

solubility, toxicity, activity, stability, and pharmacological properties. Also, there are significant physiological differences between animal models and human subjects. Therefore, translating pre-clinical information into clinically effective therapy is an unpredictable and challenging task.

[0005] Provided herein are suitable dosages, formulations, dosing regimens and patient populations for treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof.

[0005a] In some aspects, provided herein is a use of an antisense oligomer (ASO) for the manufacture of a pharmaceutical composition for treating or reducing the likelihood of developing Dravet Syndrome in a human subject in need thereof, wherein the ASO comprises a sequence according to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099, and wherein the pharmaceutical composition is to be administered via intrathecal injection at a dose of from 40 milligrams to 400 milligrams of the ASO.

[0005b] In some aspects, provided herein is a pharmaceutical formulation suitable for intrathecal injection comprising:

- (a) 40 to 400 mg of an antisense oligomer (ASO), wherein the ASO comprises a sequence according to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099; and
- (b) a pharmaceutically acceptable diluent suitable for intrathecal injection;

wherein the ASO is present in the pharmaceutical formulation at a concentration of from 0.1 mg/mL to 200 mg/mL.

[0006] In some examples, provided herein is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof, the method comprising administering to the human subject a pharmaceutical composition comprising an antisense oligomer (ASO) 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, 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, 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 reducing the likelihood of developing the disease or condition in the human subject.

[0007] In some examples, provided herein is a use of an antisense oligomer (ASO) for the manufacture of a medicament for treating or preventing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof, wherein the medicament is administered 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, 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, and 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.

[0008] In some examples, provided herein is a use of an antisense oligomer (ASO) for the manufacture of a medicament for treating or preventing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof, wherein the medicament is prepared to be administered 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, 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, and 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.

[0009] In some examples, provided herein is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof, the method comprising administering to the human subject a pharmaceutical composition comprising a first 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 reducing the likelihood of developing the disease or condition in the human subject; wherein the human subject is at most 18 years old at first dose.

[0010] In some examples, provided herein is a method of treating or reducing the likelihood of developing a disease or condition characterized by a reduced expression or function of Nav1.1 protein in a human subject in need thereof, the method comprising administering to the human subject a pharmaceutical composition comprising multiple doses 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 reducing the likelihood of developing the disease or condition in the human subject.

[0011] In some examples, the first dose is the first of multiple doses.

[0012] In some examples, the human subject is at most 18 years old at first dose.

[0013] In some examples, the method comprises administering to the human subject a pharmaceutical composition comprising an ASO 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, 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.

[0014] In some examples, the disease or condition is Dravet Syndrome.

[0015] In some examples, 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 interventions for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or (ix) any combination of (i) – (viii).

[0016] In some examples, 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).

[0017] In some examples, the human subject is 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.

[0018] In some examples, the human subject is a human 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.

[0019] In some examples, the human subject is less than a year old or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 years old.

[0020] In some examples, the pharmaceutical composition is administered into the intrathecal space of the human subject.

[0021] In some examples, the pharmaceutical composition is administered into the cerebrospinal fluid of the human subject.

[0022] In some examples, the pharmaceutical composition is administered into the brain of the human subject.

[0023] In some examples, the pharmaceutical composition is administered into the cerebrospinal fluid in the brain of the human subject.

[0024] In some examples, the pharmaceutical composition is administered as a bolus injection.

[0025] In some examples, the pharmaceutical composition is administered by infusion with a delivery pump.

[0026] In some examples, the pharmaceutical composition is administered by intracerebroventricular injection.

[0027] In some examples, the pharmaceutical composition is administered by intrathecal injection.

[0028] In some examples, the method reduces or ameliorates at least one symptom of Dravet Syndrome in the human subject.

[0029] In some examples, the symptom of Dravet Syndrome is a seizure.

[0030] In some examples, the administration reduces or ameliorates seizure frequency, seizure intensity, or seizure duration.

[0031] In some examples, the ASO 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.

[0032] In some examples, 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.

[0033] In some examples, the ASO comprises at least one modified sugar moiety.

[0034] In some examples, the ASO comprises T-methoxyethyl sugar moiety.

[0035] In some examples, the T-methoxyethyl sugar moiety is a T-2'-methoxyethyl sugar moiety.

[0036] In some examples, the ASO comprises a 2'-O-methoxyethyl moiety.

[0037] In some examples, the ASO comprises a thymidine comprising a 2'-O-methoxyethyl moiety.

[0038] In some examples, each nucleobase of the ASO comprises a 2'-O-methoxyethyl moiety.

[0039] In some examples, the ASO consists of from 8 to 50 nucleobases.

[0040] In some examples, the ASO consists of from 16 to 20 nucleobases.

[0041] In some examples, the ASO consists of from 12 to 20 nucleobases.

[0042] In some examples, the ASO consists of from 8 to 20 nucleobases.

[0043] In some examples, the ASO comprises a 5'-methylcytosine (5'-MeC).

[0044] In some examples, each cytosine of the ASO is a 5'-methylcytosine (5'-MeC).

[0045] In some examples, the ASO comprises a phosphorothioate linkage.

[0046] In some examples, each internucleoside linkage of the ASO is a phosphorothioate linkage.

[0047] In some examples, the ASO comprises a locked nucleic acid (LNA).

[0048] In some examples, the method further comprises assessing tolerability or effectiveness of the pharmaceutical composition.

[0049] In some examples, the method further comprises administering to the human subject a pharmaceutical composition comprising the ASO at subsequent doses of 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.

[0050] In some examples, the subsequent dose is lower than the previous dose following an indication that administration of the previous dose is not tolerated.

[0051] In some examples, the subsequent dose is the same as the previous dose following an indication that administration of the previous dose is tolerated.

[0052] In some examples, the subsequent dose is higher than the previous dose following an indication that administration of the previous dose is tolerated.

[0053] In some examples, the subsequent dose is the same as the previous dose following an indication that administration of the previous dose is effective.

[0054] In some examples, the subsequent dose is lower than the previous dose following an indication that administration of the previous dose is effective.

[0055] In some examples, the subsequent dose is higher than the previous dose following an indication that administration of the previous dose is not effective.

[0056] In some examples, the subsequent doses are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the previous dose.

[0057] In some examples, dose frequency is maintained or reduced following an indication that the previous dose is effective.

[0058] In some examples, dose frequency is increased following an indication that the previous dose is not effective.

[0059] In some examples, the method further comprises administering at least one additional therapeutic agent or therapy.

[0060] In some examples, the at least one additional therapeutic agent or therapy is administered at the same time as the dose.

[0061] In some examples, the at least one additional therapeutic agent or therapy is administered prior to administration of the dose.

[0062] In some examples, the at least one additional therapeutic agent or therapy is administered after administration of the dose.

[0063] In some examples, the pharmaceutical composition comprises a pharmaceutically acceptable excipient, carrier or diluent.

[0064] In some examples, the pharmaceutical composition is a liquid composition.

[0065] In some examples, the pharmaceutical composition comprises from 0.1 mL to 50 mL of a diluent, wherein the ASO is solubilized or diluted in the diluent.

[0066] In some examples, 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.

[0067] In some examples, 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.

[0068] In some examples, the diluent comprises a cerebral spinal fluid (CSF) sample from the subject or an artificial cerebral spinal fluid (aCSF) solution.

- [0069]** In some examples, the method comprises obtaining a cerebral spinal fluid sample from the subject.
- [0070]** In some examples, the method comprises solubilizing or diluting the ASO in a CSF sample from the subject.
- [0071]** In some examples, the method comprises administering the pharmaceutical composition as a bolus injection.
- [0072]** In some examples, 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.
- [0073]** In some examples, the method comprises administering the pharmaceutical composition as a bolus injection using a spinal anesthesia needle.
- [0074]** In some examples, the ASO is solubilized or diluted in an artificial cerebral spinal fluid (aCSF) solution.
- [0075]** In some examples, the solution comprises a cerebral spinal fluid (CSF) sample from the subject.
- [0076]** In some examples, the ASO is solubilized or diluted in an isotonic solution.
- [0077]** In some examples, the ASO is solubilized or diluted in a phosphate-buffered solution with at least pH 5.8.
- [0078]** In some examples, the ASO is solubilized or diluted in a phosphate-buffered (pH 6.6 – 7.6) solution.
- [0079]** In some examples, the ASO is solubilized or diluted in a buffer comprising 25-250 mM NaCl.
- [0080]** In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-20 mM KCl.
- [0081]** In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM Na₂HPO₄.
- [0082]** In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM NaH₂PO₄.
- [0083]** In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM CaCl₂.
- [0084]** In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM MgCl₂.
- [0085]** In some examples, the ASO is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na₂HPO₄, 0.1-50 mM NaH₂PO₄, 0.1-50 mM CaCl₂, and 0.1-50 mM MgCl₂.
- [0086]** In some examples, the ASO is solubilized or diluted in a buffer comprising 150 mM NaCl, 3.0 mM KCl, 0.7 mM Na₂HPO₄, 0.3 mM NaH₂PO₄, 0.79 mM MgCl₂, and 1.4 mM CaCl₂.
- [0087]** In some examples, the ASO is solubilized or diluted in a buffer further comprising carbohydrates. In some examples, the carbohydrates comprise D-glucose. In some examples, the ASO is solubilized or diluted in a buffer further comprising 1-100 mM D-glucose.
- [0088]** In some examples, the ASO is solubilized or diluted in a buffer further comprising 1-100 mM NaHCO₃, 1-100 mM KHCO₃, or a combination thereof.
- [0089]** In some examples, the ASO is solubilized or diluted in a buffer further comprising an antioxidant. In some examples, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof.
- [0090]** In some examples, the pharmaceutical formulation does not comprise a preservative.

[0091] In some examples, the ASO is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL.

[0092] In some examples, the ASO 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 examples, the ASO 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 examples, the ASO 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 examples, the ASO is present in the pharmaceutical composition at 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.

[0093] In some examples, the reduced expression or function of Nav1.1 protein is associated with an altered splicing of a non-sense mediated RNA decay-inducing exon (NMD exon) in a pre-mRNA that encodes Nav1.1 protein and contains the NMD exon.

[0094] In some examples, the ASO promotes exclusion of the NMD exon from the pre-mRNA.

[0095] In some examples, the ASO binds to a targeted portion of a pre-mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein.

[0096] In some examples, the ASO promotes exclusion of the NMD exon from the pre-mRNA that contains the NMD exon and that encodes Nav1.1 protein.

[0097] In some examples, the ASO increases a level of processed mRNA encoding the Nav1.1 protein when the ASO is introduced into the cell.

[0098] In some examples, the ASO increases a level of the Nav1.1 protein when the ASO is introduced into the cell.

[0099] In some examples, the targeted portion is within an intron sequence flanking the NMD exon.

[0100] In some examples, the targeted portion comprises at least one nucleotide of the NMD exon.

[0101] In some examples, the targeted portion is within the NMD exon.

[0102] In some examples, the method treats the disease or condition.

[0103] In some examples, provided herein is a pharmaceutical formulation comprising: (a) 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 (b) a pharmaceutically acceptable diluent; wherein the ASO is dissolved or suspended in a solution at a concentration of from 0.1-200 mg/mL.

[0104] In some examples, the pharmaceutically acceptable diluent comprises an artificial cerebral spinal fluid (aCSF) solution.

[0105] In some examples, the solution comprises a cerebral spinal fluid (CSF) sample from the subject.

[0106] In some examples, the ASO 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 examples, the ASO 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.

[0107] In some examples, the ASO is present in the pharmaceutical composition at 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.

[0108] In some examples, the ASO is solubilized or diluted in an isotonic solution.

[0109] In some examples, the ASO is solubilized or diluted in a phosphate-buffered solution with at least pH 5.8.

[0110] In some examples, the ASO is solubilized or diluted in a phosphate-buffered (pH 6.6 – 7.6) solution.

[0111] In some examples, the ASO is solubilized or diluted in a buffer comprising 25-250 mM NaCl.

[0112] In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-20 mM KCl.

[0113] In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM Na₂HPO₄.

[0114] In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM NaH₂PO₄.

- [0115] In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM CaCl_2 .
- [0116] In some examples, the ASO is solubilized or diluted in a buffer comprising 0.1-50 mM MgCl_2 .
- [0117] In some examples, the ASO 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 .
- [0118] In some examples, the ASO 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 .
- [0119] In some examples, the ASO is solubilized or diluted in a buffer further comprising carbohydrates. In some examples, the carbohydrates comprise D-glucose. In some examples, the ASO is solubilized or diluted in a buffer further comprising 1-100 mM D-glucose.
- [0120] In some examples, the ASO is solubilized or diluted in a buffer further comprising 1-100 mM NaHCO_3 , 1-100 mM KHCO_3 , or a combination thereof.
- [0121] In some examples, the ASO is solubilized or diluted in a buffer further comprising an antioxidant. In some examples, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof.
- [0122] In some examples, the pharmaceutical formulation does not comprise a preservative.
- [0123] In some examples, the pharmaceutical formulation is suitable for an intracerebroventricular or intrathecal injection.
- [0124] In some examples, the pharmaceutical formulation is packaged in a single use vial.
- [0125] In some examples, provided herein is a kit comprising: (i) 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 (ii) a diluent, wherein the concentrate is miscible with the diluent; and (iii) instructions for diluting or solubilizing the ASO in the diluent.
- [0126] In some examples, the diluent is an artificial cerebral spinal fluid (aCSF) solution.
- [0127] In some examples, the diluent comprises an isotonic solution.
- [0128] In some examples, the diluent comprises phosphate-buffered solution with at least pH 5.8.
- [0129] In some examples, the diluent comprises a phosphate-buffered (pH 6.6 – 7.6) solution.
- [0130] In some examples, the diluent comprises 25-250 mM NaCl .
- [0131] In some examples, the diluent comprises 0.1-20 mM KCl .
- [0132] In some examples, the diluent comprises 0.1-50 mM Na_2HPO_4 .
- [0133] In some examples, the diluent comprises 0.1-50 mM NaH_2PO_4 .
- [0134] In some examples, the diluent comprises 0.1-50 mM CaCl_2 .
- [0135] In some examples, the diluent comprises 0.1-50 mM MgCl_2 .
- [0136] In some examples, 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 .
- [0137] In some examples, 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 .

[0138] In some examples, the diluent further comprises carbohydrates. In some examples, the carbohydrates comprise D-glucose. In some examples, the diluent further comprises 1-100 mM D-glucose.

[0139] In some examples, the diluent further comprises 1-100 mM NaHCO₃, 1-100 mM KHCO₃, or a combination thereof.

[0140] In some examples, the diluent further comprises an antioxidant. In some examples, the antioxidant is t-butylhydroxyquinoline (TBHQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, or any combination thereof.

[0141] In some examples, the diluent does not comprise a preservative.

[0142] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing the ASO to a concentration of from 0.1 mg/mL to 250 mg/mL in the diluent.

[0143] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing the ASO 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 the diluent.

[0144] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing the ASO to 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 the diluent.

[0145] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing the ASO to 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 diluent.

[0146] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing from about 0.5 milligrams to about 500 milligrams of the ASO in the diluent.

[0147] In some examples, the instructions for diluting or solubilizing the ASO in the diluent comprise instructions for diluting or solubilizing 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 ASO in the diluent.

[0148] In some examples, provided herein is a use of an antisense oligomer (ASO) for the manufacture of a medicament for treating or preventing a disease or condition characterized by a reduced expression or function of NaV1.1 protein in a human subject in need thereof, wherein the medicament is administered at a first dose of from about 0.5 milligrams to about 500 milligrams, and 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. In some examples, the medicament is administered 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, 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.

INCORPORATION BY REFERENCE

[0149] 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

[0150] 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:

[0151] FIGs. 1A-1B depict a schematic representation of a target pre-mRNA that contains a non-sense 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

CLAIMS

WHAT IS CLAIMED IS:

1. Use of an antisense oligomer (ASO) for the manufacture of a pharmaceutical composition for treating or reducing the likelihood of developing Dravet Syndrome in a human subject in need thereof, wherein the ASO comprises a sequence according to any one of SEQ ID NOs: 21-67, 210-256 or 304- 1099, and wherein the pharmaceutical composition is to be administered via intrathecal injection at a dose of from 40 milligrams to 400 milligrams of the ASO.
2. The use according to claim 1, wherein multiple doses of the ASO are to be administered to the human subject.
3. The use according to claim 1 or 2, wherein the human subject is at most 18 years old.
4. The use according to any one of claims 1 to 3, wherein the human 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 interventions for epilepsy is a ketogenic diet, a vagal nerve stimulator, or a cannabinoid or marijuana-derived product; or

- (ix) any combination of (i) – (viii).
5. The use according to any one of claims 1 to 4, wherein the human 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 administration, 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 administration;
 - (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 administration;
 - (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).

6. The use according to any one of claims 1 to 5, wherein the pharmaceutical composition is to be administered as a bolus injection.
7. The use according to any one of claims 1 to 5, wherein the pharmaceutical composition is to be administered by infusion with a delivery pump.
8. The use according to any one of claims 1 to 7, wherein the administration reduces or ameliorates seizure frequency, seizure intensity, or seizure duration.
9. The use according to any one of claims 1 to 8, wherein the ASO comprises at least one modified sugar moiety.
10. The use according to any one of claims 1 to 9, wherein the ASO comprises a 2'-O-methoxyethyl moiety.
11. The use according to any one of claims 1 to 10, wherein the ASO comprises a thymidine comprising a 2'-O-methoxyethyl moiety.
12. The use according to any one of claims 1 to 11, wherein each nucleobase of the ASO comprises a 2'-O-methoxyethyl moiety.
13. The use according to any one of claims 1 to 12, wherein the ASO consists of from 16 to 20 nucleobases.
14. The use according to any one of claims 1 to 13, wherein each cytosine of the ASO is a 5'-methylcytosine (5'- MeC).
15. The use according to any one of claims 1 to 14, wherein each internucleoside linkage of the ASO is a phosphorothioate linkage.
16. The use according to any one of claims 1 to 15, wherein a subsequent dose of from 0.5 milligrams to 500 milligrams of the ASO is to be administered to the human subject.
17. The use according to claim 16, wherein the subsequent dose is to be administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months after administration of the previous dose.
18. The use according to any one of claims 1 to 17, wherein the pharmaceutical composition comprises from 0.1 mL to 50 mL of a diluent.

19. The use according to any one of claims 1 to 6 or 8-18, wherein the pharmaceutical composition is to be administered to the human subject 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.
20. The use according to any one of claims 1 to 6 or 8-19, wherein the pharmaceutical composition is to be administered to the human subject as a bolus injection using a spinal anesthesia needle.
21. The use according to any one of claims 1 to 20, wherein the ASO is diluted in an artificial cerebral spinal fluid (aCSF) solution.
22. The use according to any one of claims 1 to 20, wherein the ASO is diluted in a phosphate-buffered solution with a pH of from 6.6 – 7.6.
23. The use according to any one of claims 1 to 20, wherein the ASO is diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM CaCl₂, and 0.1-50 mM MgCl₂.
24. The use according to any one of claims 1 to 23, wherein the pharmaceutical formulation does not comprise a preservative.
25. The use according to any one of claims 1 to 24, wherein the ASO is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 250 mg/mL.
26. A pharmaceutical formulation suitable for intrathecal injection comprising:
 - (a) 40 to 400 mg of an antisense oligomer (ASO), wherein the ASO comprises a sequence with according to any one of SEQ ID NOs: 21-67, 210-256 or 304-1099; and
 - (b) a pharmaceutically acceptable diluent suitable for intrathecal injection;wherein the ASO is present in the pharmaceutical formulation at a concentration of from 0.1 mg/mL to 200 mg/mL.
27. The pharmaceutical formulation of claim 26, wherein the pharmaceutically acceptable diluent comprises an artificial cerebral spinal fluid (aCSF) solution.
28. The pharmaceutical formulation of claim 26, wherein the solution comprises a cerebral spinal fluid (CSF) sample from the subject.

29. The pharmaceutical formulation of claim 26, wherein the ASO is solubilized or diluted in an isotonic solution.
30. The pharmaceutical formulation of claim 26, wherein the ASO is solubilized or diluted in a phosphate-buffered (pH 6.6 – 7.6) solution.
31. The pharmaceutical formulation of claim 26, wherein the ASO is solubilized or diluted in a buffer comprising 25-250 mM NaCl, 0.1-20 mM KCl, 0.1-50 mM Na₂HPO₄, 0.1-50 mM NaH₂PO₄, 0.1-50 mM CaCl₂, and 0.1-50 mM MgCl₂.
32. The pharmaceutical formulation of claim 26, wherein the ASO is solubilized or diluted in a buffer comprising carbohydrates.
33. The pharmaceutical formulation of claim 26, wherein the ASO is solubilized or diluted in a buffer comprising an antioxidant.
34. The pharmaceutical formulation of any one of claims 26-33, wherein the pharmaceutical formulation does not comprise a preservative.
35. The pharmaceutical formulation of any one of claims 26-34, wherein the pharmaceutical formulation is suitable for an intracerebroventricular or intrathecal injection.
36. The pharmaceutical formulation of any one of claims 26-35, wherein the pharmaceutical formulation is packaged in a single use vial.