

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 SEQ ID NO:42 or 231, 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 SEQ ID NO:42 or 231; 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,

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 SEQ ID NO: 42 or 231, 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 according to SEQ ID NO: 42 or 231; 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 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.