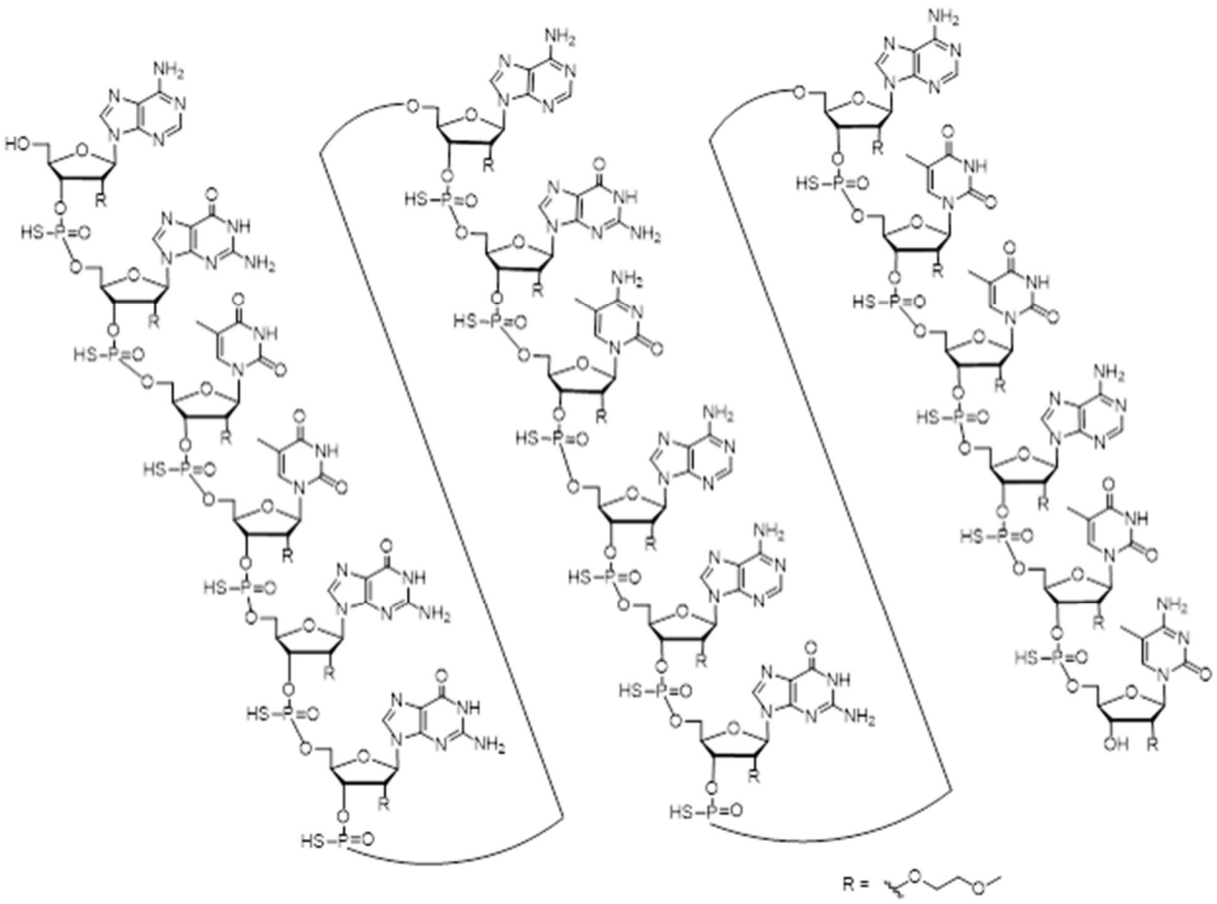
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound according to the following chemical structure:



(I), or a salt thereof, in the manufacture of a pharmaceutical composition 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, wherein the treatment comprises administering to the human subject the pharmaceutical composition comprising the compound at a first dose, one or more loading doses, and one or more maintenance doses, thereby treating or reducing the likelihood of developing the disease or condition in the human subject,

wherein the administration of the first dose is followed by administration of one or more loading doses,

wherein the one or more maintenance doses is administered after the administration of the one or more loading doses,

wherein the first dose contains the compound at a first dose amount of from about 25 to about 80 mg,

wherein the one or more maintenance doses contains the compound at a dose amount that is different from the first dose amount, and

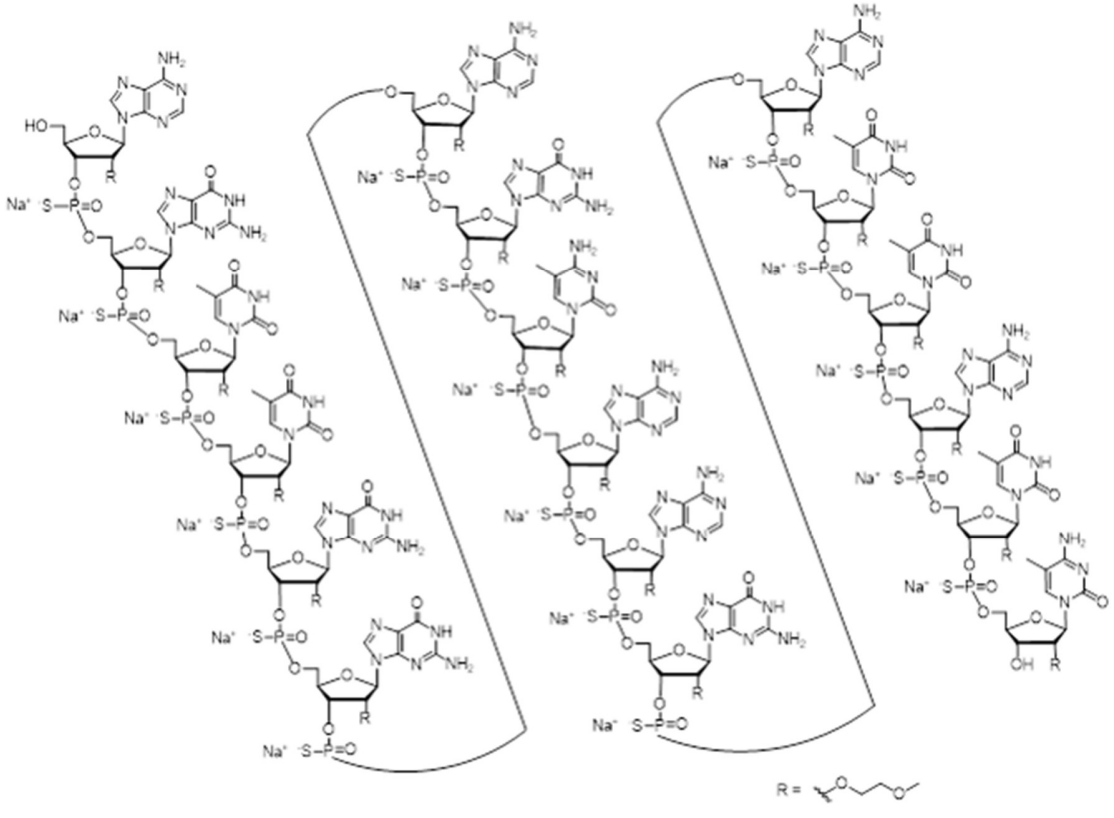
wherein:

(a) a subsequent dose of the one or more maintenance doses is higher than a previously administered maintenance dose,

(b) a subsequent dose of the one or more maintenance doses is the same as a previously administered maintenance dose, or

(c) a subsequent dose of the one or more maintenance doses is lower than a previously administered maintenance dose.

2. The use of claim 1, wherein the compound has the following structure:



(II).

3. The use of claim 1 or 2, wherein the treatment comprises administering to the human subject the pharmaceutical composition comprising the compound at the first dose of about 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, or 80 mg.
4. The use of any one of claims 1-3, wherein the dose amount of the one or more maintenance doses is from about 0.5 milligrams to about 500 milligrams.
5. The use of any one of claims 1-4, wherein the first 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 dose, or the first 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 dose.
6. The use of any one of claims 1-5, wherein the pharmaceutical composition comprises a pharmaceutically acceptable excipient, carrier, or diluent, and/or the pharmaceutical composition is a liquid composition.
7. The use of any one of claims 1-6, 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.
8. The use of claim 7, wherein the compound is dissolved or suspended in the diluent and the first dose has a volume of 5 mL or higher, 10 mL, 15 mL, 20 mL, 25 mL, or 30 mL.
9. The use of claim 7 or 8, wherein the compound is dissolved or suspended in the diluent and each of the one or more maintenance doses has a volume of 5 mL, 10 mL, 15 mL, 20 mL, 25 mL, or 30 mL.
10. The use of any one of claims 7-9, wherein the diluent comprises a cerebral spinal fluid (CSF) sample from the human subject or an artificial cerebral spinal fluid (aCSF) solution.
11. The use of any one of claims 1-10, wherein the pharmaceutical composition is administered:
    (a) into the intrathecal space of the human subject;
    (b) into the cerebrospinal fluid of the human subject;
    (c) into the brain of the human subject;
    (d) into the cerebrospinal fluid in the brain of the human subject;
    (e) as a bolus injection;
    (f) by infusion with a delivery pump;

(g) by intracerebroventricular injection;

(h) by intrathecal injection; and/or

(i) by lumbar injection.

12. The use of any one of claims 1-11, wherein the compound is solubilized or diluted in an isotonic solution, a phosphate-buffered solution with at least pH 5.8, or a phosphate-buffered solution with pH 6.6-7.6.

13. The use of any one of claims 1-12, wherein the compound is solubilized or diluted in a buffer comprising:

(a) 25-250 mM NaCl;

(b) 0.1-20 mM KCl;

(c) 0.1-50 mM Na_2HPO_4;

(d) 0.1-50 mM NaH_2PO_4;

(e) 0.1-50 mM $CaCl_2$; and/or

(f) 0.1-50 mM $MgCl_2$.

14. The use of any one of claims 1-13, wherein the compound 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.

15. The use of any one of claims 1-14, wherein the pharmaceutical formulation does not comprise a preservative.

16. The use of any one of claims 1-15, wherein the compound is present in the pharmaceutical composition at a concentration of from 0.1 mg/mL to 100 mg/mL, or 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, 20 mg/mL, 22.5 mg/mL, or 25 mg/mL.

17. The use of any one of claims 1-16, wherein the human subject is at most 18 years old at first dose.

18. The use of any one of claims 1-17, wherein the disease or condition is Dravet Syndrome.

19. The use of any one of claims 1-18, 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 a variant of uncertain significance in an SCN1A gene;
(vi) at least 2 prior treatments for epilepsy that had lack of adequate seizure control;
(vii) 4 or more convulsive seizures during the 28 days prior to administering, wherein the convulsive seizure 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).

20. The use of any one of claims 1-19, wherein the treatment further comprises administrating at least one additional therapeutic agent or therapy.