium ion (Na^{+}) at a concentration of about 25 mM to about 250 mM;

(e) chloride ion (Cl^{-}) at a concentration of about 25 mM to about 250 mM; and

(f) water.

284. The method of any one of claims 1, 2, 10-209, and 216-265 or the dosing regimen of any one of claims 3-153 and 210-265, wherein the pharmaceutical composition comprises the compound at a concentration of about 0.1 mg/mL to about 500 mg/mL,

(a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM;

(b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM;

(c) potassium ion (K^{+}) at a concentration of about 3 mM;

(d) sodium ion (Na^{+}) at a concentration of about 160 mM;

(e) chloride ion (Cl^{-}) at a concentration of about 160 mM; and

(f) water.

285. The method or the dosing regimen of any one of claims 260-284, wherein the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4.

286. The method or the dosing regimen of any one of claims 260-285, wherein the pharmaceutical composition lacks phosphate ion.

287. The method or the dosing regimen of any one of claims 260-286, wherein each dose of the pharmaceutical composition comprises 10 mL of the diluent.

288. The method or the dosing regimen of any one of claims 217-287, wherein the diluent further comprises an antioxidant.

289. The method or the dosing regimen of claim 288, wherein the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof.

290. The method of any one of claims 1, 2, 10-209, and 216-289 or the dosing regimen of any one of claims 3-153 and 210-289, wherein the pharmaceutical composition is administered into the intrathecal space of the human subject.

291. The method of any one of claims 1, 2, 10-209, and 216-289 or the dosing regimen of any one of claims 3-153 and 210-289, wherein the pharmaceutical composition is administered into the cerebrospinal fluid of the human subject.

292. The method of any one of claims 1, 2, 10-209, and 216-289 or the dosing regimen of any one of claims 3-153 and 210-289, wherein the pharmaceutical composition is administered into the brain of the human subject.

293. The method of any one of claims 1, 2, 10-209, and 216-289 or the dosing regimen of any one of claims 3-153 and 210-289, wherein the pharmaceutical composition is administered into the cerebrospinal fluid in the brain of the human subject.

294. The method of any one of claims 1, 2, 10-209, and 216-293 or the dosing regimen of any one of claims 3-153 and 210-293, wherein the pharmaceutical composition is administered as a bolus injection.

295. The method or the dosing regimen of claim 294, wherein the method or the dosing regimen comprises administering the pharmaceutical composition as a bolus injection over 1 to 60 minutes, 1 to 50 minutes, 1 to 40 minutes, 1 to 30 minutes, 1 to 20 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes.

296. The method of any one of claims 1, 2, 10-209, and 216-293 or the dosing regimen of any one of claims 3-153 and 210-293, wherein the pharmaceutical composition is administered by infusion with a delivery pump.

297. The method of any one of claims 1, 2, 10-209, and 216-293 or the dosing regimen of any one of claims 3-153 and 210-293, wherein the pharmaceutical composition is administered by intracerebroventricular injection.

298. The method of any one of claims 1, 2, 10-209, and 216-293 or the dosing regimen of any one of claims 3-153 and 210-293, wherein the pharmaceutical composition is administered by intrathecal injection.

299. The method or dosing regimen of claim 298, wherein each dose of the pharmaceutical composition comprises a diluent of a volume of 10 mL, and the diluent is an aCSF solution that lacks sodium phosphate.

300. The method of any one of claims 1, 2, 10-209, and 216-293 or the dosing regimen of any one of claims 3-153 and 210-293, wherein the pharmaceutical composition is administered by lumbar injection.

301. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the pharmaceutical composition does not comprise a preservative.

302. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the concentration of the compound in the pharmaceutical composition is about 0.1 mg/mL to about 250 mg/mL.

303. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the concentration of the compound in the pharmaceutical composition is from 6.7 mg/mL to 188 mg/mL, from 6.8 mg/mL to 187 mg/mL, from 3 mg/mL to 100 mg/mL, or from 3 mg/mL to 33 mg/mL.

304. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the concentration of the compound in the pharmaceutical composition is about 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.5 mg/mL, 3 mg/mL, 4 mg/mL, 4.5 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, 20 mg/mL, 22 mg/mL, 25 mg/mL, 28 mg/mL, or 33 mg/mL.
305. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the concentration of the compound in the pharmaceutical composition is 11 mg/mL, 22 mg/mL, 33 mg/mL, 44 mg/mL, 55 mg/mL, 66 mg/mL, 77 mg/mL, 88 mg/mL, 99 mg/mL, or 100 mg/mL.
306. The method of any one of claims 1, 2, 10-209, and 216-300 or the dosing regimen of any one of claims 3-153 and 210-300, wherein the concentration of the compound in the pharmaceutical composition is about 3 mg/mL, 4 mg/mL, 4.5 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12 mg/mL, 13 mg/mL, 14 mg/mL, 15 mg/mL, 16 mg/mL, 17 mg/mL, 18 mg/mL, 19 mg/mL, 20 mg/mL, 22.5 mg/mL, 25 mg/mL, 27.5 mg/mL, 30 mg/mL, 32.5 mg/mL, 35 mg/mL, 37.5 mg/mL, 40 mg/mL, 42.5 mg/mL, 45 mg/mL, 47.5 mg/mL, 50 mg/mL, 52.5 mg/mL, 55 mg/mL, 57.5 mg/mL, 60 mg/mL, 62.5 mg/mL, 65 mg/mL, 67.5 mg/mL, 70 mg/mL, 72.5 mg/mL, 75 mg/mL, 77.5 mg/mL, 80 mg/mL, 82.5 mg/mL, 85 mg/mL, 87.5 mg/mL, 90 mg/mL, 92.5 mg/mL, 95 mg/mL, 97.5 mg/mL, 100 mg/mL, 102.5 mg/mL, 105 mg/mL, 107.5 mg/mL, 110 mg/mL, 112.5 mg/mL, 115 mg/mL, 117.5 mg/mL, 120 mg/mL, 122.5 mg/mL, 125 mg/mL, 127.5 mg/mL, 130 mg/mL, 132.5 mg/mL, 135 mg/mL, 137.5 mg/mL, 140 mg/mL, 142.5 mg/mL, 145 mg/mL, 147.5 mg/mL, 150 mg/mL, 152.5 mg/mL, 155 mg/mL, 157.5 mg/mL, 160 mg/mL, 162.5 mg/mL, 165 mg/mL, 167.5 mg/mL, 170 mg/mL, 172.5 mg/mL, 175 mg/mL, 177.5 mg/mL, 180 mg/mL, 182.5 mg/mL, 185 mg/mL, 187.5 mg/mL, 190 mg/mL, 192.5 mg/mL, 195 mg/mL, 197.5 mg/mL, 200 mg/mL, 202.5 mg/mL, 205 mg/mL, 207.5 mg/mL, 210 mg/mL, 212.5 mg/mL, 215 mg/mL, 217.5 mg/mL, 220 mg/mL, 222.5 mg/mL, 225 mg/mL, 227.5 mg/mL, 230 mg/mL, 232.5 mg/mL, 235 mg/mL, 237.5 mg/mL, 240 mg/mL, 242.5 mg/mL, 245 mg/mL, 247.5 mg/mL, or 250 mg/mL.
307. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is at most 18 years old at first loading dose.
308. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is at least 2 years old.
309. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is at least 6 months old.
310. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is from 6 months to 1 year old, or from 1 to 18, from 2 to 18, from 3 to 18, from 4 to 18, from 5 to 18, from 6 to 18, from 7 to 18, from 8 to 18, from 9 to 18, from 10 to 18, from 11 to 18, from 12 to 18, from 13 to 18, from 14 to 18, from 15 to 18, from 16 to 18, or from 17 to 18 years old.

311. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is a human from 6 months to 1 year old, or from 1 to 17, from 1 to 16, from 1 to 15, from 1 to 14, from 1 to 13, from 1 to 12, from 1 to 11, from 1 to 10, from 1 to 9, from 1 to 8, from 1 to 7, from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, or from 1 to 2 years old.
312. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is from 2 to 12 years old.
313. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is from 13 to 18 years old.
314. The method of any one of claims 1, 2, 10-209, and 216-306 or the dosing regimen of any one of claims 3-153 and 210-306, wherein the human subject is at least 13 years old.
315. The method of any one of claims 1, 2, 10-209, and 216-314 or the dosing regimen of any one of claims 3-153 and 210-314, wherein the race of the human subject is white.
316. The method of any one of claims 1, 2, 10-209, and 216-314 or the dosing regimen of any one of claims 3-153 and 210-314, wherein the race of the human subject is Asian.
317. The method of any one of claims 1, 2, 10-209, and 216-314 or the dosing regimen of any one of claims 3-153 and 210-314, wherein the race of the human subject is black or African American
318. The method of any one of claims 1, 2, 10-209, and 216-314 or the dosing regimen of any one of claims 3-153 and 210-314, wherein the human subject receives administration of at least one concomitant anti-seizure medication.
319. The method of any one of claims 1, 2, 10-209, and 216-314 or the dosing regimen of any one of claims 3-153 and 210-314, wherein the human subject receives administration of at least 3 or 4 concomitant anti-seizure medications.
320. The method or dosing regimen of claim 318 or 319, wherein the human subject receives administration of fenfluramine.
321. The method of any one of claims 1, 2, 10-209, and 216-320 or the dosing regimen of any one of claims 3-153 and 210-320, wherein the disease or condition is treated.
322. The method of claim 321, wherein the disease or condition is Dravet Syndrome.
323. The method of claim 321, wherein the disease or condition is SMEB, GEFS+, a Febrile seizure (*e.g.,* Febrile seizures, familial, 3A), autism, a migraine (*e.g.,* migraine, familial hemiplegic, 3), Alzheimer's disease, SCN2A encephalopathy, or SCN5A arrhythmia.
324. The method of any one of claims 1, 2, 10-209, and 216-322 or the dosing regimen of any one of claims 3-153 and 210-322, wherein the subject is characterized by having:
    (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia;
    (ii) no past history of causal magnetic resonance imaging lesion;
    (iii) no other known etiology of any diseases or conditions except Dravet Syndrome;
    (iv) normal development at seizure onset;

(v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene;

(vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control;

(vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures are any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic;

(viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or

(ix) any combination of (i) – (viii).

325. The method of any one of claims 1, 2, 10-209, and 216-323 or the dosing regimen of any one of claims 3-153 and 210-323, wherein the subject is additionally characterized by not having one or more of the following:

(i) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr;

(ii) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease;

(iii) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin;

(iv) clinically, significantly unstable medical conditions other than epilepsy;

(v) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy;

(vi) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation;

(vii) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt;

(viii) clinically significant abnormal laboratory values prior to administering;

(ix) aspartate aminotransferase or alanine aminotransferase >2.5-fold upper limit of normal, serum creatinine greater than an upper limit of normal or platelet count less than a lower limit of normal;

(x) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering;

(xi) a psychiatric or behavioral disorder;

(xii) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin; or

(xiii) any combination of (i) – (xiii).

326. The method of any one of claims 1, 2, 10-209, and 216-325 or the dosing regimen of any one of claims 3-153 and 210-325, wherein the human subject comprises a deletion, a truncation, a missense, or a nonsense mutation in *SCN1A* gene.

327. The method of any one of claims 1, 2, 10-209, and 216-326 or the dosing regimen of any one of claims 3-153 and 210-326, wherein at least one symptom of Dravet Syndrome in the human subject is reduced or ameliorated.

328. The method or the dosing regimen of claim 327, wherein the symptom of Dravet Syndrome is a seizure.

329. The method of any one of claims 1, 2, 10-209, and 216-328 or the dosing regimen of any one of claims 3-153 and 210-328, wherein the method or the dosing regimen reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration.

330. The method or dosing regimen of claim 329, wherein the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

331. The method of any one of claims 1, 2, 10-209, and 216-328 or the dosing regimen of any one of claims 3-153 and 210-328, wherein the method or the dosing regimen results in an improvement in a non-seizure-related aspect.

332. The method or dosing regimen of claim 331, wherein the improvement in the non-seizure-related aspect is sustained for at least 6 months, 8 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

333. The method or the dosing regimen of claim 331 or 332, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills.

334. The method or the dosing regimen of claim 333, wherein the cognitive or behavioral aspect is determined according to a standardized assessment.

335. The method or the dosing regimen of claim 334, wherein the standardized assessment comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C); or any combination thereof.

336. The method or the dosing regimen of claim 334 or 335, wherein (i) the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV); (ii) the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1; or (iii) the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1.
337. The method or the dosing regimen of claim 336, wherein the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, or 9.000.
338. The method or the dosing regimen of claim 336, wherein the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1.
339. The method or the dosing regimen of claim 336, wherein the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1.
340. The method of any one of claims 1, 2, 10-209, and 216-339 or the dosing regimen of any one of claims 3-153 and 210-339, wherein the administration (a) reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration; and (b) results in an improvement in a non-seizure-related aspect.
341. The method of any one of claims 1, 2, 10-209, and 216-340 or the dosing regimen of any one of claims 3-153 and 210-340, wherein the method or the dosing regimen results in no treatment-emergent serious adverse event (TESAE) in the human subject related to the administration of the compound of formula (I) or a salt thereof.
342. The method of any one of claims 1, 2, 10-209, and 216-341 or the dosing regimen of any one of claims 3-153 and 210-341, further comprising assessing tolerability or effectiveness of the pharmaceutical composition.
343. The method of any one of claims 1, 2, 10-209, and 216-342 or the dosing regimen of any one of claims 3-153 and 210-342, further comprising administrating at least one additional therapeutic agent or therapy.
344. The method or the dosing regimen of claim 343, wherein the at least one additional therapeutic agent or therapy is administered at the same time as the first loading dose, the second loading dose and/or the third loading dose.
345. The method or the dosing regimen of claim 343, wherein the at least one additional therapeutic agent or therapy is administered at the same time as the first maintenance dose and/or the one or more further maintenance doses.
346. The method or the dosing regimen of claim 343, wherein the at least one additional therapeutic agent or therapy is administered prior to administration of the first loading dose.
347. The method or the dosing regimen of claim 343, wherein the at least one additional therapeutic agent or therapy is administered after administration of the first loading dose.

348. The method or the dosing regimen of any one of claims 343-347, wherein the at least one additional therapeutic agent or therapy comprises fenfluramine.

349. The method of any one of claims 1, 2, 10-209, and 216-348 or the dosing regimen of any one of claims 3-153 and 210-348, wherein a predicted brain concentration of the compound in the subject after administration of the pharmaceutical composition is at least 1, 2, 4, 6, 8, or 10 μg/mL.

350. The method of any one of claims 1, 10-209, and 216-349 or the dosing regimen of any one of claims 3, 6-153 and 210-349, wherein the compound in the mean brain without thalamus of the subject is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

351. The method of any one of claims 2, 10-209, and 216-349 or the dosing regimen of any one of claims 4-153 and 210-349, wherein the compound in the mean brain without thalamus of the subject is maintained at a concentration between 5 μg/g and 40 μg/g following intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

352. The method of any one of claims 1, 10-209, and 216-349 or the dosing regimen of any one of claims 3, 6-153 and 210-349, wherein the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

353. The method of any one of claims 2, 10-209, and 216-349 or the dosing regimen of any one of claims 4-153 and 210-349, wherein the compound in the mean brain without thalamus of the subject is maintained at a concentration within the range of about 20% to 140% of about 26 μg/g after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the third loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, and intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

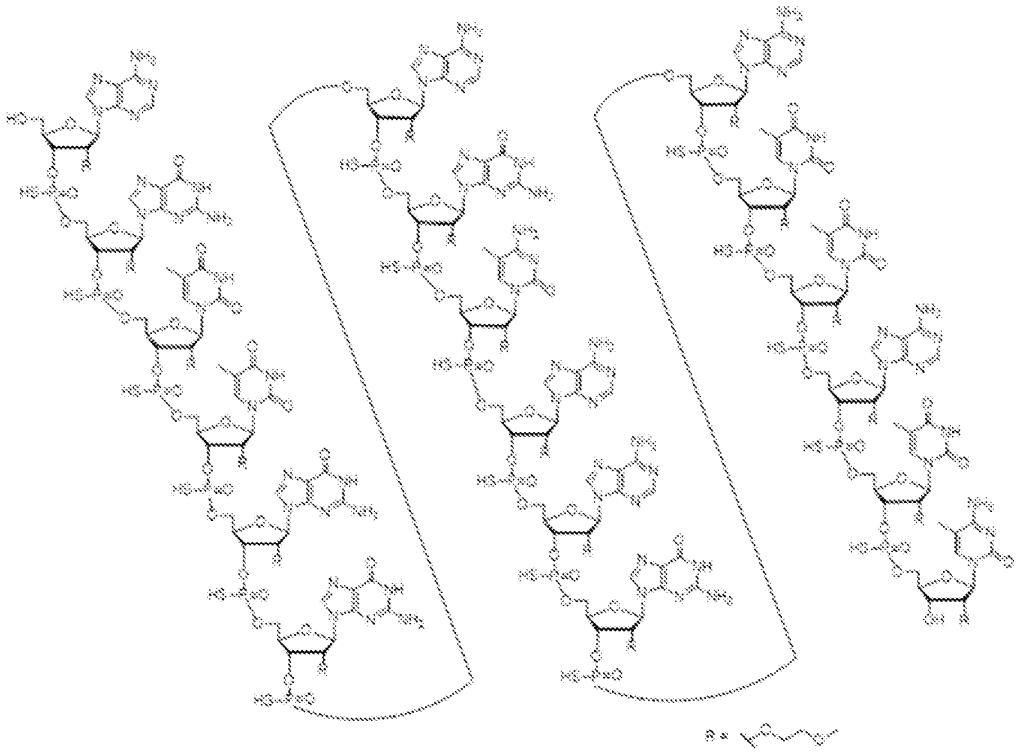
354. The method of any one of claims 1, 2, 10-209, and 216-349 or the dosing regimen of any one of claims 3-153 and 210-349, wherein after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following

intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof.

355. The method of any one of claims 1, 10-209, and 216-349 or the dosing regimen of any one of claims 3, 6-153 and 210-349, wherein after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof and intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

356. The method of any one of claims 2, 10-209, and 216-349 or the dosing regimen of any one of claims 4-153 and 210-349, wherein after intrathecal administration of the first loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, intrathecal administration of the second loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, and intrathecal administration of the third loading dose comprising 70 mg of the compound of formula (I) or a salt thereof, the compound of formula (I) or a salt thereof formulated in the pharmaceutical composition provides a maximum brain without thalamus concentration within the range of about 80% to 125% of about 26 μg/g following intrathecal administration of the first maintenance dose comprising 70 mg of the compound of formula (I) or a salt thereof.

357. A method of improving a non-seizure-related aspect in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

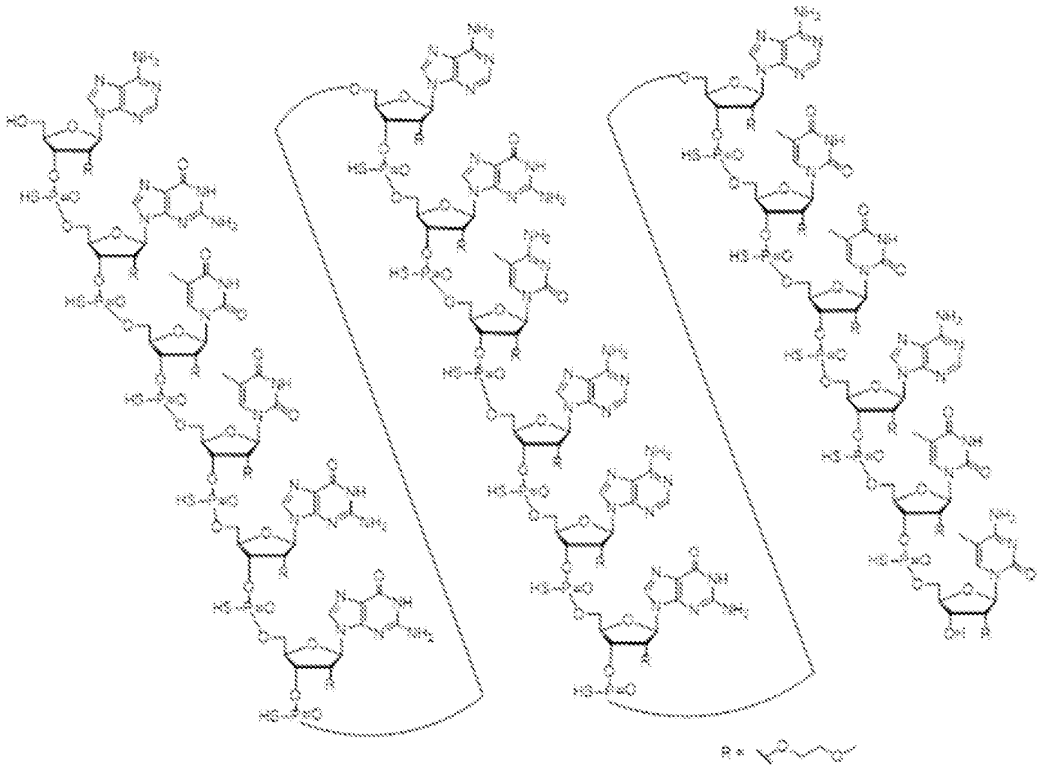
or a salt thereof, thereby improving a non-seizure-related aspect in the human subject, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills;

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 mg to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose, and wherein each maintenance dose after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

358. A method of improving a non-seizure-related aspect in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I), or a salt thereof, thereby improving a non-seizure-related aspect in the human subject, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills;

wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose, wherein each dose of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose, and wherein each maintenance after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

359. The method of claim 357 or 358, wherein the cognitive or behavioral aspect is determined according to a standardized assessment.

360. The method of claim 359, wherein the standardized assessment comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C); or any combination thereof.

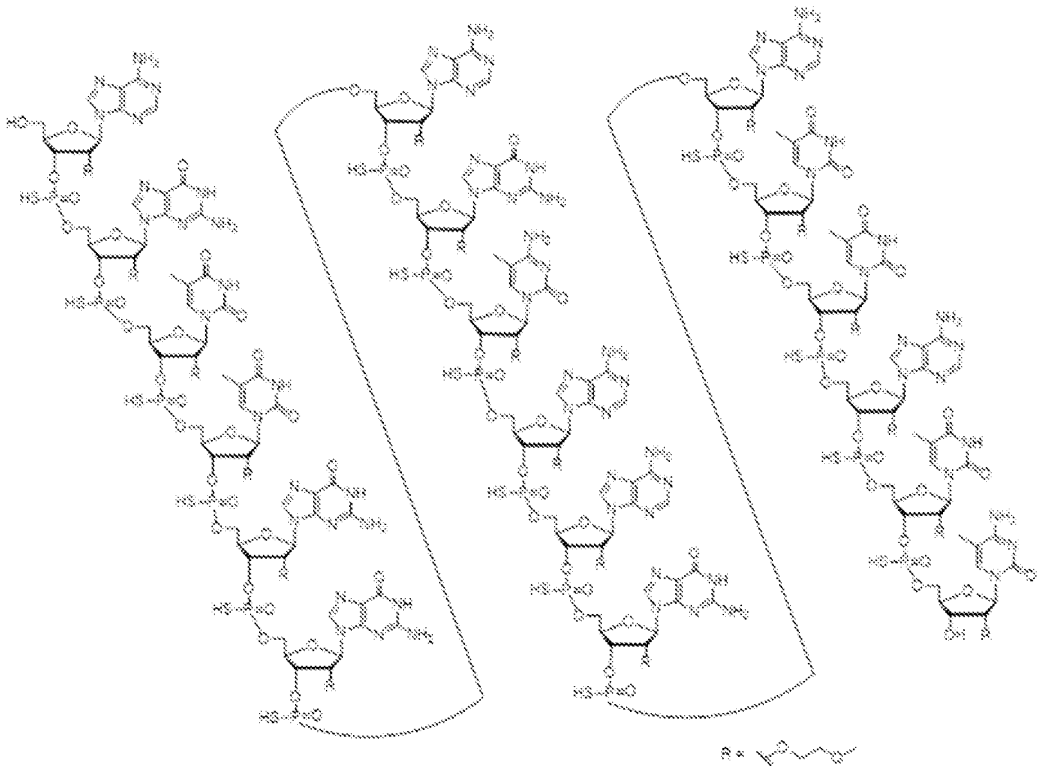
361. The method of claim 359 or 360, wherein (i) the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV); (ii) the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1; or (iii) standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1.

362. The method of claim 361, wherein the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, or 9.000.

363. The method of claim 361, wherein the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1.

364. The method of claim 361, wherein the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1.

365. A method of reducing seizure frequency, seizure intensity, and/or seizure duration in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I),

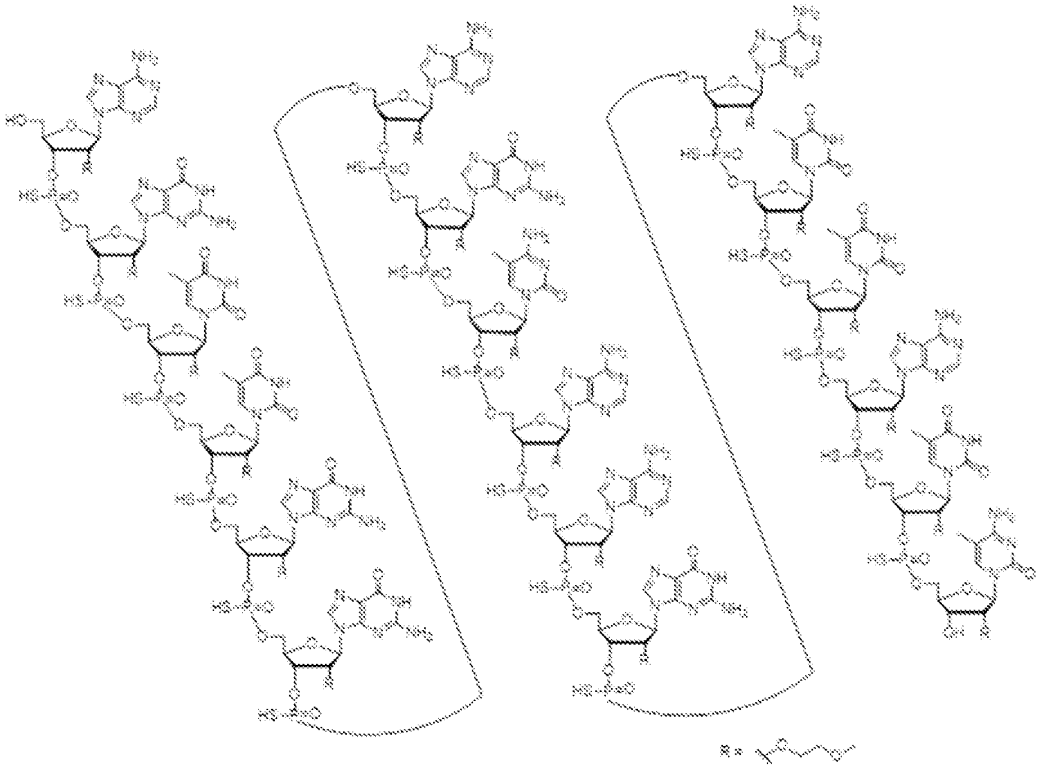
or a salt thereof, thereby reducing seizure frequency, seizure intensity, and/or seizure duration in the human subject,

wherein the multiple doses comprise a first loading dose, a second loading dose, and one or more maintenance doses following the second loading dose,

wherein each dose of the first loading dose, the second loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 mg to about 100 mg,

wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, and a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the second loading dose, and wherein each maintenance dose after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

366. A method of reducing seizure frequency, seizure intensity, and/or seizure duration in a human subject in need thereof, the method comprising administering to the human subject multiple doses of a pharmaceutical composition comprising a compound according to the following chemical structure:



(I), or a salt thereof, thereby reducing seizure frequency, seizure intensity, and/or seizure duration in the human subject,

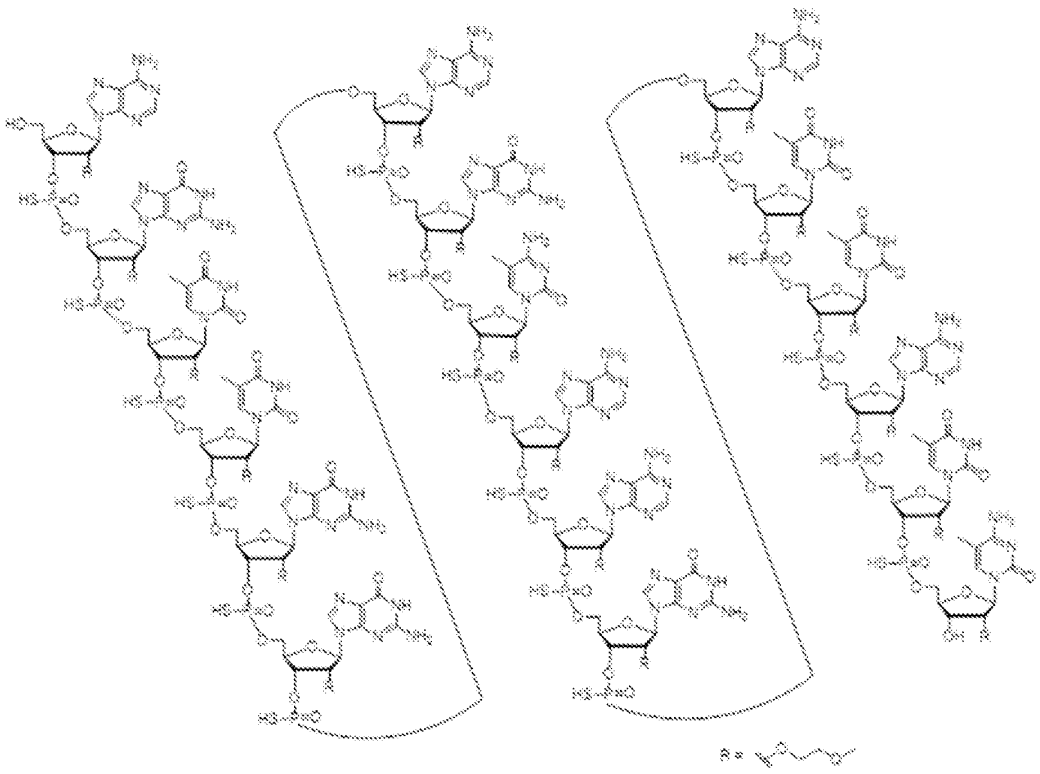
wherein the multiple doses comprise a first loading dose, a second loading dose, a third loading dose, and one or more maintenance doses following the third loading dose, wherein each dose

of the first loading dose, the second loading dose, the third loading dose, and the one or more maintenance doses independently contains the compound at an amount of from about 25 mg to about 100 mg, wherein the second loading dose is administered from 4 weeks to 12 weeks after the first loading dose, the third loading dose is administered from 2 weeks to 12 weeks after the second loading dose, a first maintenance dose of the one or more maintenance doses is administered from 8 weeks to 12 months after the third loading dose, and wherein each maintenance after the first maintenance dose is administered independently from 8 weeks to 12 months after the maintenance dose immediately preceding the respective maintenance dose.

367. A method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of $Na_V1.1$ protein in a human subject in need thereof, the method comprising:

(1) obtaining a pharmaceutical composition that is a liquid composition comprising a compound in a diluent,

wherein the compound is according to the following chemical structure:



(I),

or a salt thereof, and

(2) administering to the human subject multiple doses of the pharmaceutical composition,

wherein the multiple doses comprise a first loading dose, a second loading dose, a first maintenance dose following the second loading dose, and one or more maintenance doses following the first maintenance dose, wherein each dose of the first loading dose and the second loading dose contains the compound at an amount of about 70 mg, wherein the first

maintenance dose and each dose of the one or more maintenance doses contains the compound at an amount of about 45 mg, wherein the second loading dose is administered about 8 weeks after the first loading dose, the first maintenance dose of the one or more maintenance doses is administered about 16 weeks after the second loading dose, and each maintenance dose after the first maintenance dose is administered independently about 16 weeks after a dose immediately preceding the respective maintenance dose.

368. The method of claim 367, wherein diluent comprises:
    (a) calcium chloride ($CaCl_2$) or calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) at a concentration of about 0.1 mM to about 50 mM;
    (b) magnesium chloride ($MgCl_2$) or magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) at a concentration of about 0.1 mM to about 50 mM;
    (c) potassium chloride (KCl) at a concentration of about 0.1 mM to about 20 mM;
    (d) sodium chloride (NaCl) at a concentration of about 25 mM to about 250 mM; and
    (e) water.

369. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to one week prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

370. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to 3 days prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

371. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to 2 days prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

372. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to 24 hours prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

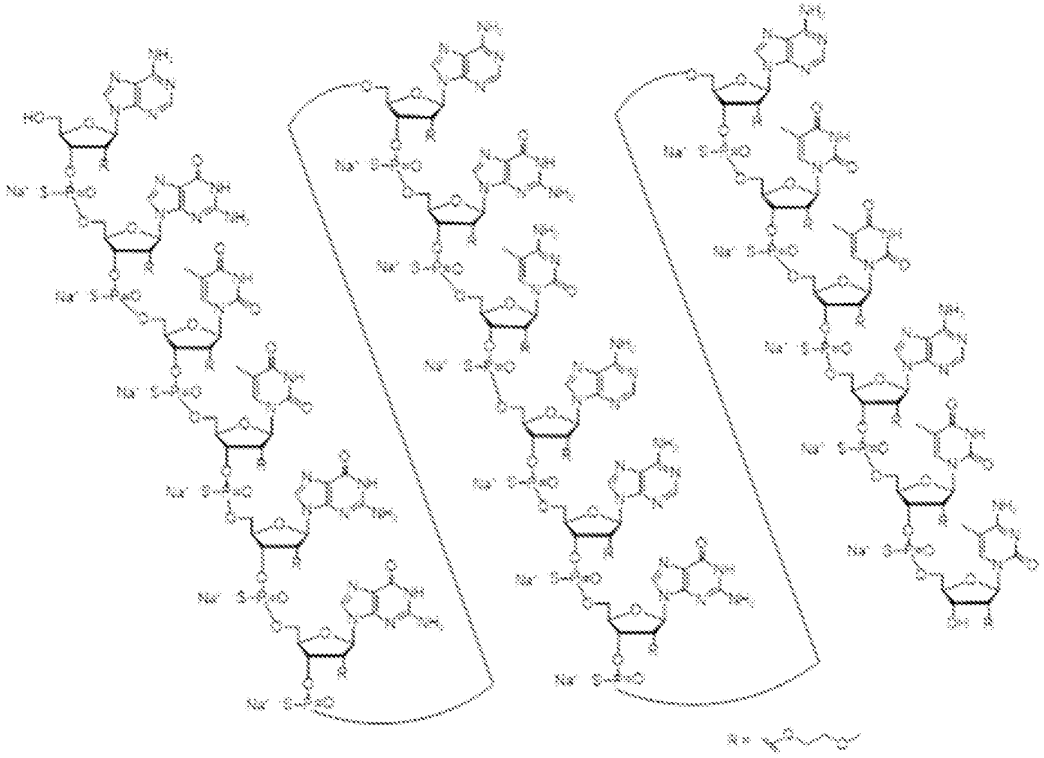
373. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to 5 hours prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

374. The method of claim 367 or 368, wherein the obtaining comprises diluting a concentrate up to one hour prior to the administering the pharmaceutical composition to the human subject, and wherein the concentrate comprises the compound or a salt thereof.

375. The method of any one of claims 367-374, wherein the obtaining comprises diluting the concentrate with the diluent.

376. The method of any one of claims 367-375, wherein the concentrate comprises the compound or a salt thereof dissolved in the diluent.

377. The method of any one of claims 367-376, wherein the compound has the following structure:



(II).

378. The method of claim 375, wherein the pharmaceutical composition comprises the compound or a salt thereof at a concentration of about 3 mg/mL, about 4.5 mg/mL or about 7 mg/mL.

379. The method of claim 378, wherein the concentrate comprises the compound or a salt thereof at a concentration of from about 20 mg/mL to about 200 mg/mL, from about 30 mg/mL to about 150 mg/mL, from about 40 mg/mL to about 120 mg/mL, from about 50 mg/mL to about 100 mg/mL, or from about 60 mg/mL to about 80 mg/mL.

380. The method of claim 378, wherein the concentrate comprises the compound or a salt thereof at a concentration of about 33 mg/mL, about 45 mg/mL, or about 70 mg/mL.

381. The method of any one of claims 367-380, wherein the diluent lacks sodium phosphate.

382. The method of any one of claims 367-381, wherein the diluent comprises 1-2 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

383. The method of any one of claims 367-381, wherein the diluent comprises about 1.4 mM $CaCl_2$ or $CaCl_2 \cdot 2H_2O$.

384. The method of any one of claims 367-383, wherein the diluent comprises 0.5-1.5 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

385. The method of any one of claims 367-383, wherein the diluent comprises about 0.79 mM $MgCl_2$ or $MgCl_2 \cdot 6H_2O$.

386. The method of any one of claims 367-385, wherein the diluent comprises from about 1 mM to about 2 mM calcium chloride dihydrate.

387. The method of any one of claims 367-385, wherein the diluent comprises about 1.4 mM calcium chloride dihydrate.

388. The method of any one of claims 367-387, wherein the diluent comprises from about 0.6 mM to about 1 mM magnesium chloride hexahydrate.

389. The method of any one of claims 367-387, wherein the diluent comprises about 0.79 mM magnesium chloride hexahydrate.

390. The method of any one of claims 367-389, wherein the diluent comprises from about 2 mM to about 5 mM potassium chloride.

391. The method of any one of claims 367-389, wherein the diluent comprises about 3 mM potassium chloride.

392. The method of any one of claims 367-391, wherein the diluent comprises from about 125 mM to 145 mM sodium chloride.

393. The method of any one of claims 367-391, wherein the diluent comprises about 130 mM sodium chloride.

394. The method of any one of claims 367-391, wherein the diluent comprises from about 140 mM to 160 mM sodium chloride.

395. The method of any one of claims 367-391, wherein the diluent comprises about 150 mM sodium chloride.

396. The method of any one of claims 367-395, wherein in the pharmaceutical composition:

(i) the concentration of the compound is about 3 mg/mL, about 4.5 mg/mL or about 7 mg/mL;

(ii) the concentration of calcium chloride dihydrate is about 1.4 mM;

(iii) the concentration of magnesium chloride hexahydrate is about 0.79 mM;

(iv) the concentration of potassium chloride is about 3 mM; and

(v) the concentration of sodium chloride is about 150 mM.

397. The method of any one of claims 367-395, wherein the pharmaceutical composition comprises:

(a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM;

(b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM;

(c) potassium ion (K^{+}) at a concentration of about 3 mM;

(d) sodium ion (Na^{+}) at a concentration of about 160 mM;

(e) chloride ion (Cl^{-}) at a concentration of about 160 mM; and

(f) water.

398. The method of claim 378, wherein in the pharmaceutical composition:

(i) the concentration of the compound is about 3 mg/mL, about 4.5 mg/mL or about 7 mg/mL;

(ii) the concentration of calcium chloride dihydrate is about 1.4 mM;

(iii) the concentration of magnesium chloride hexahydrate is about 0.79 mM;

(iv) the concentration of potassium chloride is about 3 mM; and

(v) the concentration of sodium chloride is about 150 mM.

399. The method of claim 378, wherein the pharmaceutical composition comprises:
(a) calcium ion (Ca^{2+}) at a concentration of about 1.4 mM;
(b) magnesium ion (Mg^{2+}) at a concentration of about 0.79 mM;
(c) potassium ion (K^{+}) at a concentration of about 3 mM;
(d) sodium ion (Na^{+}) at a concentration of about 160 mM;
(e) chloride ion (Cl^{-}) at a concentration of about 160 mM; and
(f) water.

400. The method of any one of claims 367-399, wherein the pharmaceutical composition lacks Na_2HPO_4 and/or NaH_2PO_4.

401. The method of any one of claims 367-399, wherein the pharmaceutical composition lacks phosphate ion.

402. The method of any one of claims 367-401, wherein each dose of the pharmaceutical composition comprises 10 mL of the diluent.

403. The method of any one of claims 367-402, wherein the pharmaceutical composition is administered as a bolus injection.

404. The method of any one of claims 367-403, wherein the method or the dosing regimen comprises administering the pharmaceutical composition as a bolus injection over 1 to 60 minutes, 1 to 50 minutes, 1 to 40 minutes, 1 to 30 minutes, 1 to 20 minutes, 1 to 10 minutes, 1 to 5 minutes, or 1 to 3 minutes.

405. The method of any one of claims 367-404, wherein the pharmaceutical composition is administered by infusion with a delivery pump.

406. The method of any one of claims 367-405, wherein the pharmaceutical composition is administered by intrathecal injection.

407. The method or dosing regimen of claim 406, wherein each dose of the pharmaceutical composition comprises a diluent of a volume of 10 mL, and the diluent is a solution that lacks sodium phosphate.

408. The method of any one of claims 367-407, wherein the pharmaceutical composition does not comprise a preservative.

409. The method of any one of claims 367-408, wherein the human subject is at most 18 years old at the first loading dose.

410. The method of any one of claims 367-408, wherein the human subject is at least 2 years old at the first loading dose.

411. The method of any one of claims 367-408, wherein the human subject is at least 6 months old at the first loading dose.

412. The method of any one of claims 367-408, wherein the human subject is from 6 months to 1 year old, or from 1 to 18, from 2 to 18, from 3 to 18, from 4 to 18, from 5 to 18, from 6 to 18, from 7 to 18, from 8 to 18, from 9 to 18, from 10 to 18, from 11 to 18, from 12 to 18, from 13 to 18, from 14 to 18, from 15 to 18, from 16 to 18, or from 17 to 18 years old at the first loading dose.

413. The method of any one of claims 367-404, wherein the human subject is a human from 6 months to 1 year old, or from 1 to 17, from 1 to 16, from 1 to 15, from 1 to 14, from 1 to 13, from 1 to 12, from 1 to 11, from 1 to 10, from 1 to 9, from 1 to 8, from 1 to 7, from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, or from 1 to 2 years old at the first loading dose.
414. The method of any one of claims 367-408, wherein the human subject is from 2 to 12 years old at the first loading dose.
415. The method of any one of claims 367-408, wherein the human subject is from 13 to 18 years old at the first loading dose.
416. The method of any one of claims 367-408, wherein the human subject is at least 13 years old at the first loading dose.
417. The method of any one of claims 367-416, wherein the race of the human subject is white.
418. The method of any one of claims 367-416, wherein the race of the human subject is Asian.
419. The method of any one of claims 367-416, wherein the race of the human subject is black or African American.
420. The method of any one of claims 367-419, wherein the human subject receives administration of at least one concomitant anti-seizure medication.
421. The method of any one of claims 367-419, wherein the human subject receives administration of at least 3 or 4 concomitant anti-seizure medications.
422. The method or dosing regimen of claim 420 or 421, wherein the human subject receives administration of fenfluramine.
423. The method of any one of claims 367-422, wherein the disease or condition is treated.
424. The method of any one of claims 367-423, wherein the disease or condition is Dravet Syndrome.
425. The method of any one of claims 367-424, wherein the subject is characterized by having:
    (i) seizure onset prior to 12 months of age with recurrent focal motor or hemiconvulsive or generalized tonic-clonic seizures, which are often prolonged and triggered by hyperthermia;
    (ii) no past history of causal magnetic resonance imaging lesion;
    (iii) no other known etiology of any diseases or conditions except Dravet Syndrome;
    (iv) normal development at seizure onset;
    (v) a pathogenic variant, or variant of uncertain significance in an *SCN1A* gene;
    (vi) at least 2 prior treatments for epilepsy that either had lack of adequate seizure control;
    (vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizures are any one selected from Hemiclonic, Focal with Motor Signs, Focal to Bilateral Tonic Clonic Convulsion, Generalized Tonic Clonic Convulsion, Tonic, Tonic or Atonic (Drop Attacks), and Clonic;
    (viii) a current intervention for epilepsy or medication with at least one antiepileptic drug at a dose which has been stable for at least 4 weeks, wherein the intervention for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or
    (ix) any combination of (i) – (viii).

426. The method of any one of claims 367-425, wherein the subject is additionally characterized by not having one or more of the following:

(a) one of the following mutations in the *SCN1A* gene: Thr226Met, Leu263Val, Val422Leu, Thr1174Ser, Trp1204Arg, Pro1345Ser, Gln1489Lys, Phe1499Leu, Arg1575Cys, Val1611Phe, Leu1624Pro, Arg1648Cys, Leu1649Gln, Leu1670Trp, Gly1674Arg, and Asp1866Tyr;

(b) a known pathogenic mutation in another gene that causes epilepsy, wherein the pathogenic mutation is homozygous in cases of known recessive disease;

(c) currently treated with a sodium channel blocker as maintenance treatment and an anticoagulant, wherein the sodium channel blocker is phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, or rufinamide, and wherein the anticoagulant is not an aspirin;

(d) clinically, significantly unstable medical conditions other than epilepsy;

(e) clinically, relevant symptoms or a clinically significant illness in the 4 weeks prior to administering, other than epilepsy;

(f) a history of brain or spinal cord disease other than epilepsy, Dravet Syndrome or a history of bacterial meningitis or brain malformation;

(g) a spinal deformity or other condition that alters the free flow of cerebrospinal fluid (CSF) or having an implanted CSF drainage shunt;

(h) clinically significant abnormal laboratory values prior to administering;

(i) aspartate aminotransferase or alanine aminotransferase >2.5-fold upper limit of normal, serum creatinine greater than an upper limit of normal or platelet count less than a lower limit of normal;

(j) clinically relevant abnormalities in the 12-lead electrocardiogram (ECG) measured at prior to administering;

(k) a psychiatric or behavioral disorder;

(l) currently or in the past 4 weeks, medication of an anticoagulant, wherein the anticoagulant is not aspirin; or

(m) any combination of (a) – (l).

427. The method of any one of claims 367-426, wherein the human subject comprises a deletion, a truncation, a missense, or a nonsense mutation in *SCN1A* gene.

428. The method of any one of claims 367-427, wherein at least one symptom of Dravet Syndrome in the human subject is reduced or ameliorated.

429. The method of claim 428, wherein the symptom of Dravet Syndrome is a seizure.

430. The method of any one of claims 367-429, wherein the method or the dosing regimen reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration.

431. The method of claim 430, wherein the reduction or amelioration of seizure frequency, seizure intensity, and/or seizure duration is sustained for at least 6 months, 9 months, 12 months, 15 months,

18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

432. The method of any one of claims 367-431, wherein the method or the dosing regimen results in an improvement in a non-seizure-related aspect.

433. The method of claim 432, wherein the improvement in the non-seizure-related aspect is sustained for at least 6 months, 8 months, 12 months, 15 months, 18 months, 24 months, 2.5 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 12 years, 14 years, 16 years, 18 years, or longer.

434. The method of claim 432 or 433, wherein the non-seizure-related aspect comprises a cognitive or behavioral domain selected from the group consisting of communication, daily living skills, socialization and motor skills, and/or wherein the non-seizure-related aspect comprises a cognitive or behavioral subdomain selected from the group consisting of receptive communication, expressive communication, writing skills, personal skills, domestic skills, community skills, interpersonal relationships, play and leisure, coping skills, gross motor skills, and fine motor skills.

435. The method of claim 434, wherein the cognitive or behavioral aspect is determined according to a standardized assessment.

436. The method of claim 435, wherein the standardized assessment comprises a Vineland Adaptive Behavior Scale, Third Edition (VABS-III); a Clinical Global Impression of Change (CGI-C); or a Caregiver Global Impression of Change (CaGI-C); or any combination thereof.

437. The method of claim 435 or 436, wherein (i) the standardized assessment comprises VABS-III and the improvement is a positive change in a Gross Scale Value (GSV); (ii) the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 3, 2, or 1; or (iii) the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 3, 2, or 1.

438. The method of claim 435, wherein the standardized assessment comprises VABS-III and the positive change in GSV is at least 0.7000, 0.8000, 0.9000, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.250, 5.500, 5.750, 6.000, 7.000, 8.000, or 9.000.

439. The method of claim 435, wherein the standardized assessment comprises CGI-C and the improvement is a CGI-C score of 2 or 1.

440. The method of claim 435, wherein the standardized assessment comprises CaGI-C and the improvement is a CaGI-C score of 2 or 1.

441. The method of any one of claims 367-440, wherein the administration (a) reduces or ameliorates seizure frequency, seizure intensity, and/or seizure duration; and (b) results in an improvement in a non-seizure-related aspect.

442. The method of any one of claims 367-441, wherein the method or the dosing regimen results in no treatment-emergent serious adverse event (TESAE) in the human subject related to the administration of the compound of formula (I) or a salt thereof.

443. The method of any one of claims 367-442, further comprising assessing tolerability or effectiveness of the pharmaceutical composition.

444. The method of any one of claims 367-443, further comprising administrating at least one additional therapeutic agent or therapy.

445. The method of claim 444, wherein the at least one additional therapeutic agent or therapy is administered at the same time as the first loading dose, the second loading dose and/or the third loading dose.

446. The method of claim 444, wherein the at least one additional therapeutic agent or therapy is administered at the same time as the first maintenance dose and/or the one or more further maintenance doses.

447. The method of claim 444, wherein the at least one additional therapeutic agent or therapy is administered prior to administration of the first loading dose.

448. The method of claim 444, wherein the at least one additional therapeutic agent or therapy is administered after administration of the first loading dose.

449. The method of any one of claims 444-448, wherein the at least one additional therapeutic agent or therapy comprises fenfluramine.