Symptoms and hallmarks associated with DEEs include seizures, hypotonia, sensory integration disorders, motor development delays and dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, sleep problems, and sudden unexpected death in epilepsy. Seizures include focal, clonic, tonic, and generalized tonic and clonic seizures, prolonged seizures (often lasting longer than 10 minutes), and frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures) (Guzzetta, F., 2011, *Epilepsia* 52:S2, 35-38; Anwar *et al*., 2019, *Cureus* 11, e5006, Wolff *et al*., 2019). Symptoms and hallmarks associated with ID and ASD include motor development delays, delayed social and language milestones, repetitive actions, uncoordinated oral movements, gastrointestinal disorders, sleep problems, and seizures (Wolff *et al*., 2019).

Currently there is a lack of acceptable options for treating DEEs such as EEs, Late Onset EEs, and BFNIS; and for treating ID and ASD. It is therefore an object herein to provide methods for the treatment of such diseases and disorders.

SUMMARY

Disclosed herein is a method of reducing frequency of seizures experienced by a subject with a SCN2A-related disorder, said method comprising administering to said subject an effective amount of an oligomeric compound, wherein: the SCN2A-related disorder is caused by a gain-of-function mutation in SCN2A gene; the oligomeric compound comprises a 6-10-4 MOE gapmer having a sequence (from 5’ to 3’) of CCACGACATATTTTTCTACA (SEQ ID NO: 3); wherein each of nucleosides 1-6 and 17-20 (from 5’ to 3’) are 2’-MOE nucleosides and each of nucleosides 7-16 are 2’-β-D-deoxynucleosides; wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages; and each cytosine is a 5-methyl cytosine.

In an aspect, the present disclosure relates to use of an effective amount of an oligomeric compound in the manufacture of a medicament for the treatment of early onset SCN2A Developmental and Epileptic Encephalopathy (DEE) in a subject in need of

treatment, wherein said treatment comprises reducing frequency of seizures experienced by the subject, wherein:

the SCN2A DEE is caused by a gain-of-function mutation in SCN2A gene;

the oligomeric compound comprises a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CCACGACATATTTTTCTACA (SEQ ID NO: 3);

wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides;

wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages; and

each cytosine is a 5-methyl cytosine;

wherein the oligomeric compound is formulated for administration at a dose of about 0.5 mg to about 8 mg;

wherein the subject is a human and is a newborn to 18 years old; and

wherein the oligomeric compound is formulated for intrathecal administration.

In some examples, the oligomeric compound is administered at a dose of about 0.1 mg to about 20 mg. In some examples, the oligomeric compound is administered at a dose of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg,

about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 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 or about 20 mg. In some examples, the oligomeric compound is administered at a dose of about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 5 mg, about 8 mg, about 12 mg or about 15 mg. In some examples, the oligomeric compound is administered at a dose of about 1 mg. In some examples, the oligomeric compound is administered at a dose of about 8 mg.

In some examples, the oligomeric compound is administered at a dose of about 0.5 mg to about 8 mg, e.g., about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg or about 8 mg. Is some examples, the oligomeric compound is administered at a dose of about 0.5 mg to about 8 mg, *e.g.*, about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg or about 8 mg, every 2-6 weeks, *e.g.*, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks or every 6 weeks. Intervals between administrations may be approximate and may be varied by a clinician based upon medical judgment and/or clinical indications such as for example patient travel, availability of medical personnel and drug, illness, or adverse event in a patient.

In some examples, the oligomeric compound is administered at a total dose of about 15 mg to about 30 mg over about 20-25 weeks, e.g., about 15 mg, about 20 mg, about 22.5 mg, about 25 mg or about 30 mg over 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks or 25 weeks. In some examples, the oligomeric compound is administered at a total dose of about 22.5 mg over 23 weeks.

In some examples, the oligomeric compound is administered once per month. In other examples, the oligomeric compound is administered more than once per month. In further examples, the oligomeric compound is administered once every two, three, four, five, or six months, or once per year.

In some examples, the seizures are selected from the group consisting of focal motor seizures, tonic seizures, generalized tonic-clonic seizures and myoclonic seizures.

In some examples, administration of the oligomeric compound results in a decrease in the average number of daily seizures experienced by the subject in a 28-day period, as compared to the average number of daily seizures experienced by the subject prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in a reduction in the number of seizures experienced by the subject in a 28-day period by 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%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%, as compared to the number of seizures experienced by the subject prior to administration of the oligomeric compound.

In one example, disclosed herein is a method of treating a subject with a SCN2A-related disorder, said method comprising administering to said subject an oligomeric compound at a dose of about 0.1 mg to about 20 mg, wherein: the SCN2A-related disorder is caused by a gain-of-function mutation in SCN2A gene; the oligomeric compound comprises a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CCACGACATATTTTTCTACA (SEQ ID NO: 3); each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides; the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages; and each cytosine is a 5-methyl cytosine.

In some examples, the oligomeric compound is administered at a dose of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 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 or about 20 mg. In some examples, the oligomeric compound is administered at a dose of about 0.5 mg, about 1 mg, about 1.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 5 mg, about 8 mg, about 12 mg or about 15 mg.

In some examples, the oligomeric compound is administered at a dose of about 1 mg. In some examples, the oligomeric compound is administered at a dose of about 8 mg.

In some examples, the oligomeric compound is administered about once per month. In other examples, the oligomeric compound is administered more frequently than about once per month. In other examples, the oligomeric compound is administered about once every two, three, four, five, or six months, or once per year.

In some examples, administration of the oligomeric compound results in a decrease in the frequency of seizures experienced by the subject, as compared to the frequency of seizures experienced by the subject prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in a reduction in the average number of daily seizures experienced by the subject in a 28-day period, as compared to the average number of daily seizures experienced by the subject in a 28-day period prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in a reduction in the number of seizures experienced by the subject in a 28-day period by 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%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80% or at least about 85%, as compared to the number of seizures experienced by the subject prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in an increase in the number of seizure-free days experienced by the subject, as compared to the number of seizure-free days experienced by the subject prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in an increase in the number of seizure-free days in a time period experienced by the subject, as compared to the number of seizure-free days experienced by the subject in the same time period prior to administration of the oligomeric compound.

In some examples, administration of the oligomeric compound results in an increase in % of seizure-free days per 28-day period experienced by the subject, as compared to % of seizure-free days per 28-day period experienced by the subject prior to administration of the oligomeric compound.

In some examples, the seizures are selected from the group consisting of focal motor seizures, tonic seizures, generalized tonic-clonic seizures and myoclonic seizures.

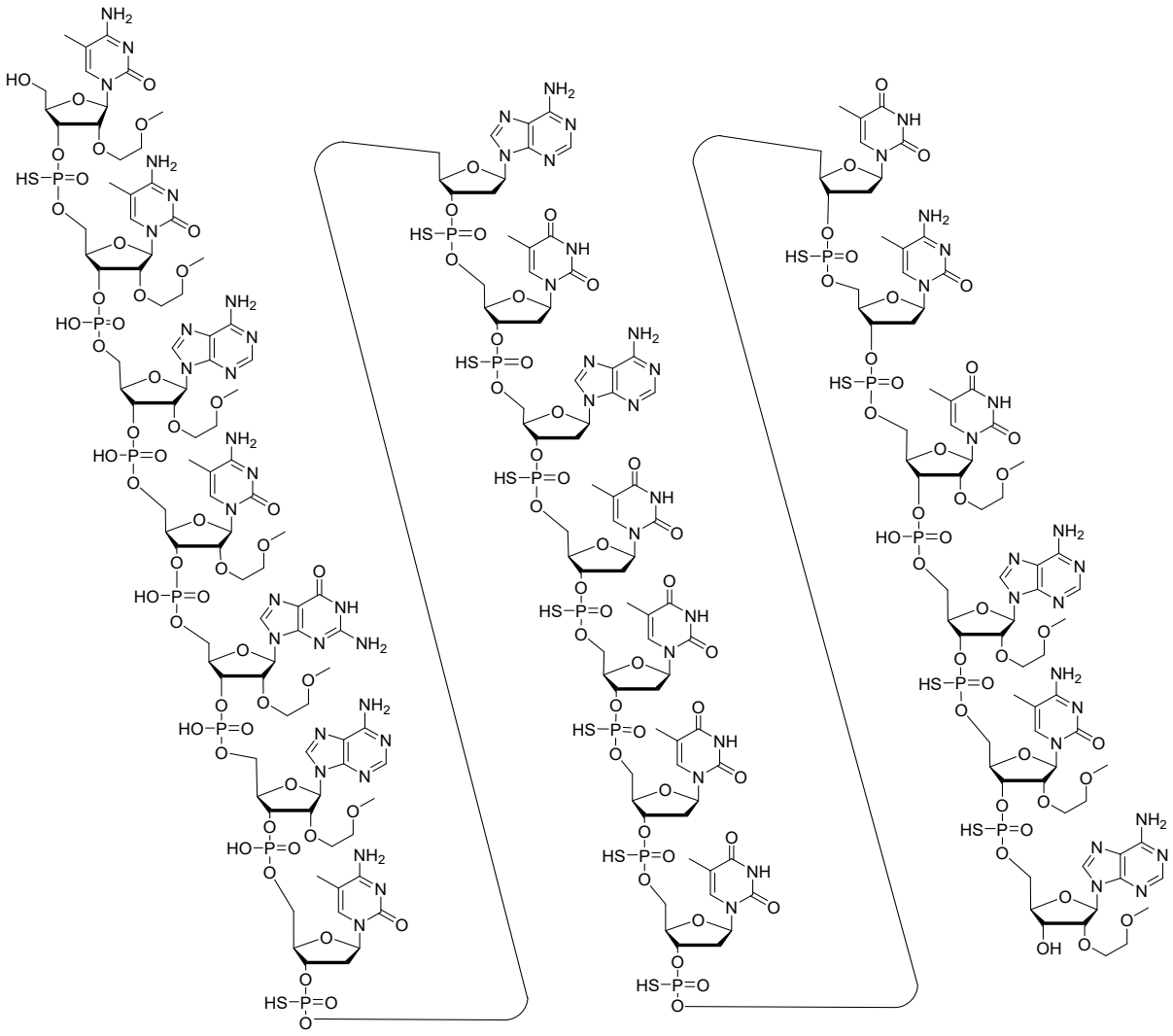
In some examples, the subject is a human. In some examples, the subject is between 2 and 18 years old. In some examples, the subject is between 0 and 24 months old. In some examples, the subject is a newborn. In some examples, the newborn is a premature newborn. In some examples, the newborn has low birth weight with or without prematurity.

In some examples, the SCN2A-related disorder is SCN2A developmental and epileptic encephalopathy (SCN2A DEE). In some examples, the SCN2A-related disorder is early seizure onset epileptic encephalopathy (EE).

In some examples, the gain-of-function mutation in SCN2A gene is selected from the group consisting of L210Q, A263V, E430A, R1882Q, G879R, Q1479H, V423L, G1593R, K1502N, V1601L, G211D, S1780I, D343H and A1329D. In some examples, the gain-of-function mutation is A1329D.

In some examples, the oligomeric compound comprises a modified oligonucleotide represented by the following chemical notation: mCesmCeoAeomCeoGeoAeomCdsAdsTdsAdsTdsTdsTdsTdsmCdsTeoAesmCesAe (SEQ ID NO: 3), wherein: A = an adenine nucleobase, mC = a 5-methyl cytosine nucleobase, G = a guanine nucleobase, T = a thymine nucleobase, e = a 2'-MOE sugar moiety, d = a 2'-β-D-deoxyribosyl sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage.

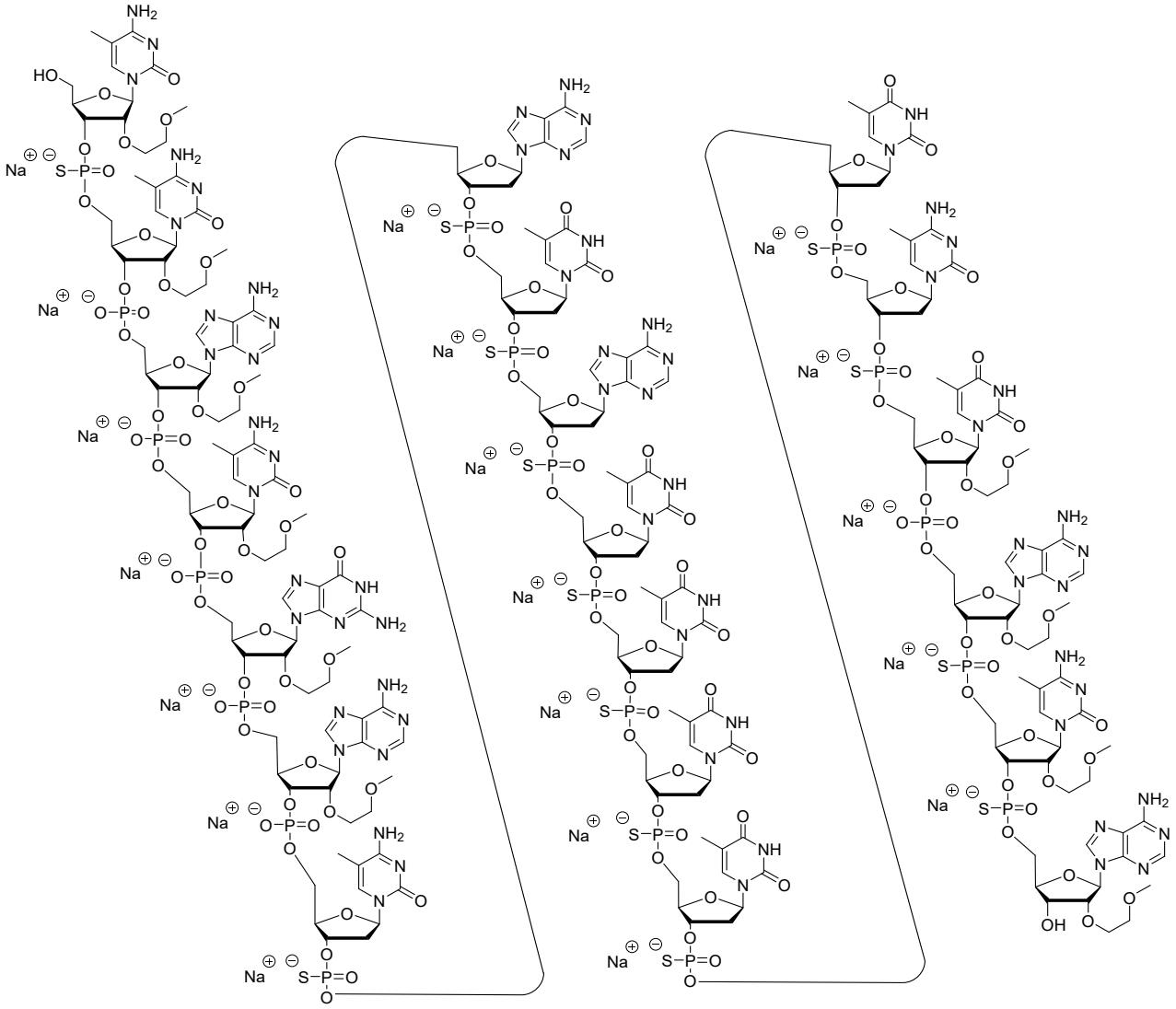
In some examples, the oligomeric compound is a modified oligonucleotide represented by the following chemical structure:



(SEQ ID NO: 3) or a salt thereof.

In some examples, the modified oligonucleotide is a sodium salt or a potassium salt. In some examples, the modified oligonucleotide is a sodium salt.

In some examples, the modified oligonucleotide represented by the following chemical structure:



(SEQ ID NO: 3).

In some examples, the oligomeric compound is administered as a part of a pharmaceutical composition comprising the oligomeric compound and a pharmaceutically acceptable diluent or carrier. In some examples, the pharmaceutically acceptable diluent is artificial CSF (aCSF) or phosphate-buffered saline (PBS). In some examples, the pharmaceutically acceptable diluent is aCSF.

In some examples, the oligomeric compound is administered intrathecally.

CLAIMS

What is claimed is:

1. Use of an effective amount of an oligomeric compound in the manufacture of a medicament for the treatment of early onset SCN2A Developmental and Epileptic Encephalopathy (DEE) in a subject in need of treatment, wherein said treatment comprises reducing frequency of seizures experienced by the subject, wherein:

the SCN2A DEE is caused by a gain-of-function mutation in SCN2A gene;

the oligomeric compound comprises a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CCACGACATATTTTTCTACA (SEQ ID NO: 3);

wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides;

wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages; and

each cytosine is a 5-methyl cytosine;

wherein the oligomeric compound is formulated for administration at a dose of about 0.5 mg to about 8 mg;

wherein the subject is a human and is a newborn to 18 years old; and

wherein the oligomeric compound is formulated for intrathecal administration.

2. The use of claim 1, wherein the oligomeric compound is formulated for administration at a dose of about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg or about 8 mg.

3. The use of claim 1 or 2, wherein the oligomeric compound is formulated for administration at a dose of about 0.5 mg, about 1 mg, about 4 mg or about 8 mg.

4. The use of any one of claims 1 to 3, wherein the oligomeric compound is formulated for administration at a dose of about 1 mg.

5. The use of any one of claims 1 to 4, wherein the oligomeric compound is formulated for administration about once per month.

6. The use of any one of claims 1 to 5, wherein the seizures are selected from the group consisting of focal motor seizures, tonic seizures, generalized tonic-clonic seizures and myoclonic seizures.

7. The use of any one of claims 1 to 6, wherein the reduction of frequency of seizures experienced by the subject comprises a reduction in the average number of daily seizures experienced by the subject in a 28-day period, as compared to the average number of daily seizures experienced by the subject prior to administration of the oligomeric compound.

8. The use of any one of claims 1 to 7, wherein the reduction of frequency of seizures experienced by a subject comprises a reduction in the number of seizures experienced by the subject in a 28-day period by 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%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%, as compared to the number of seizures experienced by the subject prior to administration of the oligomeric compound.

9. The use of any one of claims 1 to 8, wherein the subject is between 2 and 18 years old.

10. The use of any one of claims 1 to 8, wherein the subject is a newborn to 24 months old.

11. The use of any one of claims 1 to 8 and 10, wherein the subject is a newborn.

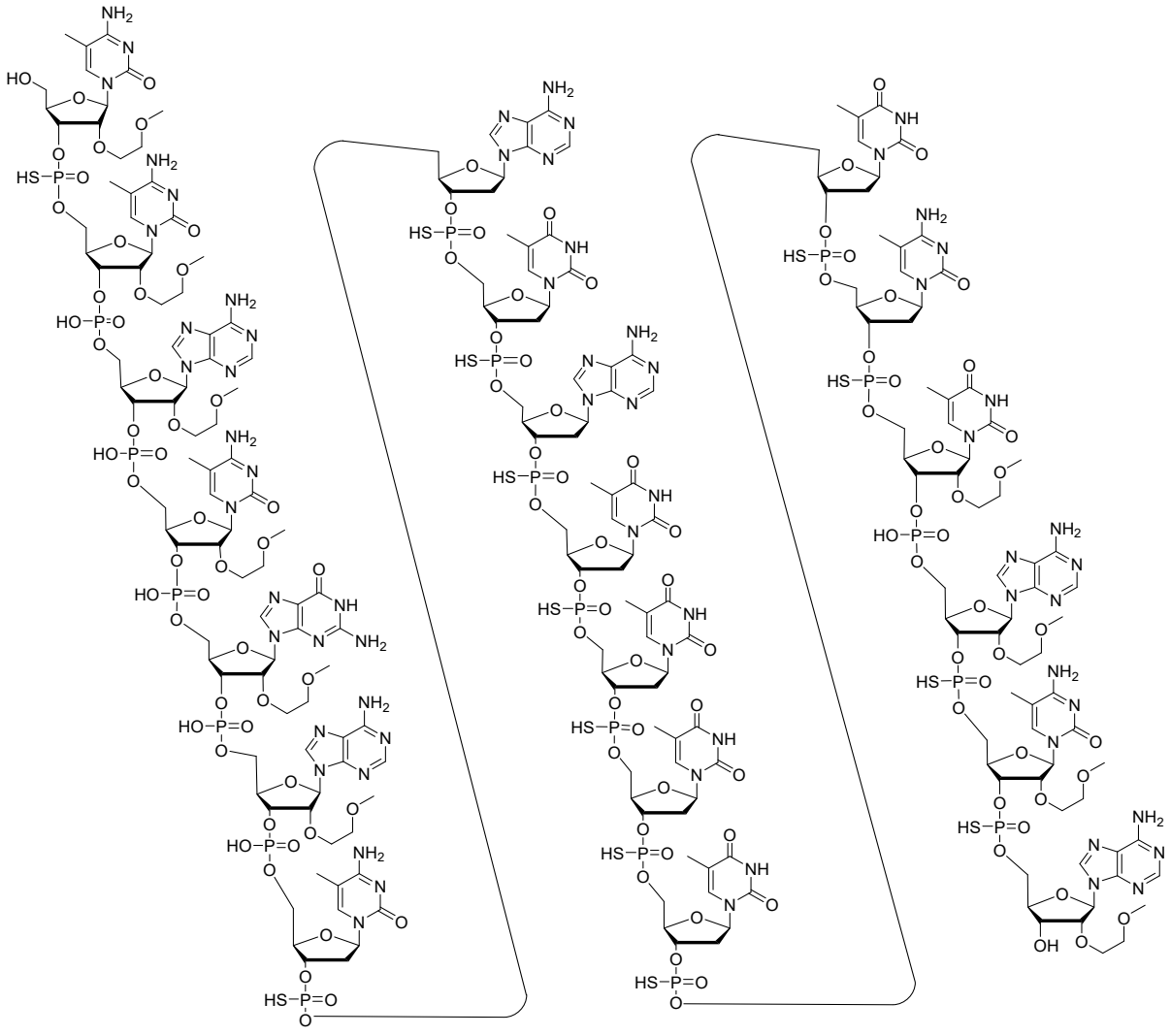
12. The use of claim 11, wherein the newborn is a premature newborn.

13. The use of any one of claims 1 to 12, wherein the gain-of-function mutation in SCN2A gene is selected from the group consisting of L210Q, A263V, E430A, R1882Q,

G879R, Q1479H, V423L, G1593R, K1502N, V1601L, G211D, S1780I, D343H and A1329D.

14. The use of claim 13, wherein the gain-of-function mutation is A1329D.

15. The use of any one of claims 1 to 14, wherein the oligomeric compound is a modified oligonucleotide represented by the following chemical structure:



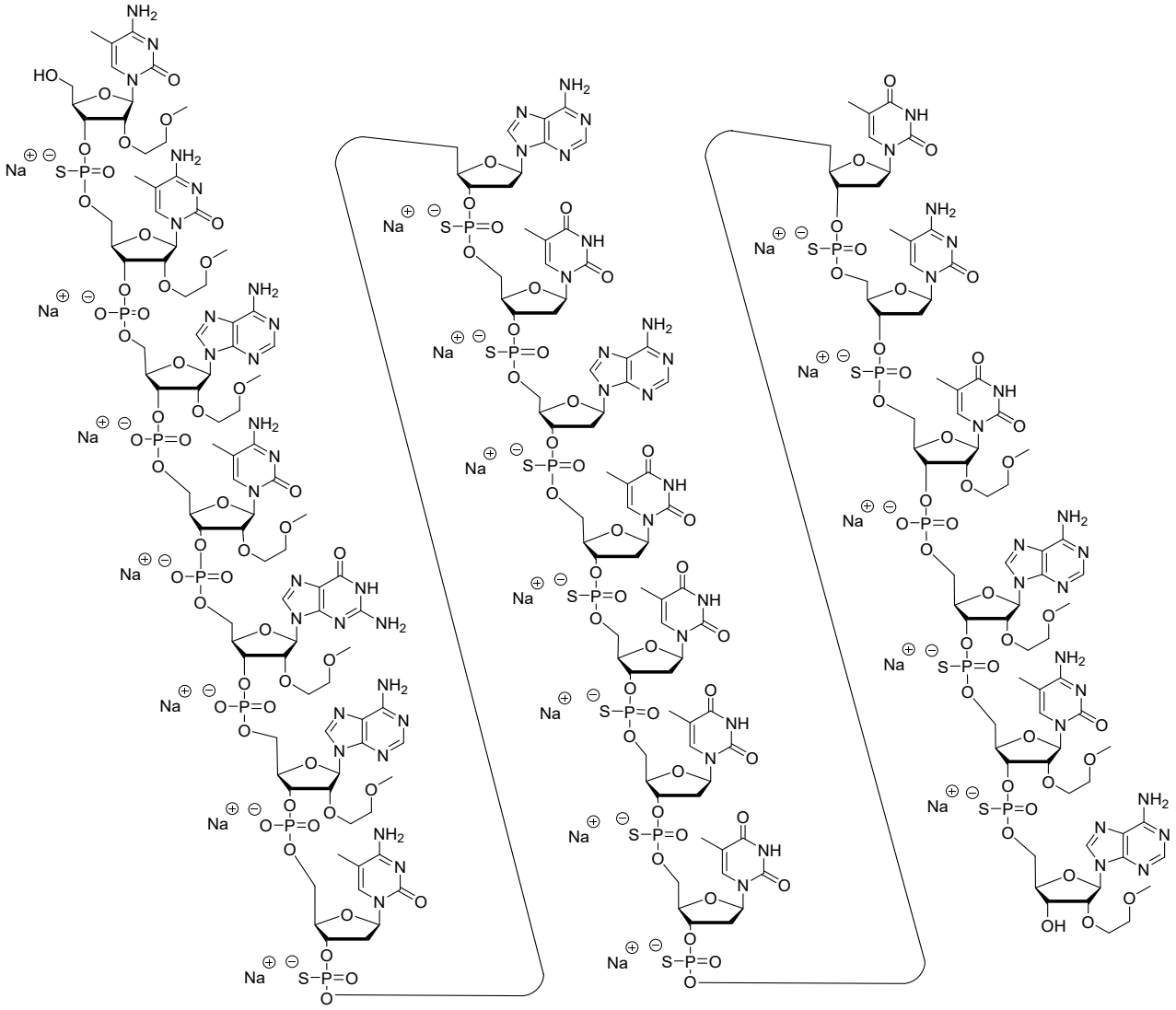
(SEQ ID NO: 3) or a salt thereof.

16. The use of claim 15, wherein the modified oligonucleotide is a sodium salt or a potassium salt.

17. The use of claim 16, wherein the modified oligonucleotide is a sodium salt.

18. The use of claim 17, wherein the modified oligonucleotide is represented by the

following chemical structure:



(SEQ ID NO: 3).

19. The use of any one of claims 1 to 18, wherein the oligomeric compound is formulated for administration as a part of a pharmaceutical composition comprising the oligomeric compound and a pharmaceutically acceptable diluent or carrier.

20. The use of claim 19, wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or phosphate-buffered saline (PBS).

21. The use of claim 20, wherein the pharmaceutically acceptable diluent is aCSF.

22. The use of any one of claims 1 to 21, wherein the oligomeric compound is formulated for administration at a dose of about 1 mg to about 8 mg.