



- (51) **International Patent Classification:**
A61K 31/5377 (2006.01) *A61K 31/4245* (2006.01)
- (21) **International Application Number:**
PCT/US2016/059262
- (22) **International Filing Date:**
28 October 2016 (28.10.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/248,891 30 October 2015 (30.10.2015) US
- (71) **Applicant:** PTC THERAPEUTICS, INC. [US/US]; 100 Corporate Court, Middlesex Business Center, South Plainfield, NJ 07080 (US).
- (72) **Inventors:** WELCH, Ellen; 33 Hollow Brook Road, Califon, NJ 07830 (US). TOMIZAWA, Yuki; 20 Newport Parkway, Apt. 2708, Jersey City, NJ 07310 (US). VAZIRANI, Priya; 12 Sandpiper Drive, South Amboy, NJ 08879 (US).
- (74) **Agents:** CHHEDA, Jennifer, J. et al.; Jones Day, 250 Vesey Street, New York, NY 10281-1047 (US).
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) **Title:** METHODS FOR TREATING EPILEPSY

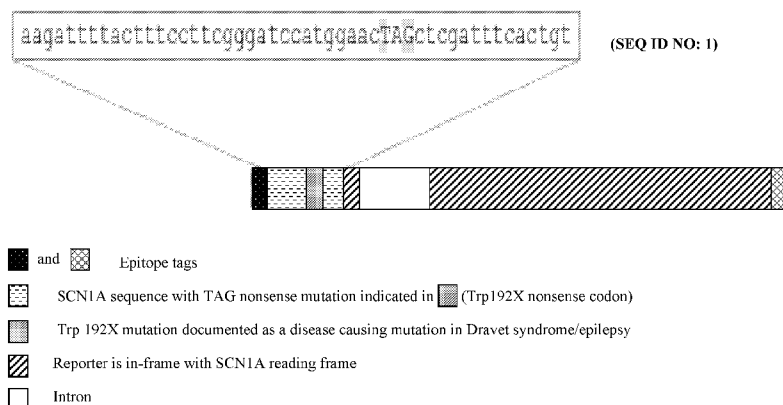


Fig. 1

(57) **Abstract:** Provided herein are methods of treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease, comprising administering a 1,2,4-oxadiazole benzoic acid to a patient having a nonsense mutation mediated epileptic disease. In particular, provided herein are methods of treating, preventing, ameliorating or managing a CDKL5 and/or SCN1A (Dravet syndrome) nonsense mutation mediated epileptic disease.



METHODS FOR TREATING EPILEPSY

[0001] This application claims the benefit of U.S. Provisional Application No. 62/248,891, filed October 30, 2015, which is incorporated herein by reference in its entirety.

1. FIELD

[0002] Provided herein are methods of treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease, comprising administering a 1,2,4-oxadiazole benzoic acid compound (e.g., 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid) to a patient having a nonsense mutation mediated epileptic disease, e.g., a patient having a nonsense mutation in the *CDKL5* or *SCN1A* gene. In particular, provided herein are methods of treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease associated with a genetic or somatic nonsense mutation in the *CDKL5* or *SCN1A* gene, wherein the nonsense mutation results in expression of a premature stop codon, comprising administering a 1,2,4-oxadiazole benzoic acid compound (e.g., 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid) to a patient having the nonsense mutation.

2. BACKGROUND

[0003] Drug-resistant epilepsy is a serious condition that negatively impacts patients' quality of life. Those with drug-resistant epilepsy are at a higher risk for sudden unexpected death in epilepsy (SUDEP). The risk factors associated with SUDEP, including frequent generalized tonic-clonic seizures, antiepileptic drug (AED) polytherapy, and common nocturnal seizures, are also factors present in those with drug-resistant epilepsy (Pack AM., SUDEP, What Are the Risk Factors? Do Seizures or Antiepileptic Drugs Contribute to an Increased Risk?, *Epilepsy Currents*, Vol. 12, No. 4 (July/August) 2012 pp. 131–132). The risk of SUDEP in those with drug-resistant epilepsy can exceed 5% per decade (Devinsky O. *N Engl J Med*. 2011;365(19):1801-11). Most patients with drug-resistant epilepsy, despite trials of multiple combinations of AEDs, have no Food and Drug Administration (FDA)-approved treatment options left. *CDKL5* and *SCN1A* related epilepsies are rare epilepsies commonly associated with drug-resistant epilepsy.

[0004] *CDKL5* is a gene that produces the cyclin-dependent kinase-like 5 (*CDKL5*) protein that is primarily expressed in the brain, thymus, and testes. The gene is composed of 24

exons; exons 2 – 11 code for the catalytic domain whereas exons 12 – 18 code for the carboxy-terminus. In mice, the expression profile suggests that the CDKL5 protein is involved in neuronal maturation (Rusconi *et al.*, J Biol Chem., 2008; 283(44):30101-11). CDKL5 phosphorylates the protein product of the *MECP2* gene in the nucleus and likely accounts for the similarity between Rett syndrome and CDKL5 related epilepsies (Mari F., Azimonti S., Bertani I., Bolognese F., Colombo E., Caselli R., Scala E., Longo I., Grosso S., Pescucci C., Ariani F., Hayek G., Balestri P., Bergo A., Badaracco G., Zappella M., Broccoli V., Renieri A., Kilstrup-Nielsen C., Landsberger N., CDKL5 Belongs to the Same Molecular Pathway of MeCP2 and it is Responsible for the Early-Onset Seizure Variant of Rett Syndrome, Human Molecular Genetics, 2005, Vol. 14, No. 14, 1935-1946). MECP2 regulates genes associated with synapse function and maintenance. Loss of this function drives phenotype and is responsible for similarities to Rett syndrome. CDKL5 also phosphorylates DNA methyltransferase 1 (DNMT1) and amphiphysin, and interacts with Rac1 to influence actin remodeling and neuronal morphogenesis.

[0005] CDKL5 related epilepsies are X-linked genetic epileptic encephalopathies most often present in females. Males are more severely affected than females (Melani *et al.*, Dev Med Child Neurol. 2011;53(4):354-60). The incidence is ~1 in 45,000 live births. Patients with CDKL5 related X-linked genetic epileptic encephalopathies exhibit early signs of poor developmental skills, (e.g., poor sucking, poor eye contact) in the first several months of life. Later, impairment of hand motor skills, lack of speech acquisition, and severe and global developmental delays become apparent (Fehr *et al.*, Eur J Hum Genet. 2013;21(3):266-73; Melani *et al.*, Dev Med Child Neurol. 2011;53(4):354-60). Eye contact and social interactions are often reduced. Many patients are never able to walk independently. CDKL5 related epilepsies are not associated with cortical atrophy or degeneration. CDKL5 deficiency causes an epileptic encephalopathy, in which epileptiform abnormalities contribute to progressive functional impairment. Epilepsy often presents with infantile spasms within the first four months of age (Mei *et al.*, Epilepsia. 2010 Apr;51(4):647-54). The average age of seizure onset is 6 weeks with more than 90% experiencing seizures in the first 3 months of life. Later, tonic-clonic seizures consisting of a vibratory tonic phase followed by a clonic phase occur and often last 2 to 4 minutes (Melani *et al.*, Dev Med Child Neurol. 2011;53(4):354-60). After age 3 years, seizures remit in many children while others continue to have drug-resistant epilepsy, with tonic

spasms and of myoclonic seizures (Mei *et al.*, *Epilepsia*. 2010 Apr;51(4):647-54). The electroencephalogram findings often include slowing of the background with interictal generalized, focal or multifocal discharges. A burst-suppression pattern may be seen in younger children (Melani *et al.*, *Dev Med Child Neurol*. 2011;53(4):354-60).

[0006] *SCN1A* (Nav1.1) is the sodium channel $\alpha 1$ subunit gene, expressed almost exclusively in the brain. Mutations in *SCN1A* can cause a variety of epilepsies that range from benign febrile seizures to severe epileptic encephalopathy and Dravet syndrome (severe myoclonic epilepsy of infancy; Mulley *et al.*, *Hum Mutat*. 2005;25(6):535-42; Catterall *et al.*, *J Physiol*. 2010;588(Pt 11):1849-59). The major mechanism underlying epilepsy appears to be impairment of gamma-Aminobutyric acid (GABA) interneuron inhibitory function (Catterall *et al.*, *J Physiol*. 2010;588(Pt 11):1849-59; Yu FH., Mantegazza M., Westenbroek RE., Robbins CA., Kalume F., Burton KA., Spain WJ., McKnight GS., Scheuer T., Catterall WA., Reduced Sodium Current in GABAergic Interneurons in a Mouse Model of Severe Myoclonic Epilepsy in Infancy, *Nature Neuroscience*, 2006, September, Vol. 9, No. 9, 1142-1149).

[0007] Dravet syndrome was initially described in 1978 as Severe Myoclonic Epilepsy of Infancy (SMEI) by Charlotte Dravet (Dravet C. *Dev Med Child Neurol*. 2011;53(Suppl 2):1-6). It causes febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures; it can also cause absence, absence-myoclonic, and complex partial seizures. Seizures typically begin in the first year of life in an otherwise normal infant. Initial seizures are often febrile status epilepticus (Dravet C., Bureau M., Oguni H., Fukuyama Y., Cokar O., Severe Myoclonic Epilepsy in Infancy: Dravet Syndrome, *Adv. Neurol.* (2005), 95, 71-102). Later, myoclonic, atypical absence, and partial seizures often develop. Seizures are usually drug-resistant but the severity of the epilepsy tends to diminish around puberty. Developmental delays in the second year of life and intellectual disability are present in more than 95% of patients (Chieffo D., Battaglia D., Lettori D., Del Re M., Brogna C., Dravet C., Mercuri E., Guzzetta F., Chieffo, D., Chieffo, D., Neuropsychological Development in Children with Dravet Syndrome, *Epilepsy Research*, (2011), 95, 86-93). Autism spectrum disorder is diagnosed in approximately 25% of patients (Genton *et al.*, *Epilepsia*. 2011;52(Suppl 2):44-9). Most patients develop cerebellar dysfunction in later childhood, manifesting as an ataxic gait disorder, dysarthria, and intention tremor (Genton *et al.*, *Epilepsia*. 2011;52(Suppl 2):44-9). The mortality rate is high. Approximately 15% of patients die by adolescence and 20% die by early adulthood (Genton *et*

al., *Epilepsia*. 2011;52(Suppl 2):44-9). SUDEP and status epilepticus are the most common causes of death.

[0008] Nonsense mutations are single-point alterations in the DNA that, when transcribed, result in conversion of a messenger ribonucleic acid (mRNA) triplet (e.g., CAG) that codes for an amino acid to a triplet (e.g., UAG) that is interpreted as a stop codon (i.e., a premature stop codon). The presence of the premature stop codon within the mRNA leads to production of a truncated, non-functional protein and consequent disease. Nonsense mutations are the basis for approximately 13% to 40% of the individual cases of most inherited disease, including CDKL5 deficiency and SCN1A deficiency (in particular, Dravet syndrome) amongst many others (Frame Kathryn, Elbri DO. The International CDKL5 Disorder Database Newsletter 1 (July 2013)).

3. SUMMARY OF THE DISCLOSURE

[0009] Provided herein are methods of treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease and/or an epileptic disease associated with a premature stop codon, comprising administering a 1,2,4-oxadiazole benzoic acid (e.g., 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid) to a patient having a nonsense mutation mediated epileptic disease. In particular, provided herein are methods of treating, preventing, ameliorating or managing an epileptic disease associated with a nonsense mutation or a premature stop codon (e.g., resulting in a CDKL5 and/or SCN1A deficiency (in particular, Dravet syndrome); or, e.g., a SCN2A, GABRG2, DEPDC5, and/or NAPB deficiency), comprising administering a 1,2,4-oxadiazole benzoic acid (e.g., 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid) to a patient having an epileptic disease associated with a nonsense mutation or a premature stop codon (e.g., resulting in a CDKL5 and/or SCN1A deficiency (in particular, Dravet syndrome); or, e.g., a SCN2A, GABRG2, DEPDC5, and/or NAPB deficiency).

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 is a schematic showing the reporter construct used to monitor readthrough activity of SCN1A nonsense codon W192X. The SCN1A nucleotide sequence used

in the reporter construct is shown (SEQ ID NO: 1) with the TAG nonsense mutation (W192X) indicated by gray shading.

[0011] Figure 2 is a schematic showing the reporter construct used to monitor readthrough activity of CDKL5 nonsense codon R59X. The CDKL5 nucleotide sequence used in the reporter construct is shown (SEQ ID NO: 2) with the TGA nonsense mutation (R59X) indicated by gray shading.

[0012] Figure 3 is a schematic showing the reporter construct used to monitor readthrough activity of CDKL5 nonsense codon (R550X). The CDKL5 nucleotide sequence used in the reporter construct is shown (SEQ ID NO: 3) with the TGA nonsense mutation (R550X) indicated by gray shading.

[0013] Figure 4 is a graph showing the fold increase in readthrough activity of a 1,2,4-oxadiazole benzoic acid compound, specifically, 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, compared to DMSO in cells harboring the SCN1A reporter construct shown in Figure 1.

[0014] Figure 5 is a graph showing the fold increase in readthrough activity of a 1,2,4-oxadiazole benzoic acid compound, specifically, 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, compared to DMSO in cells harboring the CDKL5 reporter constructs shown in Figure 2 (R59X) and Figure 3 (R550X).

[0015] Figure 6 is a schematic of the study design of the clinical protocol described in Example 6.2 herein.

5. DETAILED DESCRIPTION

5.1. Definitions

[0016] As used herein, the term “premature translation termination” has the same meaning as commonly understood by one of ordinary skill in the art. In certain embodiments, the term “premature translation termination” generally refers to the result of a mutation that changes a codon corresponding to an amino acid to a stop codon. In specific embodiments, the term “premature translation termination” refers to the event during translation where production of a functional protein ceases as the result of a nonsense mutation in DNA that changes a transcribed mRNA codon corresponding to an amino acid to a premature stop codon.

[0017] As used herein, the terms “premature termination codon” and “premature stop codon” have the same meaning as commonly understood by one of ordinary skill in the art. In certain embodiments, the terms “premature termination codon” and “premature stop codon” refer to the occurrence of a stop codon where a codon corresponding to an amino acid should be.

[0018] As used herein, the term “nonsense mutation” has the same meaning as commonly understood by one of ordinary skill in the art. In certain embodiments, the term “nonsense mutation” refers to a mutation in DNA that changes a codon in mRNA corresponding to an amino acid to a stop codon. In certain embodiments, the nonsense mutation is a mutation that occurs in DNA and is then transcribed as a premature stop codon into mRNA.

[0019] As used herein, the term “nonsense suppression” has the same meaning as commonly understood by one of ordinary skill in the art. In certain embodiments, the term “nonsense suppression” refers to the inhibition or suppression of premature translation termination, resulting in production of a functional protein.

[0020] As used herein, the term “modulation of premature translation termination” refers to an increase in the amount of functional protein produced by readthrough of a premature stop codon in the presence of a nonsense suppression agent. In certain embodiments, to treat, prevent, ameliorate or manage a nonsense mutation mediated disease, it is desirable to increase the production of a protein encoded by a mRNA with a premature stop codon, *i.e.*, to enable readthrough of the premature stop codon resulting from expression of the disease gene so translation of the mRNA can occur through the use of a nonsense suppression agent.

[0021] As used herein, the terms “active agent,” “drug,” and “drug substance” refer to a 1,2,4-oxadiazole benzoic acid compound selected from 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid (having the generic name “ataluren”) or a pharmaceutically acceptable salt thereof provided herein and collectively referred to herein as “Compound 1”.

[0022] As used herein, the term “dose(s)” means a quantity of active agent to be administered at one time.

[0023] As used herein, the term “unit dosage form(s)” includes solid dosage forms such as tablets, caplets, capsules, lozenges, dispersions, powders, granules or gels and the like or liquid dosage forms such as solutions, suspensions, emulsions or elixirs and the like and solid forms such as powders or granules that can be reconstituted to provide such liquid dosage forms, wherein such unit dosage form(s) are suitable for oral or parenteral administration to a patient.

[0024] As used herein, the terms “dosing regimen” and “dosage(s)” mean the amount of an active agent administered over a given time period, per patient weight.

[0025] As used herein, the terms “subject” and “patient” are used interchangeably to refer to an animal or any living organism having sensation and the power of voluntary movement, and which requires for its existence oxygen and organic food. Non-limiting examples include members of the human, primate, equine, porcine, bovine, leporine, rattus, murine, canine and feline species. In some embodiments, the subject is a mammal or a warm-blooded vertebrate animal. In certain embodiments, the subject is a non-human animal. In specific embodiments, the subject is a human and, further, a human patient. In certain embodiments, the subject is a fetus, embryo, infant, child, adolescent or adult. In one embodiment, the subject has been determined through genetic pre-screening to possess a nonsense mutation. In another embodiment, the subject has been determined through genetic pre-screening to have a particular premature stop codon (*i.e.*, UAA, UGA, or UAG). In another embodiment, the context of the premature stop codon in the subject has been determined from the genetic pre-screening (*i.e.*, UAAA, UAAC, UAAU, UAAG, UGAA, UGAC, UGAU, UGAG, UAGA, UAGC, UAGU or UAGG).

[0026] As used herein, the term “effective amount” in the context of the production of a functional read-through protein refers to the amount of the functional read-through protein(s) that has a prophylactic and/or therapeutic benefit to a subject. In specific embodiments, an effective amount of a functional read-through protein is the amount of protein that has in one, two or more of the following effects: (1) prevents the onset, development and/or progression of a nonsense mutation mediated epileptic disease, (2) prevents the onset, development and/or progression of one or more symptoms associated with a nonsense mutation mediated epileptic disease, (3) reduces the duration and/or severity of a nonsense mutation mediated epileptic disease, (4) reduces the number of symptoms associated with a nonsense mutation mediated epileptic disease, (5) reduces the duration of one or more symptoms associated with a nonsense mutation mediated epileptic disease, (6) reduces the severity of one or more symptoms associated with a nonsense mutation mediated epileptic disease and (7) improves the quality of life of a subject.

[0027] Symptoms of a nonsense mutation mediated epileptic disease include convulsive seizures, drop seizures, generalized unilateral (one-sided) clonic seizures or generalized tonic clonic (grand mal) seizures, characterized by unconsciousness, convulsions, and muscle rigidity;

absence seizures, characterized by a short loss of consciousness; generalized myoclonic seizures, characterized by sporadic jerks, usually on both sides of the body; generalized clonic seizures, characterized by repetitive, rhythmic jerks that involve both sides of the body at the same time; generalized tonic seizures, characterized by stiffening of the muscles; generalized atonic seizures, characterized by a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall; simple motor partial seizures, characterized by awareness, jerking, muscle rigidity, spasms, head-turning; simple sensory partial seizures, characterized by awareness and unusual sensations affecting either the vision, hearing, smell taste, or touch; simple psychological partial seizures, characterized by awareness and memory or emotional disturbances; complex partial seizures (focal dyscognitive seizures), characterized by impairment of awareness and automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements; partial seizures with secondary generalization, characterized by preservation of consciousness that then evolves into a loss of consciousness and convulsions; sudden unexpected death in epilepsy (SUDEP); and nocturnal seizures.

[0028] As used herein, the term “effective amount” in the context of the administration of a compound described herein refers to the amount of the compound that has a prophylactic and/or therapeutic benefit to a subject. In specific embodiments, an effective amount of a compound described herein that has one, two or more of the following effects: (1) prevents the onset, development and/or progression of a nonsense mutation mediated epileptic disease, (2) prevents the onset, development and/or progression of one or more symptoms associated with a nonsense mutation mediated epileptic disease, (3) reduces the duration and/or severity of a nonsense mutation mediated epileptic disease, (4) reduces the number of symptoms associated with a nonsense mutation mediated epileptic disease, (5) reduces the duration of one or more symptoms associated with a nonsense mutation mediated epileptic disease, (6) reduces the severity of one or more symptoms associated with a nonsense mutation mediated epileptic disease and/or (7) improves the quality of life of a subject. Examples of effective amounts of a compound described herein are provided in Section 5.4, *infra*. In specific embodiments, an effective amount of a compound described herein has one, two or more of the foregoing effects when used for treating, preventing, ameliorating or managing a symptom or nonsense mutation mediated epileptic disease provided herein in Section 6, *infra*.

[0029] As used herein, the term “functional” in the context of a functional read-through protein refers to a protein that is produced in a sufficient quantity to treat, prevent or ameliorate a disease that results from the absence of the protein. In addition, the term refers to a protein that has enough of the functional activity of the wild-type protein to have a beneficial effect in a cell or subject which otherwise does not produce or produces insufficient amounts of the wild-type protein as a result of a mutation (*e.g.*, a nonsense mutation) in the nucleic acid sequence (*e.g.*, gene) encoding the protein. In a specific embodiment, the functional read-through protein(s) substantially performs the function of the full-length wild-type protein(s), *i.e.*, treating, preventing, ameliorating or managing the disease. In another specific embodiment, the functional read-through protein(s) performs one, two, three or more of the functions of the full-length wild-type protein(s). In certain embodiments, the functional read-through protein(s) produced is a functional non-wild-type protein(s). In certain embodiments, the functional read-through protein(s) produced is the functional wild-type protein(s). In some embodiments, the functional non-wild-type protein produced is full-length. In some embodiments, the functional wild-type protein produced is full-length. In other embodiments, the functional non-wild-type protein(s) is not full-length. In other embodiments, the functional wild-type protein(s) produced is not full-length.

[0030] As used herein, the term “substantially performs the function of the full-length wild-type protein(s),” in the context of a functional read-through protein(s), means that the functional read-through protein(s) performs at least one, two, three, or more functions of the full-length wild-type protein(s).

[0031] As used herein, the term “nonsense mutation mediated epileptic disease” refers to an epileptic disease or condition or a type of epilepsy resulting either directly or indirectly from a nonsense mutation(s) in a gene(s), where the nonsense mutation(s) prevents production of a wild-type protein in an affected cell. For example, a nonsense mutation in the *CDKL5* gene prevents the production of a wild-type CDKL5 protein and results in a CDKL5 nonsense mutation mediated epileptic disease. Also, for example, a nonsense mutation in the *SCN1A* gene prevents the production of a wild-type SCN1A protein and results in SCN1A nonsense mutation mediated epileptic disease (in particular, Dravet syndrome). Examples of nonsense mutation mediated epileptic diseases include, but are not limited to Dravet syndrome, Severe myoclonic epilepsy of infancy (SMEI), CDKL5, SCN1A, Generalized epilepsy with febrile seizures plus

(GEFS+), Temporal lobe epilepsy, Intractable childhood epilepsy, Benign familial neonatal-infantile seizures (BFNIS), Benign familial neonatal seizures (BFNIS), Juvenile myoclonic epilepsy (JME), Childhood absence epilepsy (CAE), Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Cryptogenic generalized epilepsy (CGE), Cryptogenic focal epilepsy (CFE), Myoclonic astatic epilepsy (MAE), Severe idiopathic generalized epilepsy of infancy (SIGEI), Infantile spasms (IS), and Early-onset epileptic encephalopathy (EOEE).

[0032] As used herein, “in combination” in the context of the administration of therapies refers to the use of more than one therapy. The use of the term “in combination” does not restrict the order in which therapies are administered to a subject with a disease. In certain embodiments, administration of one or more therapies to a subject with a disease includes, without limitation, a first therapy that can be administered prior to (*e.g.*, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject which had, has, or is susceptible to a disease. The therapies are administered to a subject in a sequence and within a time interval such that a unit dosage form(s) described herein can act together with another therapy to provide an increased benefit than if the therapies were administered alone.

[0033] As used herein, the terms “manage,” “managing” and “management” refer to the beneficial effects that a patient derives from the administration of a pharmaceutical composition provided herein comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof, which does not result in treating, preventing or ameliorating the nonsense mutation mediated disease.

[0034] As used herein, the terms “prevent,” “preventing” and “prevention” refer to the prevention (*e.g.*, avoidance) of the onset, recurrence, spread or worsening of the nonsense mutation mediated disease or a symptom thereof (and thus treat or, at least, ameliorate such disease) in a patient from the administration of a pharmaceutical composition provided herein comprising administering Compound 1 or a salt thereof to a patient with such a disease. Since diseases associated with a nonsense mutation have a genetic or somatic basis, requiring a patient

to be screened for the presence of a nonsense mutation. When it is determined through screening that a patient has a nonsense mutation, an effective amount of a pharmaceutical composition comprising an effective amount of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof provided herein can be administered to the patient to prevent the onset, recurrence, spread or worsening of the disease or a symptom thereof.

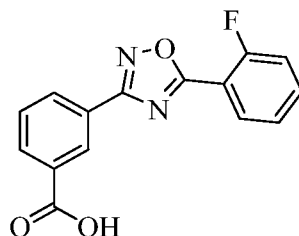
[0035] As used herein, the terms “treat,” “treating” and “treatment” refer to the eradication or amelioration of the disease or symptoms associated with the disease. In certain embodiments, such terms refer to minimizing the spread or worsening of the disease in a patient from the administration of a pharmaceutical composition provided herein comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof provided herein to a patient with such a disease. When it is determined that a patient has a disease associated with a genetic or somatic nonsense mutation, an effective amount of a pharmaceutical composition comprising an effective amount of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof provided herein can be administered to the patient to eradicate, ameliorate, or minimize the spread or the worsening of the disease or a symptom thereof.

[0036] As used herein, the term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0037] As used herein, the term “wild-type” in the context of a protein refers to a protein that is found in nature (often, but not necessarily, the protein that is the predominant protein whose absence is responsible for the disease) and is designated as a standard or reference protein.

5.2. The Compound

[0038] A compound for use in the preparation of the pharmaceutical compositions and salts provided herein is 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid (generically referred to as ataluren), having the structure of Formula (I):



(I).

[0039] A compound of Formula (I) can be prepared according to the methods described in U.S. Pat. No. 6,992,096, U.S. Pat. No. 7,678,922 and U.S. Pat. No. 8,367,841, the disclosure of each of which is incorporated by reference herein in its entirety. Alternatively, a compound of Formula (I) can be also prepared according to other methods apparent to those of skill in the art based upon the teaching herein. All such alternative methods are intended to be included within the scope of the methods described herein. The compound of Formula (I) and salts provided herein are collectively referred to as “Compound 1.”

[0040] In one embodiment, the compound of Formula (I) used in the pharmaceutical compositions, processes, and methods provided herein is a free acid. In one embodiment, the free acid is a solid. In yet another embodiment, the solid free acid is a crystalline form described in U.S. Pat. No. 7,863,456, the disclosure of which is incorporated by reference herein in its entirety. In yet another embodiment, the solid free acid is a crystalline Form A. In yet another embodiment, the solid free acid is a crystalline Form B. These solid forms of the compound of Formula (I) can also be prepared according to the methods described in U.S. Pat. No. 7,863,456, the disclosure of which is incorporated by reference herein in its entirety. Alternatively, the solid forms of the compound of Formula (I) can be also prepared according to other methods apparent to those of skill in the art based upon the teaching herein.

[0041] In another embodiment, the free acid of the compound of Formula (I) is a pharmaceutically acceptable solvate. In one embodiment, the free acid is a hydrate. In another embodiment, the compound of Formula (I) is a pharmaceutically acceptable anhydrous form.

[0042] In another embodiment, Compound 1 used in the pharmaceutical compositions, processes, and methods provided herein is a pharmaceutically acceptable free acid of the compound of Formula (I). In another embodiment, Compound 1 used in the pharmaceutical compositions, processes, and methods provided herein is a pharmaceutically acceptable salt of the compound of Formula (I). In another embodiment, Compound 1 used in the pharmaceutical compositions, processes, and methods provided herein is a pharmaceutically acceptable anhydrous free acid or salt of the compound of Formula (I).

5.3. Salt forms

[0043] In certain embodiments, the methods provided herein comprise the use of salt forms of Formula (I), including salts selected from L-arginine, L-histidine, L-lysine, N-methyl glucamine, magnesium methoxide, potassium hydroxide, sodium hydroxide or tromethamine (PCT Application No. PCT/US2015/018889, filed March 5, 2015, published as International Patent Application No. WO 2015/134711, which is incorporated by reference herein in its entirety). More particularly, the methods provided herein comprise the use of salt forms of Formula (I) selected from L-lysine, sodium and tromethamine.

5.4. Pharmaceutical Compositions

[0044] Pharmaceutical compositions and single unit dosage forms comprising an effective amount of Compound 1 can be used in the methods provided herein. Individual dosage forms may be suitable for oral, dermal, mucosal (including, without limitation, sublingual, buccal, rectal, nasal, or vaginal) or parenteral (including, without limitation, subcutaneous, intramuscular, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intrasynovial, intravesical or intravenous) or ocular administration. Preferred pharmaceutical compositions and single unit dosage forms are suitable for oral administration.

[0045] In certain embodiments, the pharmaceutical composition comprises from about 0.1% to about 99%, from about 5% to about 90%, from about 5% to about 50%, from about 10% to about 40%, from about 20% to about 30%, from about 0.1% to about 5%, from about 0.1% to about 2.5%, from about 0.1% to about 1% or from about 0.25% to about 0.5% by weight of Compound 1. In certain embodiments, the pharmaceutical composition comprises about 0.1%,

about 0.25%, about 0.5%, about 1%, about 2%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90% by weight of Compound 1. In certain embodiments, the pharmaceutical composition comprises about 0.25%, about 0.5% or about 1% by weight of Compound 1.

[0046] In certain embodiments, the pharmaceutical composition provided herein comprises from about 1 mg to about 5,000 mg, from about 10 mg to about 2,000 mg, from about 50 mg to about 1,000 mg, from about 100 mg to about 1,000 mg, or from about 100 mg to about 500 mg of Compound 1. In certain embodiments, the pharmaceutical composition provided herein comprises about 125 mg, about 200 mg, about 325 mg, about 400 mg, or about 500 mg of Compound 1. In certain embodiments, the pharmaceutical composition provided herein comprises from about 120 mg to about 130, from about 195 mg to about 205 mg, from about 320 mg to about 330 mg, from about 395 mg to about 405 mg, or from about 495 mg to about 505 mg of Compound 1.

[0047] In certain embodiments, Compound 1 in the pharmaceutical compositions provided herein is the free acid of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a salt of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, as provided herein.

[0048] The pharmaceutical compositions provided herein can be provided in a unit dosage form or multiple-dosage form. A unit dosage form, as used herein, refers to a physically discrete unit suitable for administration to a human or animal subject using packaging known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit dosage form include, without limitation, an individually packaged packet, sachet or bottle or dropper. A unit dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit dosage forms packaged in a single container to be administered as segregated or combined unit dosage forms. Examples of a multiple-dosage form include a packet or sachet of granules or powder, a vial or bottle of tablets or capsules, or a bottle of liquid solution in fluid ounces, pints or gallons for administration either parenterally, orally or ocularly via dropper.

[0049] The pharmaceutical compositions provided herein can be administered as a divided dose over a period of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be

determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data or by observation of certain clinical factors. It is further understood that for any particular individual, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the pharmaceutical composition.

5.4.1. Topical Formulations

[0050] In certain embodiments, the pharmaceutical compositions provided herein are formulated as topical formulations in cosolvents such as, but not limited to, dimethyl sulfoxide, propylene glycol and the like.

5.4.2. Oral Formulations

[0051] In certain embodiments, the pharmaceutical compositions provided herein are formulated for oral administration. In certain embodiments, the pharmaceutical compositions provided herein for oral administration are provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, sublingual or buccal films (i.e., “fast-melts”), chewable tablets, effervescent tablets, dispersible tablets, mini-tablets, capsules, pills, strips, troches, lozenges, pastilles, oral film, cachets, pellets, medicated chewing gum, bulk powders or granules, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient, the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, surfactants, lubricants, glidants, pH-modifiers, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, solvating agents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0052] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic

gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose (CMC), carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL[®]-PH-101, AVICEL[®]-PH-103, AVICEL[®] RC-581, AVICEL[®]-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[0053] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[0054] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methyl cellulose and carboxymethyl cellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and VEEGUM[®] HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0055] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL[®] 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL[®] (Cabot

Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0056] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL[®] (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN[®] 20), polyoxyethylene sorbitan monooleate 80 (TWEEN[®] 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric, fumaric acid, ascorbic acid and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0057] It should be understood that many carriers and excipients may serve a plurality of functions, even within the same formulation.

[0058] The pharmaceutical compositions provided herein as a tablet for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, effervescent tablets, mini tablets, beads, coated beads, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-

coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredient from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0059] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0060] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0061] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions,

elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, solvating agent or emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

[0062] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, ethylenediamine tetraacetic acid (EDTA), hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[0063] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems.

[0064] The pharmaceutical compositions provided herein for oral administration can be provided as either non-effervescent or effervescent tablets or granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[0065] In certain embodiments, the pharmaceutical composition is formulated as a solid oral dosage form. In certain embodiments, the pharmaceutical composition is formulated as a liquid oral dosage form. In certain embodiments, the unit dosage form is provided as a suspension after being mixed in a pharmaceutically acceptable liquid or semi-solid solvating agent, which includes, but is not limited to, water, milk, carbonated beverage, juice, fruit juice, fruit punch, applesauce, yogurt, pudding, ice cream, baby food, baby formula or a soy or grain based product.

[0066] In certain embodiments, provided herein are pharmaceutical compositions, which comprise 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a pharmaceutically acceptable salt thereof and one or more additional pharmaceutically acceptable excipients. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules. In another embodiment, the one or more excipients are selected from the group consisting of polydextrose, mannitol, poloxamer, polyethylene glycol, hydroxyethyl cellulose, crospovidone, artificial flavoring, and magnesium stearate. In certain embodiments, the artificial flavoring is an artificial vanilla flavor.

[0067] Additionally provided herein are pharmaceutical composition comprising about 25% by weight of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof; about 1% by weight of colloidal silicon dioxide; and one or more additional pharmaceutically acceptable excipients. In certain embodiments, pharmaceutical compositions provided herein comprise 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof and one or more excipients selected from polydextrose, poloxamer (*e.g.*, poloxamer 407), polyethylene glycol (*e.g.*, polyethylene glycol 3350), mannitol, hydroxyethyl cellulose, artificial vanilla flavoring, crospovidone, colloidal silicon dioxide, and magnesium stearate (*e.g.*, of vegetable origin). In certain embodiments, pharmaceutical compositions provided herein comprise 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof and one or more excipients selected from a suspending agent, a binding agent that can also provide taste-masking, surfactant agent, a disintegrant and other excipients can be present. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment,

the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules. In another embodiment, 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof is present in an amount such as at about 25% by weight). In another embodiment, the one or more excipients are selected from the group consisting of polydextrose, mannitol, poloxamer, polyethylene glycol, hydroxyethyl cellulose, croscopovidone, artificial vanilla flavor, and magnesium stearate. In another embodiment, the one or more excipients (and their proportions of the total formulation weight) are selected from the group consisting of a suspending agent such as Litesse® Ultra [refined polydextrose] at about 26% by weight, a binding agent such as mannitol at about 26% by weight, surfactant agents such as polyethylene glycol 3350 at about 10.0% by weight and Lutrol® micro F127 [poloxamer 407 powder] at about 4% by weight, a disintegrant such as croscopovidone at about 5% by weight, and other excipients, each less than about 2% by weight such as cab-o-sil, hydroxyethyl cellulose, magnesium stearate [non-bovine] at about 1% by weight and colloidal silicon dioxide at about 1% by weight.

[0068] Further provided herein are pharmaceutical compositions comprising about 25% by weight of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 26% by weight of polydextrose, about 26% by weight of mannitol, about 3% by weight of poloxamer, about 10% by weight of polyethylene glycol, about 2% by weight of hydroxyethyl cellulose, about 5% by weight of croscopovidone, about 1% by weight of artificial vanilla flavor, about 1% by weight of colloidal silicon dioxide and about 1% by weight of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0069] Further provided herein are pharmaceutical compositions comprising, 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof in a range of from about 120 mg to about 1005 mg, polydextrose in a range of from about 133 mg to about 1030 mg, mannitol in a range of from about 137 mg to about 901 mg, poloxamer in a range of from about 19 mg to about 147 mg, polyethylene glycol in a range of from about 52 mg to about 402 mg, hydroxyethyl cellulose in a range of from about 7 mg to about 59 mg,

crospovidone in a range of from about 26 mg to about 201 mg, artificial vanilla flavor in a range of from about 3 mg to about 29 mg, colloidal silicon dioxide in a range of from about 5 mg to about 39 mg and magnesium stearate in a range of from about 5 mg to about 39 mg. In one embodiment, the pharmaceutical composition is formulated as powder. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0070] Further provided herein are pharmaceutical compositions, comprising about 130 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 133 mg of polydextrose, about 137 mg of mannitol, about 19 mg of poloxamer, about 52 mg of polyethylene glycol, about 7 mg of hydroxyethyl cellulose, about 26 mg of crospovidone, about 3 mg of artificial vanilla flavor, about 5 mg of colloidal silicon dioxide and about 5 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0071] Further provided herein are pharmaceutical compositions, comprising about 205 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 210 mg of polydextrose, about 216 mg of mannitol, about 30 mg of poloxamer, about 82 mg of polyethylene glycol, about 12 mg of hydroxyethyl cellulose, about 41 mg of crospovidone, about 6 mg of artificial vanilla flavor, about 8 mg of colloidal silicon dioxide and about 8 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0072] Further provided herein are pharmaceutical compositions, comprising about 330 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 338 mg of polydextrose, about 348 mg of mannitol, about 48 mg of

poloxamer, about 132 mg of polyethylene glycol, about 19 mg of hydroxyethyl cellulose, about 66 mg of crospovidone, about 9 mg of artificial vanilla flavor, about 13 mg of colloidal silicon dioxide and about 13 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0073] Further provided herein are pharmaceutical compositions, comprising about 405 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 415 mg of polydextrose, about 427 mg of mannitol, about 59 mg of poloxamer, about 162 mg of polyethylene glycol, about 24 mg of hydroxyethyl cellulose, about 81 mg of crospovidone, about 12 mg of artificial vanilla flavor, about 16 mg of colloidal silicon dioxide and about 16 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0074] Further provided herein are pharmaceutical compositions, comprising about 505 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 518 mg of polydextrose, about 453 mg of mannitol, about 74 mg of poloxamer, about 202 mg of polyethylene glycol, about 30 mg of hydroxyethyl cellulose, about 101 mg of crospovidone, about 15 mg of artificial vanilla flavor, about 20 mg of colloidal silicon dioxide and about 20 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0075] Further provided herein are pharmaceutical compositions, comprising about 1005 mg of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid or a pharmaceutically acceptable salt thereof, about 1030 mg of polydextrose, about 901 mg of mannitol, about 147 mg of poloxamer, about 402 mg of polyethylene glycol, about 59 mg of hydroxyethyl cellulose,

about 201 mg of crospovidone, about 29 mg of artificial vanilla flavor, about 39 mg of colloidal silicon dioxide and about 39 mg of magnesium stearate. In one embodiment, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In one embodiment, the pharmaceutical composition is formulated as granules.

[0076] In certain embodiments, the unit dosage form comprises from about 35 mg to about 5,600 mg of Compound 1, from about 35 mg to about 2800 mg of Compound 1, from about 35 mg to about 1,400 mg of Compound 1, from about 125 mg to about 1,000 mg of Compound 1, from about 250 mg to about 1,000 mg of Compound 1, from about 325 mg to about 1,000 mg of Compound 1 or from about 500 mg to about 1,000 mg of Compound 1.

[0077] In certain embodiments, the unit dosage form comprises about 35 mg, about 50 mg, about 70 mg, about 100 mg, about 125 mg, about 140 mg, about 175 mg, about 200 mg, about 250 mg, about 280 mg, about 325 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 560 mg, about 700 mg, about 750 mg, about 1,000 mg, about 1,400 mg, about 2800 mg or about 5600 mg of Compound 1.

[0078] In a particular embodiment, the unit dosage form comprises about 125 mg, about 250 mg or about 1,000 mg of Compound 1.

[0079] In a more particular embodiment, the unit dosage form comprises 125 mg, 250 mg or 1,000 mg of Compound 1.

[0080] In certain embodiments, the pharmaceutical composition is formulated as a powder. In one embodiment, the pharmaceutical composition is formulated as a micronized powder. In one embodiment, the pharmaceutical composition is formulated as a nanoparticle. In another embodiment, the pharmaceutical composition provided herein is formulated as granules. In certain embodiments, the pharmaceutical composition provided herein is packaged in a packet or sachet. In certain embodiments, the pharmaceutical composition provided herein is packaged in a heat-sealed laminated aluminum packet or sachet. In certain embodiments, the pharmaceutical composition provided herein is packaged in a child-resistant packet or sachet. In certain embodiments, the pharmaceutical composition provided herein is packaged in a packet or sachet, which comprises layers of polyethylene terephthalate, polyethelyene, aluminum foil,

adhesive, and sealing film. In certain embodiments, the pharmaceutical composition may be provided in a bottle including, but not limited to, high density polyethylene (HDPE) bottles.

[0081] In certain embodiments, the pharmaceutical composition provided herein is formulated as granules for reconstitution. In certain embodiments, the pharmaceutical composition provided herein is formulated as granules for reconstitution as an oral suspension.

[0082] In certain embodiments, the pharmaceutical composition provided herein is reconstituted before administration by being mixed to a suspension with a pharmaceutically acceptable liquid or semi-solid solvating agent which includes, but is not limited to, water, milk, carbonated beverage, juice, fruit juice, fruit punch, applesauce, yogurt, pudding, ice cream, baby food, baby formula or a soy or grain based product.

[0083] In certain embodiments, the pharmaceutical composition provided herein is reconstituted before administration by being mixed to a suspension with water. In one embodiment, reconstitution of a 125 mg unit dosage formulation of Compound 1 is carried out by the addition of at least about 5 mL of water directly in a bottle containing Compound 1 to achieve a nominal concentration of at least about 25 mg/mL in the total volume of suspension. In another embodiment, reconstitution of a 250 mg unit dosage formulation Compound 1 is carried out by the addition of at least about 10 mL of water directly in a bottle containing Compound 1 to achieve a nominal concentration of at least about 25 mg/mL in the total volume of suspension. In another embodiment, reconstitution of a 500 mg unit dosage formulation Compound 1 is carried out by the addition of at least about 20 mL of water directly in a bottle containing Compound 1 to achieve a nominal concentration of at least about 25 mg/mL in the total volume of suspension. In another embodiment, reconstitution of a 1000 mg unit dosage formulation Compound 1 is carried out by the addition of at least about 40 mL of water directly in a bottle containing Compound 1 to achieve a nominal concentration of at least about 25 mg/mL in the total volume of suspension.

[0084] In other embodiments, a unit dosage form containing the pharmaceutical composition provided herein is only opened at the time of dose preparation. The full contents of each unit dosage form is mixed to a suspension with a liquid or a semi-solid solvating agent, wherein the liquid is at least 30 mL (1 ounce) or the semi-solid is at least 3 tablespoons. The prepared dose should be mixed well before being administered. The amount of the liquid or semi-solid solvating agent can be increased based on patient preference.

[0085] In certain embodiments, the pharmaceutical composition provided herein comprises Compound 1 as a free acid or as a pharmaceutically acceptable salt, wherein the pharmaceutically acceptable salt is a magnesium salt, a potassium salt, a sodium salt, a tromethamine salt, an L-lysine salt, an L-arginine salt, an N-methyl glucamine salt or an L-histidine salt.

5.4.3. Parenteral Formulations and Administration

[0086] The pharmaceutical compositions provided herein comprising Compound 1 can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein include, without limitation, intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[0087] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration including, without limitation, solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy, supra*).

[0088] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0089] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil,

sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[0090] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α -cyclodextrin, β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin, and sulfobutylether 7- β -cyclodextrin (CAPTISOL[®], CyDex, Lenexa, KS).

[0091] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0092] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions.

In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0093] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0094] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in the body, but allows the active ingredient in the pharmaceutical compositions to be osmotically or ionically diffused.

[0095] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0096] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

5.4.4. Particle Size

[0097] In certain embodiments, the pharmaceutical compositions provided herein comprise a micronized form of Compound 1 having enhanced solubility. In certain

embodiments, the pharmaceutical compositions provided herein comprise a nanoparticle form of Compound 1 having enhanced solubility and/or dissolution rate.

[0098] In specific embodiments, the pharmaceutical compositions provided herein comprise a micronized form of Compound 1 wherein >90% of the particles of Compound 1 have a diameter (D_{90} value) of between about 1-10 microns having enhanced solubility. In certain embodiments, the pharmaceutical compositions provided herein comprise a micronized form of Compound 1, having a D_{90} value of about 10 microns, about 9 microns, about 8 microns, about 7 microns, about 6 microns, about 5 microns, about 4 microns, about 3 microns, about 2 microns or about 1 micron having enhanced solubility. In certain embodiments, the pharmaceutical compositions provided herein comprise a micronized form of Compound 1, having a D_{90} value of between about 1-5 microns having enhanced solubility and/or dissolution rate. In certain embodiments, the pharmaceutical compositions provided herein comprise a micronized form of Compound 1, having a D_{90} value of about 5 microns, about 4 microns, about 3 microns, about 2 microns or about 1 micron having enhanced solubility and/or dissolution rate. In certain embodiments, the pharmaceutical compositions provided herein comprise a nanoparticle form of Compound 1 having enhanced solubility. In specific embodiments, the pharmaceutical compositions provided herein comprise a nanoparticle form of Compound 1 wherein >90% of the particles of Compound 1 have a D_{90} value of about 0.1 microns, about 0.09 microns, about 0.08 microns, about 0.07 microns, about 0.06 microns, about 0.05 microns, about 0.04 microns, about 0.03 microns, about 0.02 microns or about 0.01 microns.

[0099] Provided herein are micronized forms of Compound 1 having a volume weighted mean diameter $D[4,3]$ of from about 2 μm to about 12 μm . Also provided herein are micronized forms of Compound 1 having a surface weighted mean diameter $D[3,2]$ of from about 1 μm to about 3 μm . Further provided herein are forms of Compound 1 having a D_{90} particle size in the range of from about 5 μm to about 26 μm , having a D_{50} particle size in the range of from about 1 μm to about 6 μm , or having a D_{10} particle size in the range of from about 0.1 μm to about 1.5 μm .

5.4.5. Kits

[00100] The pharmaceutical compositions provided herein can be provided as an article of manufacture using packaging materials well known to those of skill in the art. Examples of

pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, packets, sachets, tubes, inhalers, pumps, bags, vials, containers, syringes, droppers, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00101] Provided herein are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of the active ingredient to a subject. In certain embodiments, the kit provided herein includes a container and a dosage form of a pharmaceutical formulation provided herein and instructions for use thereof. In certain embodiments, the instructions included with the kit provide guidance with respect to the dosage amounts and/or dosing regimens for administration of Compound 1.

[00102] In certain embodiments, the kit includes a container comprising a dosage form of the pharmaceutical formulation provided herein, in a container comprising one or more other therapeutic agent(s) described herein. In certain embodiments the pharmaceutical formulation is provided as a white to off-white powder for oral suspension. In certain embodiments, the pharmaceutical formulation comprises a matrix and/or suspending agents, surfactants, and/or excipients. In certain embodiments the pharmaceutical formulation is provided as granules for oral suspension. In certain embodiments, the pharmaceutical formulation for oral suspension is packaged in aluminum-foil, child-resistant sachets (packets) in dose strengths containing 125, 250, or 1000 mg of the active drug substance. In certain embodiments, the kit comprises packets or sachets comprising one or more dosage strengths of the pharmaceutical formulation for oral suspension (125, 250, or 1000 mg or matching placebo).

[00103] Kits provided herein can further include devices that are used to administer the active ingredient. Examples of such devices include, but are not limited to, syringes, needle-less injectors, drip bags, patches, droppers and inhalers.

[00104] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer the active ingredient. For example, if the active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration or can be reconstituted as a suspension for oral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and

Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5.5. Methods of Use

[00105] Provided herein are methods for treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease, comprising administering a 1,2,4-oxadiazole benzoic acid to a patient having a nonsense mutation mediated epileptic disease. In particular, provided herein are methods for treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease, comprising administering an effective amount of a 1,2,4-oxadiazole benzoic acid to a patient having a nonsense mutation mediated epileptic disease. Additionally provided herein are methods of treating, preventing, ameliorating or managing an epileptic disease associated with a nonsense mutation or a premature stop codon, comprising administering an effective amount of a 1,2,4-oxadiazole benzoic acid to a patient having an epileptic disease associated with a nonsense mutation or a premature stop codon.

[00106] Also provided herein are methods of treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease by modulation of premature translation termination, comprising administering to a patient having a type of a nonsense mutation mediated epileptic disease capable of being ameliorated by modulation of premature translation termination an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein.

[00107] In certain embodiments, the administration of an effective amount of 1,2,4-oxadiazole benzoic acid to a subject results in one, two or more of the following effects in a patient having a nonsense mutation-mediated epileptic disease: (1) prevents the onset, development and/or progression of a nonsense mutation mediated epileptic disease; (2) prevents the onset, development and/or progression of one or more symptoms associated with a nonsense mutation mediated epileptic disease; (3) reduces the duration and/or severity of a nonsense mutation mediated epileptic disease; (4) reduces the number of symptoms associated with a nonsense mutation mediated epileptic disease; (5) reduces the duration of one or more symptoms

associated with a nonsense mutation mediated epileptic disease; (6) reduces the severity of one or more symptoms associated with a nonsense mutation mediated epileptic disease; and (7) improves the quality of life of said subject.

[00108] In certain embodiments, the administration of an effective amount of 1,2,4-oxadiazole benzoic acid to a subject results in one, two or more of the following effects in a patient having a nonsense mutation-mediated epileptic disease, as described herein in Section 6, *infra*: (1) reduces the frequency of seizures from baseline, *e.g.*, convulsive seizures, drop seizures, motor seizures, tonic-clonic seizures, hemiconvulsive seizures, drop attacks, tonic seizures, focal motor seizures, and myoclonic seizures; (2) reduces the frequency of minor seizure types, *e.g.*, myoclonic seizures, and staring (absence or complex partial) seizures; (3) improves cognitive, motor, behavioral function, and/or quality of life; (4) reduces the number of episodes of status epilepticus, defined as a convulsive lasting more than 10 minutes; (5) reduces the number of uses of rescue medications; and (6) reduces the number of emergency room visits/hospitalizations.

[00109] Nonsense mutation mediated epileptic diseases to be treated in accordance with the methods described herein include, but are not limited to, Dravet syndrome, also known as Severe myoclonic epilepsy of infancy (SMEI), CDKL5, Febrile seizures (FS), Generalized epilepsy with febrile seizures plus (GEFS+), Familial temporal lobe epilepsy, Intractable childhood epilepsy, Benign familial neonatal-infantile seizures (BFNIS), Benign familial neonatal seizures (BFNIS), Juvenile myoclonic epilepsy (JME), Childhood absence epilepsy (CAE), Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Cryptogenic generalized epilepsy (CGE), Cryptogenic focal epilepsy (CFE), Familial focal epilepsy, Familial focal epilepsy with variable foci (FFEVF), Familial mesial temporal lobe epilepsy (FMTLE), Autosomal dominant lateral temporal epilepsy (ADLTE), Myoclonic astatic epilepsy (MAE), Severe idiopathic generalized epilepsy of infancy (SIGEI), Infantile spasms (IS), and Early-onset epileptic encephalopathy (EOEE). In certain embodiments, a patient to be treated in accordance with the methods described herein has drug-resistant epilepsy.

[00110] Symptoms of a nonsense mutation mediated epileptic disease include convulsive seizures, drop seizures, generalized unilateral (one-sided) clonic seizures or generalized tonic clonic (grand mal) seizures, characterized by unconsciousness, convulsions, and muscle rigidity; absence seizures, characterized by a short loss of consciousness; generalized myoclonic seizures,

characterized by sporadic jerks, usually on both sides of the body; generalized clonic seizures, characterized by repetitive, rhythmic jerks that involve both sides of the body at the same time; generalized tonic seizures, characterized by stiffening of the muscles; generalized atonic seizures, characterized by a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall; simple motor partial seizures, characterized by awareness, jerking, muscle rigidity, spasms, head-turning; simple sensory partial seizures, characterized by awareness and unusual sensations affecting either the vision, hearing, smell taste, or touch; simple psychological partial seizures, characterized by awareness and memory or emotional disturbances; complex partial seizures (focal dyscognitive seizures), characterized by impairment of awareness and automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements; partial seizures with secondary generalization, characterized by preservation of consciousness that then evolves into a loss of consciousness and convulsions; sudden unexpected death in epilepsy (SUDEP); and nocturnal seizures.

[00111] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from a nonsense mutation in one or both alleles of one or more genes, including but not limited to *SCN1A*, *CDKL5*, *SCN2A*, *GABRG2*, *DEPDC5*, and *NAPB*.

[00112] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in one or both alleles of the *SCN1A* gene. In certain embodiments, the one or more nonsense mutations in one or both alleles of the *SCN1A* gene is W192X, R222X, R568X, R701X, R854X, K1017X, W1261X, R1213X, W1408X, W952X, W1284X, S219fsX275, K1100fsX1107, L1670fsX1107, and/or S1846fsX1856. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of *SCN1A* and is treated in accordance with the methods of the invention is Dravet syndrome, also known as Severe myoclonic epilepsy of infancy (SMEI). In some embodiments, a patient having Dravet syndrome that results from a W192X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a R222X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some

embodiments, a patient having Dravet syndrome that results from a R568X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a R701X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a R854X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a L1017X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a W1261X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a R1213X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a W1408X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a W952X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a W1284X nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a S219fsX275 nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a K1100fsX1107 nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a L1670fsX1107 nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having Dravet syndrome that results from a S1846fsX1856 nonsense mutation in one or both alleles of the *SCN1A* gene is treated in accordance with the methods of the invention.

[00113] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in

one or both alleles of the *CDKL5* gene. In certain embodiments, the one or more nonsense mutations in one or both alleles of the *CDKL5* gene is R59X, R550X, Q834X, R79X, Q118X, R134X, L142X, Q347X, R559X, and/or R970X. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of *CDKL5* and is treated in accordance with the methods of the invention is CDKL5. In some embodiments, CDKL5 that results from a R59X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a R550X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a Q834X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a R79X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a Q118X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a R134X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a L142X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a Q347X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a R559X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, CDKL5 that results from a R970X nonsense mutation in one or both alleles of the *CDKL5* gene is the nonsense mutation mediated epileptic disease treated in accordance with the methods of the invention. In some embodiments, a patient having CDKL5 that results from a R59X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In

some embodiments, a patient having *CDKL5* that results from a R550X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a Q834X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a R79X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a Q118X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a R134X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a L142X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a Q347X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a R559X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having *CDKL5* that results from a R970X nonsense mutation in one or both alleles of the *CDKL5* gene is treated in accordance with the methods of the invention.

[00114] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in one or both alleles of the *SCN2A* gene. In certain embodiments, the one or more nonsense mutations in one or both alleles of the *SCN2A* gene is R102X. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of the *SCN2A* and is treated in accordance with the methods of the invention is Intractable Childhood Epilepsy. In some embodiments, a patient having Intractable Childhood Epilepsy that results from a R102X nonsense mutation in one or both alleles of the *SCN2A* gene is treated in accordance with the methods of the invention.

[00115] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in one or both alleles of the *GABRG2* gene. In certain embodiments, the one or more nonsense

mutations in one or both alleles of the *GABRG2* gene is R136X, W429X, Q40X, Q390X, Q1X, Q351X, W390X and/or Y444Mfs51X. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of *GABRG2* and is treated in accordance with the methods of the invention is Generalized Epilepsy with Febrile Seizures plus (GEFS+), Dravet syndrome, or Febrile Seizures (FS). In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a R136X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a W429X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Q40X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Q390X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Q1X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Q351X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a W390X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Y444Mfs51X nonsense mutation in one or both alleles of the *GABRG2* gene is treated in accordance with the methods of the invention.

[00116] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in one or both alleles of the *DEPDC5* gene. In certain embodiments, the one or more nonsense mutations in one or both alleles of the *DEPDC5* gene is R555X and/or Y306X. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of *DEPDC5* and is treated in accordance with the methods of the

invention is Familial Focal Epilepsy, Familial Focal Epilepsy with Variable Foci (FFEVF), Familial Mesial Temporal Lobe Epilepsy (FMTLE), or Autosomal Dominant Lateral Temporal Epilepsy (ADLTE). In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a R555X nonsense mutation in one or both alleles of the *DEPDC5* gene is treated in accordance with the methods of the invention. In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a Y306X nonsense mutation in one or both alleles of the *DEPDC5* gene is treated in accordance with the methods of the invention.

[00117] In some embodiments, the nonsense mutation mediated epileptic disease treated in accordance with the methods described herein results from one or more nonsense mutations in one or both alleles of the *NAPB* gene. In certain embodiments, the one or more nonsense mutations in one or both alleles of the *NAPB* gene is S160X. In certain embodiments, the nonsense mutation mediated epileptic disease that results from a nonsense mutation in one or both alleles of the *NAPB* and is treated in accordance with the methods of the invention is Early-Onset Epileptic Encephalopathy (EOEE). In some embodiments, a patient having a nonsense mutation mediated epileptic disease that results from a S160X nonsense mutation in one or both alleles of the *NAPB* gene is treated in accordance with the methods of the invention.

[00118] Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of a nonsense mutation mediated epileptic disease by modulation of premature translation termination, comprising administering to a patient having a symptom of a nonsense mutation mediated epileptic disease capable of being ameliorated by modulation of premature translation termination an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein.

[00119] Further provided herein are methods for treating, preventing, ameliorating or managing a CDKL5 related epilepsy, comprising administering to a patient having the CDKL5 related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the CDKL5 related epilepsy, comprising administering to a patient having a symptom of the CDKL5 related epilepsy an

effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the *CDKL5* related epilepsy results from certain mutations on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R59X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R550X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a Q834X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R79X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a Q118X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R134X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a L142X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a Q347X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R559X nonsense mutation on one or both alleles of the *CDKL5* gene. In certain embodiments, the *CDKL5* related epilepsy results from a R970X nonsense mutation on one or both alleles of the *CDKL5* gene.

[00120] Further provided herein are methods for treating, preventing, ameliorating or managing a *SCN1A* related epilepsy, comprising administering to a patient having the *SCN1A* related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the *SCN1A* related epilepsy, comprising administering to a patient having a symptom of the *SCN1A* related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the *SCN1A* related epilepsy results from certain mutations on one or both alleles of the *SCN1A* gene.

[00121] Further provided herein are methods for treating, preventing, ameliorating or managing a SCN1A related epilepsy such as Dravet syndrome. Also provided herein are methods for treating, preventing, ameliorating or managing Dravet syndrome, comprising administering to a patient having Dravet syndrome an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of Dravet syndrome, comprising administering to a patient having a symptom of Dravet syndrome an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, Dravet syndrome results from certain mutations on one or both alleles of the *SCN1A* gene. In certain embodiments, Dravet syndrome results from a W192X nonsense mutation on one or both alleles of the *SCN1A* gene.

[00122] Further provided herein are methods for treating, preventing, ameliorating or managing a SCN2A related epilepsy, comprising administering to a patient having the SCN2A related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the SCN2A related epilepsy, comprising administering to a patient having a symptom of the SCN2A related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the SCN2A related epilepsy results from certain mutations on one or both alleles of the *SCN2A* gene. In certain embodiments, the SCN2A related epilepsy results from a R102X nonsense mutation on one or both alleles of the *SCN2A* gene.

[00123] Further provided herein are methods for treating, preventing, ameliorating or managing a GABRG2 related epilepsy, comprising administering to a patient having the GABRG2 related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more

pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the *GABRG2* related epilepsy, comprising administering to a patient having a symptom of the *GABRG2* related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the *GABRG2* related epilepsy results from certain mutations on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a R136X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a W429X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a Q40X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a Q390X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a Q1X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a Q351X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a W390X nonsense mutation on one or both alleles of the *GABRG2* gene. In certain embodiments, the *GABRG2* related epilepsy results from a Y444Mfs51X nonsense mutation on one or both alleles of the *GABRG2* gene.

[00124] Further provided herein are methods for treating, preventing, ameliorating or managing a *DEPDC5* related epilepsy, comprising administering to a patient having the *DEPDC5* related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the *DEPDC5* related epilepsy, comprising administering to a patient having a symptom of the *DEPDC5* related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the *DEPDC5* related epilepsy results from certain mutations on one or both alleles of the *DEPDC5* gene. In certain embodiments, the *DEPDC5* related epilepsy results from a R555X nonsense mutation on

one or both alleles of the *DEPDC5* gene. In certain embodiments, the *DEPDC5* related epilepsy results from a Y306X nonsense mutation on one or both alleles of the *DEPDC5* gene.

[00125] Further provided herein are methods for treating, preventing, ameliorating or managing a NAPB related epilepsy, comprising administering to a patient having the NAPB related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. Further provided herein are methods for treating, preventing, ameliorating or managing a symptom of the NAPB related epilepsy, comprising administering to a patient having a symptom of the NAPB related epilepsy an effective amount of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein. In certain embodiments, the NAPB related epilepsy results from certain mutations on one or both alleles of the *NAPB* gene. In certain embodiments, the NAPB related epilepsy results from a S160X nonsense mutation on one or both alleles of the *NAPB* gene.

[00126] Also provided herein are methods of screening subjects having a nonsense mutation mediated epileptic disease or one or more symptoms of a nonsense mutation mediated epileptic disease for the presence of a nonsense mutation, and when a nonsense mutation is identified, an effective amount of a pharmaceutical composition comprising an effective amount of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof provided herein can be administered to the patient to prevent the onset, recurrence, spread or worsening of the disease or a symptom thereof. Methods of screening subjects for the presence of a nonsense mutation include whole-exome sequencing of a sample obtained from a patient. In certain embodiments, it has been determined through screening that the subject possesses a nonsense mutation. In certain embodiments, it has been determined through screening which premature stop codon the patient has (*i.e.*, UAA, UGA, or UAG).

[00127] In certain embodiments, a patient treated in accordance with the methods provided herein is as described herein at Section 6, *infra*.

[00128] In certain embodiments, a patient treated in accordance with the methods provided herein is two years old. In certain embodiments, a patient treated in accordance with the methods provided herein is more than two years old. In certain embodiments, a patient

treated in accordance with the methods provided herein is less than twelve years old. In certain embodiments, a patient treated in accordance with the methods provided herein is twelve years old. In certain embodiments, a patient treated in accordance with the methods provided herein is two-twelve years old.

[00129] In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for SCN1A deficiency (in particular, Dravet syndrome). In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for CDKL5 deficiency. In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for SCN2A deficiency. In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for GABRG2 deficiency. In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for DEPDC5 deficiency. In certain embodiments, a patient treated in accordance with the methods provided herein has been diagnosed with a nonsense mutation in one or more alleles for NAPB deficiency.

[00130] In certain embodiments, a patient treated in accordance with the methods provided herein has drug-resistant epilepsy. In certain embodiments, a patient treated in accordance with the methods provided herein is refractory to treatment with or more antiepileptic drugs. In certain embodiments, a patient treated in accordance with the methods provided herein is refractory to treatment with one or more of the following antiepileptic drugs: Valproic acid, Divalproex sodium, Phenytoin, Primidone, Phenobarbital, Carbamazepine, Diazepam, Clonazepam, Ethosuximide, Eslicarbazepine, Felbamate, Perampanel, Tiagabine, Topiramate, Levetiracetam, and/or Lamotrigine.

[00131] In certain embodiments, the methods provided herein comprise the administration of a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, in three doses in a 24 hour period according to the formula: 1X, 1X, 2X, where X is a particular dose (*e.g.*, 2 mg/kg, 5 mg/kg, 8 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg) of the active agent. In a specific embodiment, a pharmaceutical composition

comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period for a plurality of 24 hour periods at doses of about 1 mg/kg to about 3 mg/kg (*e.g.*, about 2 mg/kg), about 3 mg/kg to about 7 mg/kg (*e.g.*, about 5 mg/kg), about 6 mg/kg to about 10 mg/kg (*e.g.*, about 8 mg/kg), about 7 mg/kg to about 13 mg/kg (*e.g.*, about 10 mg/kg), about 13 mg/kg to about 17 mg/kg (*e.g.*, about 15 mg/kg), or about 18 mg/kg to about 22 mg/kg (*e.g.*, about 20 mg/kg) of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, for a plurality of 24 hour periods including, but not limited to, days, weeks, months or years. In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of about 5 mg/kg to about 9 mg/kg (*e.g.*, about 7 mg/kg), about 5 mg/kg to about 9 mg/kg (*e.g.*, about 7 mg/kg) and 12 mg/kg to about 16 mg/kg (*e.g.*, about 14 mg/kg) of the active agent for weeks, months or years. In a specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of about 8 mg/kg to about 12 mg/kg (*e.g.*, about 10 mg/kg), about 8 mg/kg to about 12 mg/kg (*e.g.*, about 10 mg/kg) and about 18 mg/kg to about 22 mg/kg (*e.g.*, about 20 mg/kg) of the active agent for days, weeks, months or years. In a specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of about 18 mg/kg to about 22 mg/kg (*e.g.*, about 20 mg/kg), about 18 mg/kg to about 22 mg/kg (*e.g.*, about 20 mg/kg) and about 38 mg/kg to about 42 mg/kg (*e.g.*, about 40 mg/kg) of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper).

[00132] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more

pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 2 mg/kg, 2 mg/kg, and 4 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper). In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 2 mg/kg in the morning, 2 mg/kg at midday, and 4 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 2 mg/kg in the morning, 2 mg/kg at midday, and 4 mg/kg in the evening for 12 weeks.

[00133] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 5 mg/kg, 5 mg/kg, and 10 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper). In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening for 12 weeks.

[00134] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 8 mg/kg, 8 mg/kg, and 16 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper). In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 8 mg/kg in the morning, 8 mg/kg at midday, and 16 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 8 mg/kg in the morning, 8 mg/kg at midday, and 16 mg/kg in the evening for 12 weeks.

[00135] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 10 mg/kg, 10 mg/kg, and 20 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper). In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as

provided herein, is continuously administered three times per 24 hour period at doses of 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 12 weeks.

[00136] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 15 mg/kg, 15 mg/kg, and 30 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper).

In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 15 mg/kg in the morning, 15 mg/kg at midday, and 30 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 15 mg/kg in the morning, 15 mg/kg at midday, and 30 mg/kg in the evening for 12 weeks.

[00137] In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 20 mg/kg, 20 mg/kg, and 40 mg/kg of the active agent for days, weeks, months or years. In each 24 hour period that the active agent is administered, it is preferably administered three times at approximately 6-, 6, and 12-hour intervals (*e.g.*, at ~7:00 AM after breakfast, ~1:00 PM after lunch, and at ~7:00 PM after supper).

In another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 20 mg/kg in the morning, 20 mg/kg at midday, and 40 mg/kg in the evening for days, weeks, months or years. In yet another specific embodiment, a pharmaceutical composition comprising 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic

acid or a salt thereof and one or more pharmaceutically acceptable carriers and excipients, as provided herein, is continuously administered three times per 24 hour period at doses of 20 mg/kg in the morning, 20 mg/kg at midday, and 40 mg/kg in the evening for 12 weeks.

[00138] In specific embodiments, a pharmaceutical composition provided herein is administered to a patient in accordance with the treatment regimen provided herein at Section 6, *infra*.

[00139] Compound 1 therapeutic efficacy follows a bell-shaped dose-response curve, wherein achieving and maintaining a certain steady-state plasma concentration within a particular range results in maximal activity. Thus, it is believed that individual patients may require particular dosage amounts (*i.e.*, 1X, 1X, 2X, where X is a particular dose such as 2 mg/kg, 5 mg/kg, 8 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg) in order to achieve a therapeutically effective plasma concentration of Compound 1.

[00140] In certain embodiments, the methods provided herein comprise maintaining a plasma concentration of Compound 1 of greater than: about 0.1 µg/mL, about 0.5 µg/mL, about 2 µg/mL, about 5 µg/mL, about 10 µg/mL, about 20 µg/mL, about 25 µg/mL, about 40 µg/mL, about 50 µg/mL, about 100 µg/mL, about 150 µg/mL, about 200 µg/mL, about 250 µg/mL or about 500 µg/mL in a patient for at least about 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12 or 24 hours or longer. Levels of Compound 1 in plasma can be measured, for example, by high performance liquid chromatography (HPLC).

[00141] In another embodiment, the methods provided herein comprise maintaining a plasma concentration of Compound 1 of about 0.1 µg/mL to about 500 µg/mL, about 2 µg/mL to about 40 µg/mL, about 2 µg/mL to about 20 µg/mL, about 2 µg/mL to about 10 µg/mL or about 10 µg/mL to about 20 µg/mL in a patient for at least about 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12 or 24 hours or longer.

[00142] In some embodiments, Compound 1 is administered in combination with at least one additional therapeutic agent. In some embodiments, the additional therapeutic agent is administered before administration of Compound 1, after administration of Compound 1, simultaneously with administration of Compound 1, or a combination thereof. In some embodiments, the additional therapeutic agent is laronidase (more specifically, α-L-iduronidase) and/or one or more anti-histamine(s).

[00143] In certain embodiments, Compound 1 is used in combination with one or more therapies to treat a nonsense mutation mediated epileptic disease. In a specific embodiment, the one or more therapies used for the treatment, prevention, amelioration or management of a nonsense mutation mediated epileptic disease in combination with Compound 1 or a pharmaceutical composition provided herein are anticonvulsant drug(s). In a specific embodiment, the one or more therapies used for the treatment, prevention, amelioration or management of a nonsense mutation mediated epileptic disease in combination with Compound 1 or a pharmaceutical composition provided herein are Valproic acid, Divalproex sodium, Phenytoin, Primidone, Phenobarbital, Carbamazepine, Diazepam, Clonazepam, Ethosuximide, Eslicarbazepine, Felbamate, Perampanel, Tiagabine, Topiramate, Levetiracetam, and/or Lamotrigine.

[00144] It will be understood that the amounts of a pharmaceutical composition or active agent administered to a patient in need thereof are or can be calculated based upon the actual weight of the patient in question or the average weight of the patient population in question (*e.g.*, male or female, including adults and children).

6. EXAMPLES

6.1. Ataluren promotes concentration-dependent readthrough premature stop codons in SCN1A and CDKL5 mRNA sequences.

[00145] Luciferase reporter constructs were generated to evaluate readthrough activity of compounds at premature stop codons present in SCN1A and CDKL5 mRNA sequences. Figure 1 is a schematic of the reporter construct used to monitor readthrough activity of SCN1A nonsense mutation W192X (UAG premature stop). Figure 2 is a schematic of the reporter construct used to monitor readthrough activity of CDKL5 nonsense mutation R59X (UGA premature stop). Figure 3 is a schematic of the reporter construct used to monitor readthrough activity of CDKL5 nonsense mutation R550X (UGA premature stop). In each of the constructs, luciferase reporter is flanked by a 3XHA epitope tag at the amino-terminus and a FLAG epitope tag at the C-terminus. An intron from the TPI gene was inserted in the luciferase gene. Sequences from SCN1A (see Figure 1) and CDKL5 (see Figures 2 and 3) harboring disease-associated nonsense mutations were introduced in-frame with the reporter sequence such that

readthrough at the premature stop codon results in the production of a functional luciferase protein.

[00146] 293H cells were transfected with either construct SCN1A-Trp192x (Figure 1), construct CDKL5-R59X (Figure 2), or construct CDKL5-R550X (Figure 3). The cells were treated with solvent (DMSO) or 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid (ataluren) (decreasing concentrations, starting at 3uM) for 24 hours. The ability of ataluren to promote readthrough at the premature stop codon in each of the constructs was measured and reported as the relative light units (y-axis). The results are shown in Figure 4 (SCN1A) and Figure 5 (CDKL5). The results demonstrate that ataluren promotes concentration-dependent readthrough of premature stop codons inserted in sequences from the SCN1A and CDKL5 mRNA.

6.2. Protocol for a Phase 2 Randomized, Double-Blind Placebo-Controlled Cross-Over Safety and Tolerability Study of Ataluren for Drug-resistant Epilepsy in Patients with Nonsense Mutation CDKL5 or Dravet Syndrome

[00147] This Example describes a clinical research protocol for a human research study. This study is conducted in accordance with the protocol, United States (US) government research regulations, and applicable international standards of Good Clinical Practice (GCP), and institutional research policies and procedures. See Table 1 below for a synopsis of the clinical protocol. See Table 2 below for a List of Abbreviations.

Table 1: Clinical Protocol Synopsis

Phase:	Phase 2
Methodology:	Interventional study
Study Duration:	32 weeks with extension available
Objectives:	The primary objective of this study is to: • Characterize the safety profile of ataluren in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation The secondary objectives of this study are to: • Evaluate change in convulsive and/or drop seizure frequency from Baseline following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation • To determine changes in minor seizure types following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation. (Seizure types as defined by the International League Against Epilepsy [ILAE] criteria. (International League Against Epilepsy. Seizure Classification. 2014. EpilepsyDiagnosis.org)) The exploratory objectives of this study are to: • Evaluate change from Baseline in cognitive, motor, and behavioral function as well as quality of life (QOL) following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation
Number of Patients:	16 evaluable (8 with a CDKL5 nonsense mutation, 8 with a SCN1A nonsense mutation(Dravet syndrome))

Diagnosis and Main Inclusion Criteria:	Age ≥ 2 years old and ≤ 12 years old, male or female, at Week 0 (at time informed consent/assent is signed) Documentation of a diagnosis of nonsense mutation in 1 allele for SCN1A deficiency (in particular, Dravet syndrome) or CDKL5 deficiency as evidenced by medical records, genetic testing, and the following clinical feature: • Failure to control seizures despite appropriate trial of 2 or more antiepileptic drug (AEDs) at therapeutic doses • Current regimen of 1 to 3 baseline AEDs at stable doses for a minimum for 4 weeks prior to enrollment (ie, randomization/ Baseline Visit). (Vagus nerve stimulator [VNS], ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to enrollment.) • Minimum of 6 convulsive or drop seizures with duration > 3 seconds over the 4 weeks of diary screening prior to randomization
Study Product, Dose, Route, Regimen:	Ataluren (oral powder/granules for suspension) Dose: 3 times daily (10 mg, 10 mg and 20 mg/kg morning, midday and evening, respectively) Titration: None Maximum dose: 3 times daily (10 mg, 10 mg, 20 mg/kg morning, midday and evening respectively)
Duration of administration:	Each patient receives a total of 12-weeks of active drug (ataluren) and 12-weeks of placebo, in a blinded fashion

Table 2: List Of Abbreviations

Abbreviation	Definition
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CMP	comprehensive metabolic panel
EOS	End of Study
IB	Investigator's Brochure
ILAE	International League Against Epilepsy
ITT	Intent-to-Treat
IVRS/IWRS	interactive voice response system/interactive web response system
LFT	liver function test
LOAEL	lowest-observed-adverse-effect level
mRNA	messenger ribonucleic acid
PI	Principal investigator
PK	pharmacokinetics

Abbreviation	Definition
QOL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy
SAE	Serious adverse event
SMEI	severe myoclonic epilepsy of infancy
SUDEP	sudden unexpected death in epilepsy
TEAE	Treatment-emergent adverse event
TID	three (3) times per day
VNS	vagus nerve stimulator

6.2.1. Ataluren

[00148] Ataluren (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid) for use in this study is in the form of a white to off-white powder/granules for suspension packaged in child-resistant aluminum foil packets or sachets. Each packet or sachet contains 125, 250 or 1000 mg of drug substance, which is 25% of the total formulation weight.

6.2.1.1. Placebo

[00149] The placebo for placebo-controlled clinical studies is provided as a white to off-white powder/granules for suspension. The placebo powder/granules is supplied in packets or sachets matching the fill weights of the active drug product that contain 125, 250, or 1000 mg of the drug substance. The placebo is similar to the active product except that ataluren is replaced by the addition of a filler (microcrystalline cellulose) and an increased amount of mannitol, which together comprise about 50% of the powder/granules.

6.2.2. Study Design

[00150] Crossover designs are usually statistically efficient and thus require fewer subjects. Additionally, the influence of confounding covariates is reduced because each crossover patient serves as his or her own control. A 12-week treatment period provides sufficient time to assess changes in the patient's seizure activity and QOL while still allowing appropriate monitoring of the patient. Because treatment options for this patient population are minimal, the dropout rate in this crossover study is expected to be low.

[00151] The study is a Phase 2 interventional study which includes the following: Screening (Week -4 to Week 0/Day 1), Treatment Period 1 (Week 0/Day 1 – Week 12), Washout

Period (Week 12 – Week 16), crossover to Treatment Period 2 (Week 16 – Week 28), and Follow-up (Week 28 – Week 32).

[00152] The study design is shown in Figure 6. The Schedule of Events is provided in Table 3.

6.2.2.1. Drug Administration Plan

[00153] Patients receive 12 weeks of ataluren or placebo during each treatment period. Treatment Period 1 is followed by a 4-week Washout Period. Based on ataluren PK and pharmacodynamic data, the 4-week washout period is deemed an appropriate length of time to eliminate any ataluren drug effects. Following the Washout Period, patients crossover to receive the opposite treatment during Treatment Period 2.

- Patients receiving ataluren during Treatment Period 1 receive placebo during Treatment Period 2.
- Patients received placebo during Treatment Period 1 receive ataluren during Treatment Period 2.

[00154] Study drug is administered 3 times per day (TID). The dose level to be administered is: 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening.

[00155] Dosing is based on the patient's body weight at baseline. Weight is assessed at every clinic visit. If the patient's body weight changes by $\geq 10\%$ from baseline, the actual dose may be re-calculated.

[00156] The first dose of study drug is administered in the clinic and the date and time of administration is recorded. At the end of each Treatment Period, the last dose of study drug is taken on the evening before the clinic visit (ie, the night before the Visit 6/Week 12 [end of Treatment Period 1] and the night before Visit 18/Week 28 [end of Treatment Period 2]).

6.2.2.2. Research Risks & Benefits

6.2.2.2.1. Risk of Study Drug

[00157] All patients are closely monitored for adverse events throughout the study.

[00158] Ataluren is a weak inhibitor of CYP2C9 and CYP2C8. Clinical drug interaction studies between ataluren and CYP2C8 and CYP2C9 substrates have not been conducted. Ataluren has the potential to increase the plasma concentration of drugs that are primarily metabolized by CYP2C8 or CYP2C9, which includes drugs with a narrow therapeutic index that are substrates of CYP2C8 or CYP2C9. The effects of other concomitant AEDs and other drug

levels metabolized by these enzyme systems are not known, but it may increase their levels leading to potential toxicities. Therefore, AED plasma levels are measured at Baseline and 4 weeks following the first ataluren dose in each Treatment Period (ie, Visit 4/Week 4 and Visit 14/Week 20). AEDs may be adjusted as needed based on signs and symptoms of toxicity and/or changes in drug levels.

6.2.3. Study Objectives

[00159] The primary objective of this study is to:

- Characterize the safety profile of ataluren in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation.

[00160] The secondary objectives of this study are to:

- Evaluate change in convulsive and/or drop seizure frequency from baseline following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation.
- To determine changes in minor seizure types (absence, myoclonic, complex partial/focal dyscognitive) following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation.

[00161] The exploratory objectives of this study are to:

- Evaluate changes from Baseline in cognitive, motor, and behavioral function as well as QOL following ataluren treatment in patients with CDKL5 related epilepsy or SCN1A related epilepsy such as Dravet syndrome resulting from a nonsense mutation.

6.2.4. Endpoints

6.2.4.1. Primary Endpoint

[00162] The primary study endpoints of this study include:

- Overall safety profile of ataluren characterized by type, frequency, severity, timing, and relationship to study drug of any adverse events or serious adverse events (SAEs); changes in physical examination, laboratory test results, and drug discontinuations due to adverse events or SAE.

6.2.4.2. Secondary Endpoints Primary Endpoint

[00163] The secondary endpoints of this study are as follows:

- Change in seizure frequency from baseline. Motor seizures to be counted are tonic-clonic seizures, hemiconvulsive seizures, drop attacks, tonic seizures, and focal motor seizures.
- The effect on myoclonic seizures (ie, persistence or disappearance) are also be evaluated.
- Data is collected during baseline and at each 4 week post-baseline visit to identify changes in:
 - Number of episodes of status epilepticus, defined as a convulsive lasting > 10 minutes
 - Number of uses of rescue medications

- Number of emergency room visits/hospitalizations

6.2.4.3. Exploratory Endpoints

[00164] Exploratory endpoints include:

- Changes in minor seizure types:
 - Number of myoclonic seizures
 - Number of staring (absence or complex partial) seizures

[00165] In addition, the severity of epilepsy, cognitive and motor scales, QOL, and safety and tolerability are assessed using the following instruments:

1. Assess clinical and adaptive measures of personality and behavior using the Behavior Assessment System for Children: Third Edition (Sabaz *et al.* Epilepsy Behav. 2003, 4(6):680-91)
2. Linguistic skills as measured by the Preschool Language Scale, Fourth Edition (PSL-4) (Zimmerman et al 2002)
3. Adaptive level of behavioral function as measured by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (Sparrow et al 2005)
4. Quality of Life as assessed by the Quality of Life in Childhood Epilepsy (QOLCE) (Sabaz *et al.* Epilepsy Behav. 2003, 4(6):680-91)

6.2.4.4. Inclusion Withdrawal

[00166] Patients selected for this study must meet the following criteria:

1. Age ≥ 2 years old ≤ 12 years old, male or female, at Week 0 (at time informed consent/assent is signed)
2. Documentation of a diagnosis of nonsense mutation in 1 allele for SCN1A deficiency (in particular, Dravet syndrome) or CDKL5 deficiency as evidenced by medical records, genetic testing, and the following clinical feature:
 - a. Failure to control seizures despite appropriate trial of 2 or more AEDs at therapeutic doses
3. Between 1 to 3 baseline AEDs at stable doses for a minimum for 4 weeks prior to the Screening visit
 - a. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to enrollment.
4. VNS must be on stable settings for a minimum of 3 months prior to the Screening visit
5. If on ketogenic or modified Atkins diet, must be on stable ratio for a minimum of 3 months prior to the Screening visit
6. Written consent obtained from the patient or patient's legal representative must be obtained prior to performing any study procedures
7. Minimum of 6 convulsive or drop seizures with duration > 3 seconds over the 4 weeks of diary screening prior to randomization

6.2.4.5. Exclusion Criteria

[00167] Patients cannot be included in the study if any of the following exclusion criteria are met:

1. Patient is less than 2 years old or more than 12 years old
2. Epilepsies associated with genetic disorders other than SCN1A deficiency (in particular, Dravet syndrome) or CDKL5 deficiency
3. Patient has SCN1A (Dravet) or CDKL5 genetic mutations that are NOT nonsense mutations
4. Felbatol has been initiated within the past 12 months prior to enrollment (Baseline Visit)
5. Patients who are currently or have participated in clinical trials in the past 30 days prior to enrollment (Baseline Visit)
6. Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition), medical history, physical findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the patient, makes it unlikely that the course of study drug administration or follow-up would be completed, or could impair the assessment of study results.

6.2.4.6. Patient Recruitment and Screening

[00168] Eight nonsense mutation SCN1A (Dravet syndrome) patients and 8 nonsense mutation CDKL5 patients are recruited for the study from the principal investigator (PI) or sub-investigator's clinical practice. During a routine visit, patients/parents/legal guardians that meet criteria for the study are asked if they would like to participate in the study. Male and female patients of any ethnicity between ages of 2 and 12 is assessed for inclusion. During the routine visit, the investigator informs each prospective patient/parent/legal guardian of the nature of the study, explain the potential risks and study-related procedures. If the patient/parent/legal guardian agrees, they are given the informed consent documents to read and sign prior to starting any study procedures. Only the PI, sub-investigators, and other research personnel listed on the study have access to patient information. Once the study patient/parent/legal guardian has signed the informed consent, screening procedures may begin.

6.2.4.7. Randomization

[00169] After a patient has completed the necessary screening assessments and has been confirmed to be eligible by the investigator, the patient can be randomized into the study.

[00170] Sixteen patients (8 with a CDKL5 nonsense mutation and 8 with a SCN1A nonsense mutation) are enrolled. Within each disorder group, patients are randomized in a 1:1 ratio to 1 of 2 possible treatment assignments during Treatment Period 1:

- Placebo
- Ataluren (10, 10, 20 mg/kg/day)

6.2.4.8. Blinding

[00171] The identity of the treatments is concealed by the use of a placebo that is matched to the active drug in appearance, taste, odor, packaging, labeling, and schedule of administration. Unblinding only occurs in the case of patient emergencies before study completion, if requested by the DMC at the time of the interim DMC review, and at the conclusion of the study. Except for emergency unblinding, individual patients, parents/caregivers, and site personnel are not be informed of the randomized treatment assignments until the implications of revealing such data for the overall ataluren clinical development program have been determined by the investigator.

6.2.5. Early Withdrawal of Patients

6.2.5.1. When and How to Withdraw Patients

[00172] A patient may be discontinued from study drug at any time if the patient or patient's legal guardian, or the investigator feels that it is not in the patient's best interest to continue. The following is a list of possible reasons for study drug discontinuation:

1. Parental/guardian withdrawal of consent.
2. Patient is not compliant with study procedures.
3. Protocol violation requiring discontinuation of study drug.
4. Severe adverse events, including significant toxicity such as severe cognitive or behavioral toxicity, impaired liver and renal function, or impaired hematopoiesis.
5. Seizures exacerbation not attributable to other known provocative factors.
6. Interaction with concomitant AED regimen that leads to unacceptable toxicity. Medication adjustments are avoided, if possible, and may require the subject to exit the study, at the discretion of the Investigator.

[00173] If patient must discontinue study drug, the method for discontinuation from study drug is determined based on type of reaction and/or reason for withdrawal. For example, if the patient experiences a rapidly progressive rash it would lead to abrupt cessation of study drug, but

if patient experiences excess tiredness study drug may be tapered off. A discussion of the method of cessation occurs between the patient and/or patient's parent/legal guardian and the physician.

6.2.5.2. Data Collection and Follow-up for Withdrawn Patients

[00174] For all patients who withdraw from the study, there is one final visit 4 weeks after the last dose of study drug. If the patient/parent/legal guardian cannot be contacted after 4 phone calls to patient/parent/legal guardian, a certified letter is sent to patient/parent/legal guardian.

6.2.6. Study Drug

6.2.6.1. Ataluren

[00175] Ataluren is provided as a white to off-white powder/granules for oral suspension. The drug substance and drug product are manufactured under current Good Manufacturing Practices (cGMP) conditions. The formulation includes matrix and suspending agents, surfactants, and various excipients that aid in the manufacturing process. The powder/granules for oral suspension is packaged in aluminum-foil, child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. All of the excipients have been tested to pharmaceutical or food grade and are generally recognized as safe.

6.2.6.2. Placebo

[00176] A white to off-white powder/granules placebo formulation is provided for oral suspension. The placebo formulation has been manufactured under cGMP conditions. The dry powder/granules and the liquid suspension of the drug match the active formulation in appearance, odor, and taste. The placebo formulation contains excipients similar to those used in the active product. The placebo is packaged in the same aluminum-foil, child-resistant sachets (packets) matching each of the 125, 250, and 1000 mg dose strengths of active drug sachets.

6.2.6.3. Drug Kits

[00177] Drug kits are provided, each of which contains 65 packets or sachets of one of the dose strengths (125, 250, or 1000 mg or matching placebo).

6.2.6.4. Treatment Regimen

[00178] Patients receive 12 weeks of blinded ataluren or placebo during each treatment period. Each patient starts at a dose based on their weight in kilograms. The study drug is to be administered in a TID fashion of 10 mg/kg, 10 mg/kg and 20 mg/kg (morning, midday, and evening, respectively). The dose is administered from 125, 250, and 1000 mg foil packets or sachets.

[00179] Dosing is based on the patient's body weight at baseline. Weight is assessed at every clinic visit. If the patient's body weight changes by $\geq 10\%$ from baseline, the actual dose may be re-calculated.

[00180] The first dose of study drug is administered in the clinic and the date and time of administration is recorded. At the end of each Treatment Period, the last dose of study drug is taken on the evening before the clinic visit (ie, the night before the Visit 6/Week 12 [end of Treatment Period 1] and the night before Visit 18/Week 28 [end of Treatment Period 2]).

[00181] Each dose should be taken within ~30 minutes before or after a meal. Intervals for dosing should be ~6 hours (± 1 hour) between morning and mid-day doses, ~6 hours (± 1 hour) between mid-day and evening doses, and ~12 hours (± 1 hour) between evening doses and the morning dose on the next day.

6.2.6.5. Instructions for Delays in Dosing

[00182] Dosing delays in study drug (blinded ataluren or placebo) administration should adhere to the following guidelines:

- If dosing of study drug is delayed by ≤ 1 hour, the planned dose should be taken with no changes to the subsequent dose schedules;
- If study drug dosing is delayed by > 1 hour but ≤ 4 hours, the planned dose should be taken; however, all future doses for that day should be shifted later by an approximately corresponding amount;
- If study drug dosing is delayed by > 4 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be taken and the planned timing of subsequent study drug dosing should not be altered.

6.2.6.6. Study Drug Preparation and Storage

[00183] Study drug sachets should be stored at room temperature, away from the reach of children until time of reconstitution and should only be opened at the time of dose preparation. The full contents of each sachet should be mixed with at least 30 mL (1 ounce) of liquid (water,

milk, fruit punch), or 3 tablespoons of semi-solid food (yogurt or applesauce). The full contents of the sachets should be mixed with at least 30 mL (1 ounce) of liquid (eg water, milk), or 3 tablespoons of semi-solid food (yogurt, pudding, or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference.

[00184] Each prepared dose is best administered immediately after preparation. The prepared dose should be discarded if not consumed within 24 hours of preparation if kept refrigerated (2 to 8°C), or within 3 hours at room temperature (15 to 30°C). The clinic staff instructs each patient or parent/caregiver on the specific number of sachets to be taken from each kit for each dose and provides detailed oral directions regarding drug preparation. In addition, detailed written drug mixing and dosing instructions are provided to the patient or parent/caregiver when drug supplies are dispensed.

6.2.6.7. Method for Assigning Patients to Treatment Groups

[00185] This interventional study contains a placebo portion where patients do not receive active drug therapy beyond the existing background AED regimen. The allocation of ataluren and placebo to treatment number is completed according to a blinded randomization schedule.

[00186] Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. The permuted block randomization technique is used. Such a method allows treatment arms to be balanced with respect to the predefined stratification factors as well as for the number of patients in each arm. The process is established and performed by an experienced clinical research organization (CRO) through an interactive voice response system/interactive web response system (IVRS/IWRS) system to maximize the integrity and security of the randomization and ensure appropriate access and convenience-of-use by the investigational sites. The method should be sufficient to preclude site personnel from making inferences regarding treatment assignments based on known block sizes. A 1:1 randomization of ataluren:placebo is planned in order to avoid the loss of statistical power associated with an unbalanced randomization.

[00187] To minimize the potential compromise of study drug blinding and to reduce the chance of inadvertent dosing errors or intentional attempts to mix active drug and placebo within families, if the case occurs, the randomization system allocates subsequently enrolled family

members (eg, siblings) to the same treatment group as the first family member enrolled. There is past precedence for this approach [Ballard 2006].

[00188] When a patient is randomized in the study and is ready to begin study drug, the PI or qualified designee dispenses the appropriate quantity of blinded study medication and distributes it to the patient and/or patient's parent/legal guardian. Extensive instructions of the correct dosage administration and schedule are discussed and fully understood prior to leaving the appointment.

6.2.6.8. Patient Compliance Monitoring

[00189] The study team assesses and tracks patient compliance with the study drug regimen via clinical evaluations and follow-up email or phone calls. The patients are seen for clinical evaluations every month for up to the next 10 months on study drug regimen, with a visit during the first two weeks after first dose of study medication. Any patient who is significantly non-compliant with the study drug regimen ($< 80\%$ or $> 120\%$) is withdrawn from the study as per the PI.

6.2.6.9. Prior and Concomitant Therapy

[00190] Throughout the study, including during the Treatment Periods with study drug administration, patients continue their current AED regimen consisting of 1 to 3 drugs at stable doses for at least 4 weeks prior to the Baseline Visit. Concomitant AED concentrations are collected at the Baseline Visit and during the study to assess for the potential interactions. If the patient has a VNS, the settings must be on stable ratio for a minimum of 4 weeks prior to the Baseline Visit. In addition, if the patient is on the ketogenic diet, a stable ratio must have been present for at least 3 months prior to the Baseline Visit. All concomitant AEDs are permitted during the study; felbatol is allowed if dosing has been on a stable dose for ≥ 12 months prior to enrollment (Baseline). Medication adjustments are avoided, if possible, and may require the subject to exit the study at the discretion of the Investigator.

6.2.6.10. Storage

[00191] Sachets containing study drug are stored at controlled room temperature (~ 15 to $30\text{ }^{\circ}\text{C}$) in a locked room accessible only to study personnel. The available stability data from representative samples support the use of the drug product for 48 months when stored at room

temperature. The stability of the clinical study samples or representative samples may be monitored, as appropriate, to support the clinical study.

6.2.6.11. Dispensing of Study Drug

[00192] Dosing of ataluren is based on mg/kg of patient body weight and is adjusted to allow for dosing with up to 3 of the available sachet dose strengths (125 mg, 250 mg, and/or 1000 mg). The entire contents of the sachet is constituted with the constitution medium and is administered. Supply of study drug is calculated based on patient weight and is provided by the PI or qualified designee. Quantity of study drug sachets distributed to each study patient is noted in a study log upon dispensation. Regular study drug reconciliation is performed to document drug assigned and drug remaining. This reconciliation is logged on the drug reconciliation form, and signed and dated by the study team.

6.2.6.12. Overdose Precautions

[00193] For any patient experiencing an overdose (administration of an ataluren dose > 4 times the intended total daily dose level for this protocol [i.e., > 160 mg/kg/day]), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. Pending the acquisition of sufficient human experience with the drug, use of gastric lavage or induction of emesis is not specifically recommended nor contraindicated.

6.2.7. Schedule of Events

[00194] The types and timing of data to be recorded are summarized in Table 3.

Table 3: Schedule of Events

Protocol Activities	Screening ^a	Treatment Period 1 ^b					4-week Washout/ Crossover	Treatment Period 2 ^{b,c}				EOS Visit ^d	Follow-up ^e
Week (±7 days)	-4 (Week -4 to Week 0; Day 28 to Day -1)	0	2	4	8	12		16	18	20	24	28	32
Visit	1	2 ^f	3	4	6	8		10	12	14	16	18	20
Informed consent/assent	X												
Medical history	X												

Protocol Activities	Screening ^a	Treatment Period 1 ^b					4-week Washout/ Crossover	Treatment Period 2 ^{b,c}				EOS Visit ^d	Follow-up ^e
Serum viral screen	X												
Physical examination	X	X				X		X				X	X
Height and weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Seizure data diary provided	X	X	X	X	X	X		X	X	X	X	X	
Seizure data diary collected		X	X	X	X	X		X	X	X	X	X	
Study drug dispensed		X ^g	X	X	X			X ^g	X	X	X		
Study drug administration		X ^h						X ^h					
Study drug compliance and return			X	X	X	X			X	X	X	X	
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X
Blood for CBC, CMP, LFTs, BUN, creatinine levels, serum HCG ⁱ	X	X						X				X	X
Blood for plasma PK for AED assessment ^j		X		X				X		X			
Urinalysis	X	X				X		X				X	X
Behavior Assessment System for Children		X				X		X				X	X
Preschool Language Scale		X				X		X				X	X
Vineland Adaptive Behavior Scales		X				X		X				X	X
Quality of Life in Childhood Epilepsy		X				X		X				X	X

Protocol Activities	Screening ^a	Treatment Period 1 ^b	4-week Washout/ Crossover	Treatment Period 2 ^{b,c}	EOS Visit ^d	Follow-up ^e
---------------------	------------------------	---------------------------------	------------------------------	-----------------------------------	------------------------	------------------------

Abbreviations: AED = antiepilepsy drug; BUN = blood urea nitrogen; CBC = complete blood count; CMP = comprehensive metabolic panel; EOS = end of study; HCG = human chorionic gonadotropin; LFTs = liver function tests; PK = pharmacokinetics

- a. Screening occurs from Week -4 to Week 0 (i.e., 28 days). The ± 7 day visit window is not applicable to the Screening Period.
- b. Odd-numbered visits not shown are conducted by telephone and/or email evaluation
- c. During Treatment Period 2, patients crossover and begin receiving blinded study drug opposite of what they received during Treatment Period 1 (i.e., patients previously receiving blinded ataluren now receive placebo and patients previously receiving placebo now receive ataluren).
- d. The EOS visit is completed for all patients who complete the study and for any patient who discontinues early from the study.
- e. The Follow-up visit is to occur 4 weeks after the EOS visit or last dose of study drug.
- f. Visit 2 is considered the Baseline Visit. Visit 2 must occur no sooner than 28 days and up to 42 days after Visit 1. All study and laboratory assessments must be completed prior to the first dose of study drug administration.
- g. The first dose of study drug at Visit 2 (Baseline) and Visit 10 (Week 16) should be given in the clinic.
- h. The last dose of study drug prior to Visit 8/Week 12 (Treatment Period 1) and Visit 18/Week 28 (EOS Visit) should be taken the night before, at home. No morning dose should be taken prior to the clinic visit.
- i. Serum HCG samples taken only for female patients of childbearing potential
- j. Sample to be obtained immediately prior to the morning dose of study drug (trough level only).

6.2.7.1. Screening, Treatment, and Follow-up Periods

[00195] Screening evaluations for the study are performed at the clinical research facility. Study participants report to the clinic on the morning of each scheduled on-site visit and remain in the clinic until released by the investigator after all the study-related procedures have been completed and the patient has been instructed regarding drug storage, reconstitution, and administration.

[00196] Adverse events are assessed beginning at the time of informed consent through the end of the follow-up period.

Patients must return to the clinic for a follow-up assessment at 4 weeks after the last dose.

6.2.7.1.1. Visit 1 (Screening, 4 Weeks Prior to Baseline Visit 2)

[00197] The Screening Visit (Visit 1) occurs 4 weeks prior to Baseline Visit 2 during a routine visit. Screening procedures proceed as follows:

- Obtain written informed consent/assent.
- Determine if the patient meets the preliminary eligibility criteria:
 - Collect demographic information
 - Collect current and relevant medical history
 - Identify concomitant medications used
 - Identify and confirm stable use AED medications

[00198] If the patient meets the preliminary eligibility criteria, the following assessments are performed:

- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): perform in sitting position
- Physical examination
- Height and weight
- Blood draw for clinical laboratory evaluations:
 - blood urea nitrogen (BUN), complete blood count (CBC), comprehensive metabolic panel (CMP), liver function tests (LFTs)
 - Serum HCG, as applicable (sample taken only for female patients of childbearing potential)
 - Serum viral screen
- Urinalysis
- Instruct patient or patient's parent/legal guardian to keep a seizure diary for the next 4 weeks, including the following information:
 - Seizure type, duration, intensity
 - Presence or absence of cyanosis
 - Use of rescue medications

6.2.7.1.2. Visit 2 (Baseline, Week 0)

[00199] After the 4-week Screening period, the diary card provided at the Screening Visit is reviewed and all Inclusion/Exclusion criteria are confirmed. Eligible patients complete the Baseline Visit (Visit 2/Week 0) as follows:

- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following QOL assessments:
 - Behavior Assessment System for Children
 - Preschool Language Scale
 - Vineland Adaptive Behavior Scales
 - QOLCE
- Blood draw for clinical laboratory evaluations
 - CBC, CMP, LFTs, BUN, creatinine, serum HCG
 - Plasma PK for AED level assessment

- Urinalysis
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions
 - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
 - The first dose of study drug should be administered in the clinic *after* completion of all other assessments and procedures required at this visit.

6.2.7.1.3. Visit 3 (Week 2)

[00200] The patient returns to the site for Visit 3. Procedures at Visit 3 proceed as follows:

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions

TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)

6.2.7.1.4. Visit 4 (Week 4)

[00201] The patient returns to the site for Visit 4. Procedures at Visit 4 proceed as follows:

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw plasma PK for AED level assessment
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions

TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)

6.2.7.1.5. Visit 6 (Week 8)

[00202] The patient returns to the site for Visit 6. Procedures at Visit 6 proceed as follows:

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions
- TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Remind patient/parent/legal guardian that prior to the next clinic visit (Visit 8), the patient should take their final dose of study drug the night before the visit.

6.2.7.1.6. Visit 8 (Week 12 [Beginning of 4 Week Washout])

[00203] The patient returns to the site for Visit 8. Visit 8 proceeds as follows:

- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following QOL assessments:
 - Behavior Assessment System for Children
 - Preschool Language Scale
 - Vineland Adaptive Behavior Scales
 - QOLCE
- Dispense new seizure diary and review instructions for completion
- No study drug is dispensed at this visit.

6.2.7.1.7. Treatment Period 2 - Visit 10 (Week 16 [Crossover Visit])

[00204] The patient returns to the site for Visit 10. Patients crossover and begin receiving blinded study drug opposite of what they received during Treatment Period 1 (i.e., patients

previously receiving blinded ataluren now receive placebo and patients previously receiving placebo now receive ataluren). Visit 10 proceeds as follows:

- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for clinical laboratory evaluations

CBC, CMP, LFTs, BUN, creatinine, serum HCG

- Urinalysis
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions

TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)

The first dose of study drug should be administered in the clinic *after* completion of all other assessments and procedures required at this visit.

6.2.7.1.8. Visit 12 (Week 18)

[00205] The patient returns to the site for Visit 12. Visit 12 proceeds as follows:

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Dispense new seizure diary and review instructions for completion
- Dispense blinded study drug and review administration instructions

TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)

6.2.7.1.9. Visit 14 (Week 20)

[00206] The patient returns to the site for Visit 14. Visit 14 proceeds as follows:

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes

- Collect seizure diary and review entries
 - Record any adverse events occurring since last visit and any that occur during this visit
 - Blood draw plasma PK for AED level assessment
 - Record any changes in concomitant medications
 - Dispense new seizure diary and review instructions for completion
 - Dispense blinded study drug and review administration instructions
- TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)

6.2.7.1.10. Visit 16 (Week 24)

[00207] The patient returns to the site for Visit 16. Visit 16 proceeds as follows:

- Height and weight
 - Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
 - Collect seizure diary and review entries
 - Record any adverse events occurring since last visit and any that occur during this visit
 - Record any changes in concomitant medications
 - Dispense new seizure diary and review instructions for completion
 - Dispense blinded study drug and review administration instructions
- TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Remind patient/parent/legal guardian that prior to the next clinic visit (Visit 18), the patient should take their final dose of study drug the night before the visit.

6.2.7.1.11. Visit 18 (Week 28 – End of Study Visit [or Early Termination Visit])

[00208] The patient returns to the site for Visit 18. This visit is be considered the End of Study (EOS) visit and should be completed for all patients. Patients should have taken their final dose of study drug the night before the clinic visit.

[00209] Additionally, any patient who discontinues early from the study should complete this visit.

[00210] Visit 18 proceeds as follows:

- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes

- Collect seizure diary and review entries
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following QOL assessments:
 - Behavior Assessment System for Children
 - Preschool Language Scale
 - Vineland Adaptive Behavior Scales
 - QOLCE
- Blood draw for clinical laboratory evaluations
 - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- No study drug is dispensed at this visit.

6.2.7.1.12. Visit 20 (Week 32 [Follow-up Visit])

[00211] The patient returns to the site for Visit 20. This visit should occur 4 weeks after the final dose of study drug and EOS visit. Visit 20 proceeds as follows:

- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the patient has been in a sitting position for 3 – 5 minutes
- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following QOL assessments:
 - Behavior Assessment System for Children
 - Preschool Language Scale
 - Vineland Adaptive Behavior Scales
 - QOLCE
- Blood draw for clinical laboratory evaluations
 - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis

6.2.7.1.13. Telephone/Email: Visits 5, 7, 9, 11, 13, 15, 17, and 19

[00212] Patients are asked about their study drug dosage to check compliance and how they are tolerating it. Adverse events are assessed and any concerns the patient may have are addressed.

[00213] During the contact for Visit 7 and Visit 17, the patient/parent/legal guardian should be reminded that the last dose of study drug should be taken the night before the next clinic visit and no study drug should be taken on the morning of the clinic visit (i.e., Visit 8 or Visit 18).

6.2.7.1.14. Serum Viral Screen

[00214] Tests conducted at screening include hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV). The study manual is referenced for collection, processing, and shipping information.

6.2.7.1.15. Physical Examination

[00215] The physical examination (including general appearance, head, eyes, ears, nose, mouth, throat, heart, thyroid, chest and lungs, abdomen, extremities, neuromuscular system, skin, and lymph nodes) is conducted at Screening, Visit 2 (Baseline), Visit 8, Visit 10, Week 18 (EOS or Early Termination), and Follow-up.

[00216] Physical examinations may also be performed at any time during the study as clinically indicated.

6.2.7.1.16. Vital Signs

[00217] Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature) are monitored at each clinic visit.

6.2.7.1.17. Height and Weight

[00218] Height (in cm) is measured at each clinic visit. Weight (in kg) is measured at each clinic visit.

6.2.7.1.18. Adverse Events

[00219] Adverse events are assessed and documented at each scheduled clinic visit, beginning at Screening. If the patient does not visit the clinic on the scheduled day, a telephone call to the patient by qualified site personnel is required to assess adverse events. In addition,

subjects/caregivers are encouraged to report adverse events of concern at any time in the intervals between visits.

[00220] Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an adverse event are obtained when clinically indicated. Patients are followed for adverse events for at least 28 days after the last dose of study drug administration, or until any drug-related adverse events and/or ongoing SAEs have resolved or become stable, whichever is later.

6.2.7.1.19. Concomitant Medications

[00221] Concomitant medication information is collected and documented at each scheduled clinic visit. Any concomitant drugs (prescribed or over-the-counter) used during the course of the study and the reason for use is recorded. Information regarding the timing, type, and amount is recorded in a CRF.

6.2.8. STATISTICS

6.2.8.1. Sample Size Determination

[00222] This study is not powered for statistical testing since the primary objective is to characterize the safety profile of ataluren in patients with a CDKL5 or a SCN1A (Dravet syndrome) epileptic disease resulting from a nonsense mutation. Sixteen (16) patients (8 with a CDKL5 nonsense mutation and 8 with a SCN1A nonsense mutation [Dravet syndrome]) are included in this study.

6.2.8.2. Randomization

[00223] Sixteen patients (8 with a CDKL5 nonsense mutation and 8 with a SCN1A nonsense mutation [Dravet syndrome]) are enrolled. Within each disorder group, patients are randomized in a 1:1 ratio to 1 of 2 possible treatment assignments during Treatment Period 1:

- Placebo
- Ataluren (10, 10, 20 mg/kg/day)

[00224] After the completion of Treatment Period 1 and a 4-week Washout Period, patients crossover and begin receiving blinded study drug opposite of what they received during

Treatment Period 1 (i.e., patients previously receiving blinded ataluren now receive placebo and patients previously receiving placebo now receive ataluren).

6.2.8.3. Populations for Analyses

[00225] Intent-to-Treat (ITT) population - The ITT population contain all randomized patients.

6.2.8.4. Efficacy Endpoint Definitions

6.2.8.4.1. Seizures

[00226] Seizure activity is assessed based on ILAE criteria for the following:

- Motor seizure including tonic-clonic seizures, hemiconvulsive seizures, drop attacks, tonic seizures, focal motor seizures.
- Staring seizure is an absence seizure or a complex partial seizure.
- Myoclonic seizure is the persistence or disappearance seizure.
- Episode of status epilepticus: a convulsive state lasting longer than 10 minutes.

[00227] Baseline total number of seizures/ER visits/hospitalizations is defined as the total number of seizures/ER visits/hospitalizations at 4 weeks screening period (Week -4 to Week 0 (Day 1)).

6.2.8.4.2. Clinical and Adaptive Measures of Personality and Behavior

[00228] Assessment of clinical and adaptive measures of personality and behavior are made using the Behavior Assessment System for Children (3rd Edition). This is a screening system for measuring behavioral and emotional strengths and weaknesses conducted by the PI or Clinical Research Nurse/Coordinator.

6.2.8.4.2.1. Linguistic Skills

[00229] Linguistic skills are measured by the Preschool Language Scale, Fourth Edition (PSL-4) (Zimmerman et al 2002). The assessment is used to evaluate basic communication and language skills in young children and is conducted by the PI or Clinical Research Nurse/Coordinator.

6.2.8.4.2.2. Adaptive Level of Behavioral Function

[00230] Adaptive level of behavioral function is measured by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (Sparrow et al 2005). The assessment is used to evaluate the child's ability to adapt to practical, everyday skills that are required to function and meet environmental demands. The assessment is conducted by the PI or Clinical Research Nurse/Coordinator.

6.2.8.4.2.3. Quality of Life

[00231] Quality of Life is assessed by the QOLCE (Sabaz *et al.* Epilepsy Behav. 2003, 4(6):680-91). This questionnaire is used to evaluate the QOL of these children living with epilepsy and is distributed to the parents to complete.

6.2.8.5. Statistical Analyses

[00232] The confidence interval (CI) for the proportion, if presented, is computed using normal approximation, if the number of the events is at least 5. Otherwise, CI using an exact method is provided. For safety summaries, CI is not presented, unless specified otherwise. Summary statistics are analyzed within each disorder group. All analyses are performed using Statistical Analysis System (SAS[®]), (Version 9.0 or higher).

6.2.8.5.1. Study Conduct

[00233] All protocol deviations are listed and summarized.

6.2.8.5.2. Study Population

[00234] Frequency distributions or summary statistics of data pertaining to patient disposition, demographics, baseline characteristics, and medical history are tabulated.

6.2.8.5.2.1. Patient Disposition

[00235] The disposition of patients, including the number of patients screened, the number of patients randomized, the number of randomized patients who received at least one dose of study drug, and the number of patients who prematurely discontinue study drug are tabulated.

6.2.8.5.2.2. Demographics and Baseline Characteristics

[00236] Demographic and baseline characteristics of patients are summarized descriptively by means and standard deviations for continuous variables, and frequency distribution for categorical variables. Summaries are performed based on all randomized patients (ie, ITT population).

6.2.8.5.2.3. Medical History and Prior Medication

[00237] Medical history and prior medication information are summarized.

6.2.8.6. Extent of exposure

[00238] The extent of exposure to ataluren treatment is defined as the last dose date minus the first dose date + 1 day. The frequency is presented according to the duration ranges (in days): ≤ 28 (≤ 4 weeks), 29 to 56 (4 to 8 weeks), 57 to 84 (8 to 12 weeks), and > 84 (> 12 weeks). The number of patients in each category as well as the mean duration is also be displayed.

6.2.8.6.1. Discontinuation of Study Therapy

[00239] The ITT population is used to summarize discontinuation from study drug as well as the reason for the premature termination of study drug. The proportion of patients who discontinue study drug is summarized using point estimates and 95% CI.

6.2.8.6.2. Treatment Compliance

[00240] Study drug compliance is assessed by analysis of unused study drug reported. This information is used to describe and summarize compliance by disorder group and treatment arm. Compliance is assessed in terms of the percentage of drug actually taken relative to the amount that should have been taken during the study.

6.2.8.7. Safety Analyses

[00241] All safety presentations are based on the ITT Population and are based only on data included in the analysis period of interest. Listings of all adverse events are also based on all available data at the scheduled analysis time point. SAE and AE summaries are represented for the following periods:

- Up to the end of Visit 8 (Week 12)
- Up to the end of Visit 18 (Week 28, EOS Visit)
- Between the start of Week 13 and the end of Week 28.

[00242] Additional frequency tables summarizing the occurrence of AEs and SAEs after the end of the analysis period of interest is also provided. All AEs and SAEs are summarized by treatment group. Marked laboratory abnormalities are also descriptively summarized. No statistical tests are performed for AEs or laboratory marked abnormalities.

6.2.8.7.1. Adverse Events

[00243] Summary information (the number and percent of patients by treatment) is tabulated for:

- TEAEs, including clinical and laboratory adverse events
- Treatment-related adverse events
- TEAEs by severity
- Treatment-related adverse events by severity
- Serious adverse events
- Adverse events leading to discontinuation

[00244] Summaries are presented by treatment groups and categorized by System Organ Class and Preferred Term. The frequencies of adverse events displayed are the crude rates that represent the number of patients experiencing adverse events divided by the total number of patients.

6.2.8.7.2. Adverse Events Laboratory Parameters

[00245] Changes in clinical laboratory tests from baseline (last measurement prior to randomization) and laboratory marked abnormalities (laboratory adverse events) using pre-defined abnormality criteria are descriptively summarized. In the by-patient analysis, a patient

having the same abnormality more than once is counted only once based on the worst severity grade observed.

6.2.8.7.3. Other Parameters

Height, weight, vital signs and physical examination data are descriptively summarized. Concomitant medications by Week 12 and Week 28 are summarized.

6.2.8.8. Efficacy Analyses

[00246] All efficacy endpoints are summarized within each disorder group (Dravet or CDKL5) and by treatment group.

[00247] Summary statistics for the total numbers of the following measurements during every 4 weeks period since Day 1 (Week 0 to Week 4, Week 4 to Week 8, etc., defined as at “Week 4xX”, X=1, 2, ..., 6), along with changes from baseline are tabulated for the following:

- Motor seizures
- Staring seizures
- Myoclonic seizures
- Use of rescue medications
- ER visits/hospitalizations

[00248] To assess the change in total number of motor seizures in each Treatment Period (Treatment Period 1 [from Baseline to Week 12] and Treatment Period 2 [From Visit 10 to the EOS Visit]), ANCOVA models, with the total number of motor seizures at Baseline, body weight, and age as covariates, and the treatment group as factors may be used. In the situation of high level of unbalanceness, mixed effect models are considered. Statistical method for analyzing repeated measures data may also be explored for the change in total number of motor seizures from baseline, as appropriate.

[00249] Summary statistics at each measurement time point, along with changes from baseline are tabulated for:

- Behavior Assessment System for Children
- Preschool Language Scale
- Vineland Adaptive Behavior Scales
- QOLCE

6.2.9. SAFETY AND ADVERSE EVENTS

6.2.9.1. Definitions

6.2.9.1.1. Unanticipated Problems Involving Risk to Patients or Others

[00250] Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (ie, not described in study-related documents such as the Institutional Review Board (IRB)-approved protocol or consent form, the IB, etc)
- Related or possibly related to participation in the research (ie, possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places patients or others at greater risk of harm (including physical, psychological, economic, or social harm).

6.2.9.1.2. Adverse Event

[00251] An adverse event is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

[00252] For this protocol, untoward medical occurrences that should be reported as adverse events include the following:

- All adverse events that are suspected or are not suspected to be due to study drug.
- Overdose (administration of a study drug dose >4 times the highest intended total daily dose level for this protocol [>160 mg/kg/day]) of study drug.
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity.
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a preexisting illness.

- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- A pre-existing condition (eg, allergic rhinitis) must be noted on the appropriate CRF for Visit 1, but should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the source documents. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an adverse event. Note that, as described in the SAE paragraph below, any inpatient hospitalization occurring as the consequence of an adverse event during the study period should be reported as an SAE.

[00253] Each adverse event is to be classified as serious or non-serious by the investigator using medical and scientific judgment.

6.2.9.1.3. Serious Adverse Event

[00254] Adverse events are classified as serious or non-serious. A *serious adverse event* is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

[00255] Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the patient, and may require intervention to prevent one of the other serious outcomes noted above. For example, study drug or other drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

[00256] Overdose of study drug is considered to be administration of a study drug dose > 4 times the intended total daily dose level for this protocol (> 160 mg/kg/day). All adverse events that do not meet any of the criteria for serious should be regarded as nonserious adverse events. Note that any SAEs occurring within 4 weeks of the date of last dose should be reported to the investigator.

[00257] It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, the invention described herein is not to be limited in scope by the specific embodiments herein disclosed. These embodiments are intended as illustrations of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description, which modification also intended to be within the scope of this invention.

What is claimed is:

1. A method for treating, preventing, ameliorating or managing a nonsense mutation mediated epileptic disease associated with a nonsense mutation, comprising administering an effective amount of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid or a pharmaceutically acceptable salt thereof to a patient having the nonsense mutation mediated epileptic disease.
2. The method of claim 1, wherein the nonsense mutation mediated epileptic disease is associated with a CDKL5 or SCN1A (Dravet syndrome) nonsense mutation.
3. The method of either of claim 1 or 2, wherein the salt is selected from the group consisting of a magnesium salt, a potassium salt, a sodium salt, a tromethamine salt, an L-lysine salt, an L-arginine salt, an N-methyl glucamine salt and an L-histidine salt.

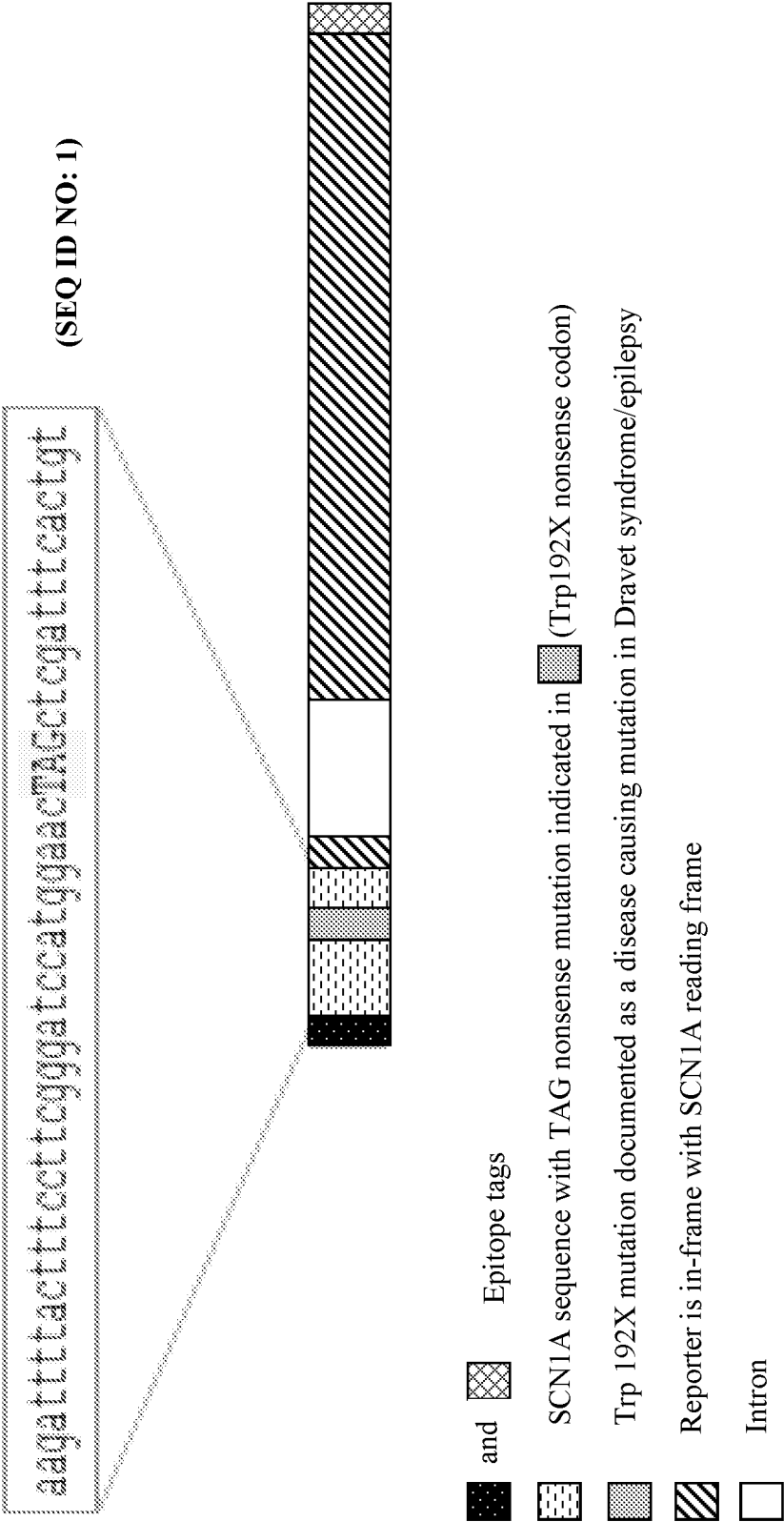
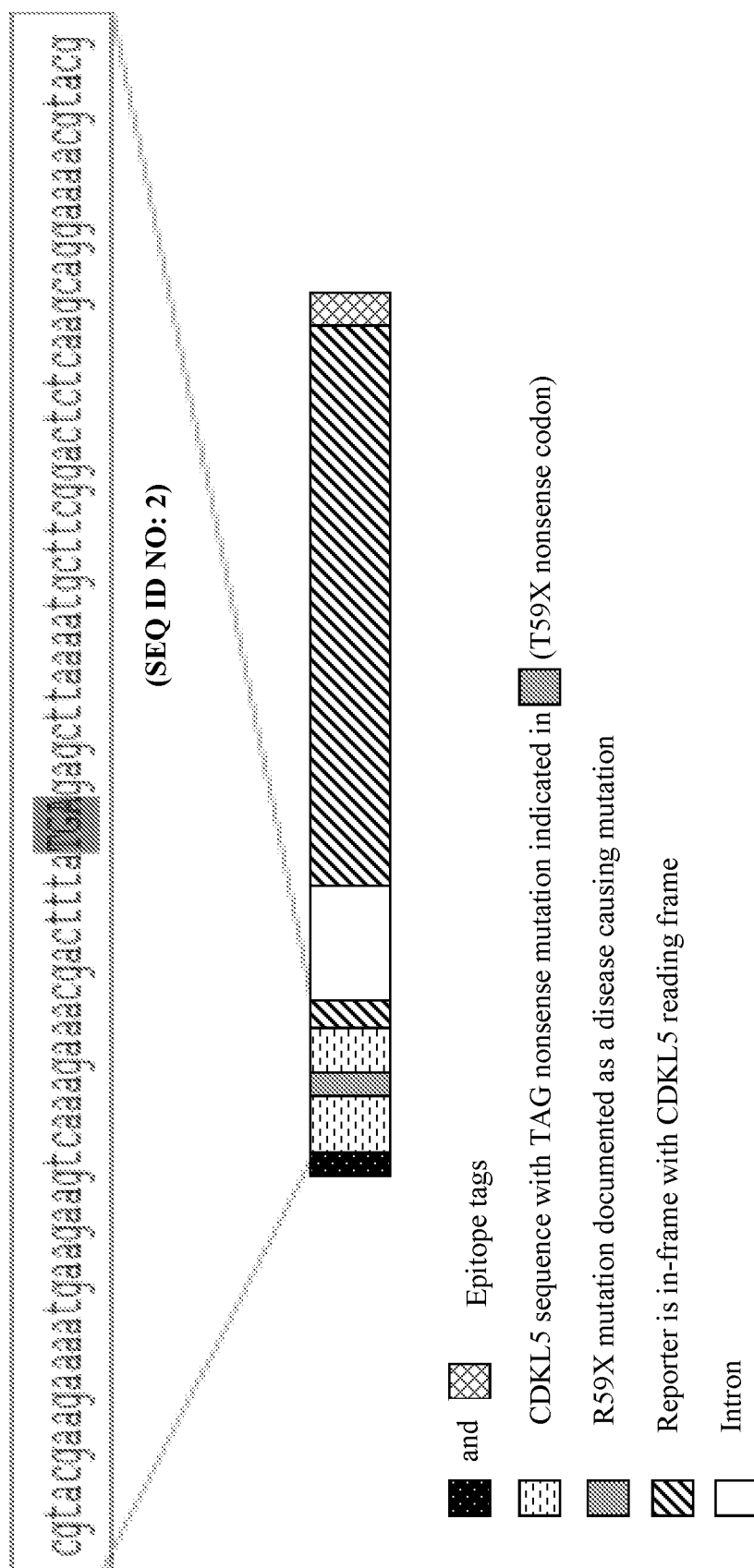


Fig. 1



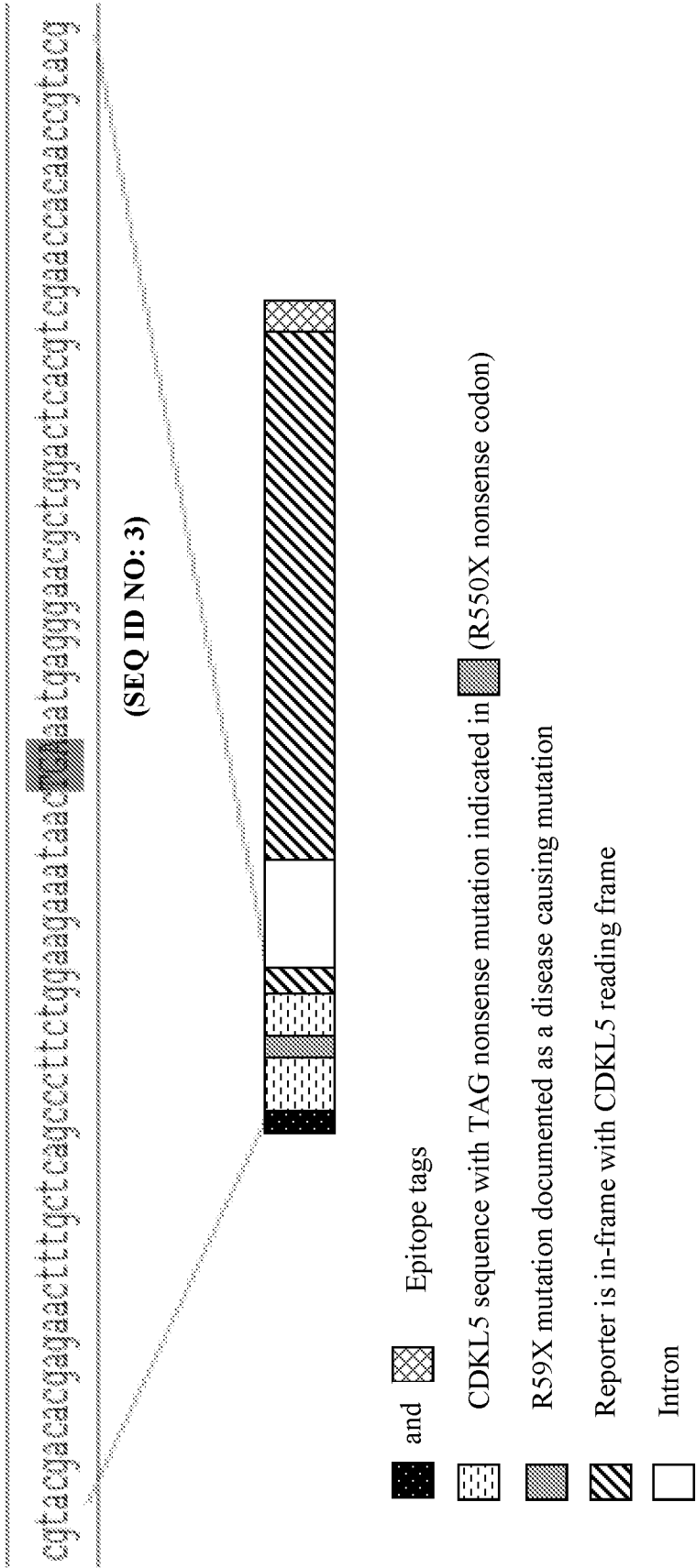


Fig. 3

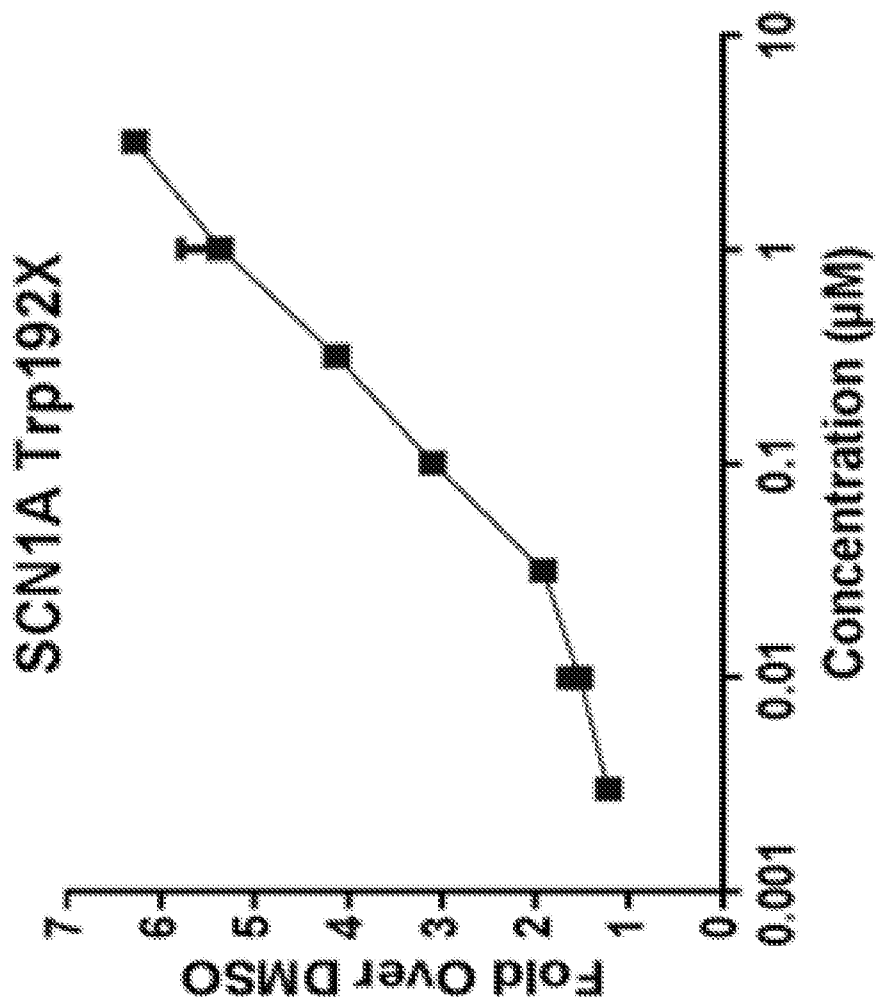


Fig. 4

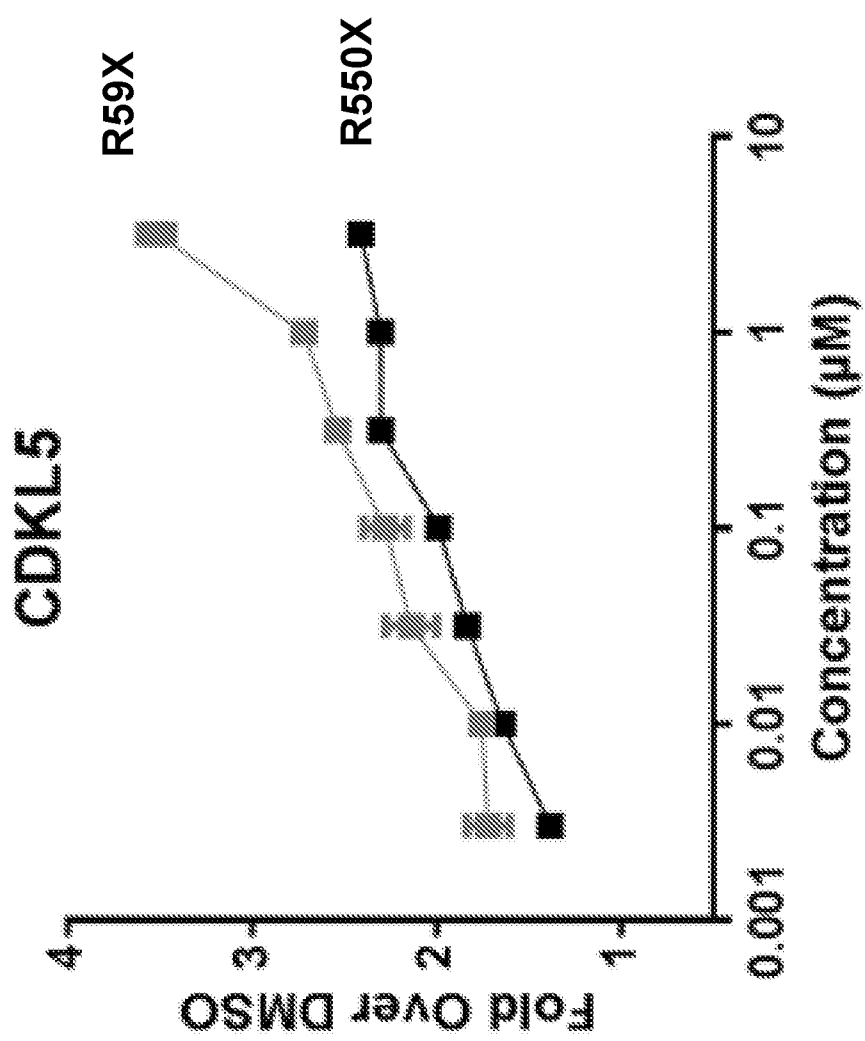


Fig. 5

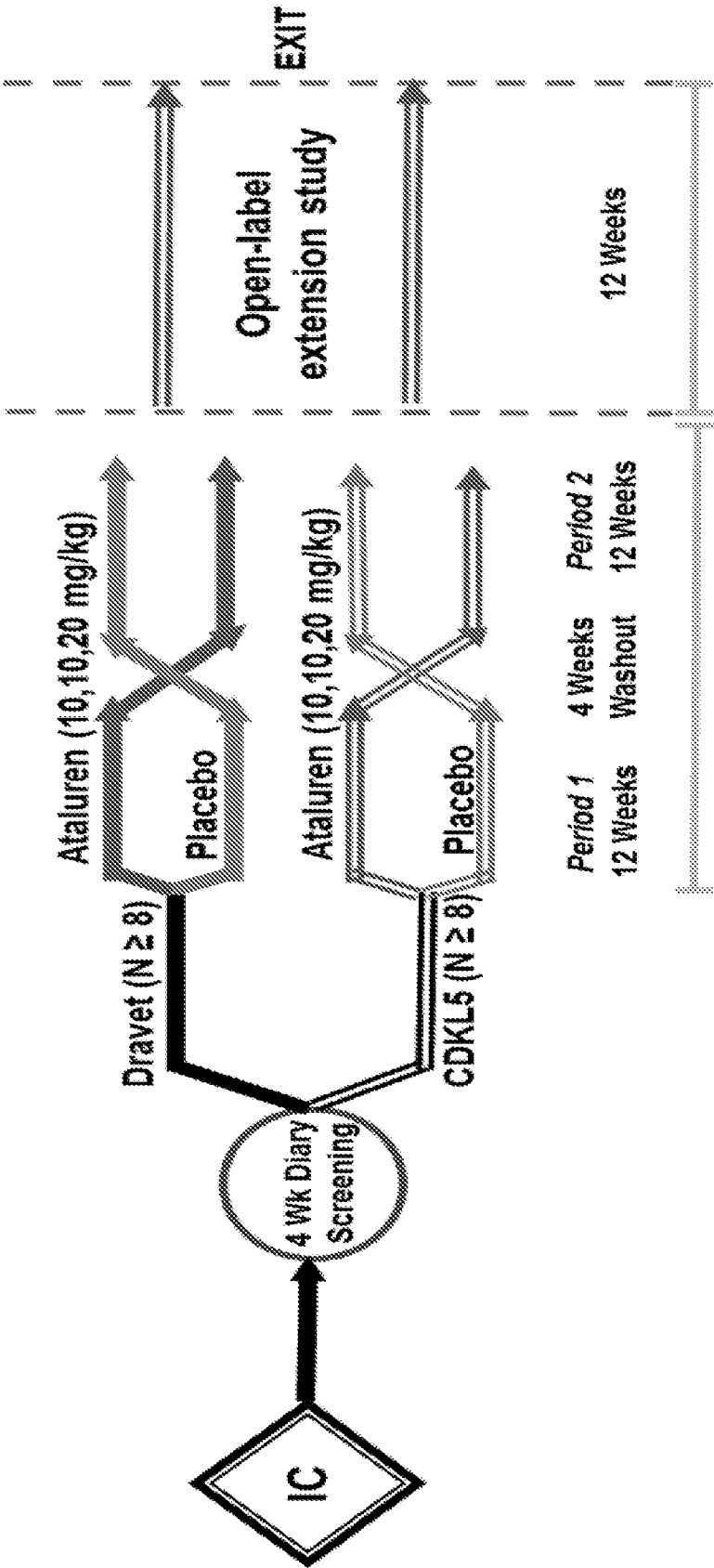


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/59262

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/5377, A61K 31/4245 (2016.01)

CPC - A61K 31/4245, A61K 31/655

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/5377, A61K 31/4245 (2016.01)

CPC - A61K 31/4245, A61K 31/655

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/236.2; 514/318, 514/326, 514/340Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
pubWEST; PatBase; Google Scholar

search terms - Epilepsy, epilep*, nonsense, mutat*, mutation, CDKL5, SCN1A, Dravet syndrome, 1,2,4-oxadiazole, benzoic acid, 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]benzoic acid, 3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, Fluoro-phenyl, ma,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0168109 A1 (KARP et al.) 01 July 2010 (01.07.2010) para [0002]; [0013]; [0075]; [0096]; [0100].	1-3
Y	US 2010/0088778 A1 (MULLEY et al.) 08 April 2010 (08.04.2010) abstract; para [0023]; [0024].	1-3

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 December 2016

Date of mailing of the international search report

24 JAN 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774



(12)发明专利申请

(10)申请公布号 CN 108348527 A

(43)申请公布日 2018.07.31

(21)申请号 201680063273.8

(22)申请日 2016.10.28

(30)优先权数据

62/248,891 2015.10.30 US

(85)PCT国际申请进入国家阶段日

2018.04.27

(86)PCT国际申请的申请数据

PCT/US2016/059262 2016.10.28

(87)PCT国际申请的公布数据

W02017/075312 EN 2017.05.04

(71)申请人 PTC医疗公司

地址 美国新泽西州

(72)发明人 埃伦·韦尔奇 富泽友希

普里亚·瓦齐拉尼

(74)专利代理机构 北京安信方达知识产权代理有限公司 11262

代理人 贺淑东

(51)Int.Cl.

A61K 31/5377(2006.01)

A61K 31/4245(2006.01)

权利要求书1页 说明书49页

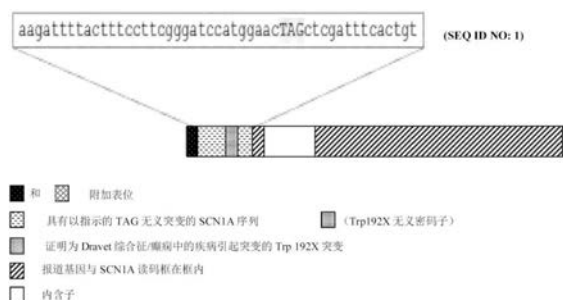
序列表1页 附图6页

(54)发明名称

用于治疗癫痫的方法

(57)摘要

本文提供了治疗、预防、改善或管理无义突变介导的癫痫疾病的方法,所述方法包括将1,2,4-噁二唑苯甲酸施用于患有无义突变介导的癫痫疾病的患者。具体地,本文提供了治疗、预防、改善或管理CDKL5和/或SCN1A(Dravet综合征)无义突变介导的癫痫疾病的方法。



1. 一种用于治疗、预防、改善或管理与无义突变相关的无义突变介导的癫痫疾病的方法,所述方法包括将有效量的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其药学可接受的盐施用于患有无义突变介导的癫痫疾病的患者。

2. 根据权利要求1所述的方法,其中所述无义突变介导的癫痫疾病与CDKL5或SCN1A (Dravet综合征) 无义突变相关。

3. 根据权利要求1或2所述的方法,其中所述盐选自镁盐、钾盐、钠盐、氨丁三醇盐、L-赖氨酸盐、L-精氨酸盐、N-甲基葡萄糖胺盐和L-组氨酸盐。

用于治疗癫痫的方法

[0001] 本专利申请要求于2015年10月30日提交的美国临时申请号62/248,891的权益,所述美国临时申请以引用的方式全文并入本文。

1. 技术领域

[0002] 本文提供了治疗、预防、改善或管理无义突变介导的癫痫疾病的方法,所述方法包括将1,2,4-噁二唑苯甲酸化合物(例如3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸)施用于患有无义突变介导的癫痫疾病的患者,例如在CDKL5或SCN1A基因中具有无义突变的患者。具体地,本文提供了治疗、预防、改善或管理与CDKL5或SCN1A基因中的遗传或体细胞无义突变相关的无义突变介导的癫痫疾病的方法,其中所述无义突变导致提前终止密码子的表达,所述方法包括将1,2,4-噁二唑苯甲酸化合物(例如3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸)施用于具有无义突变的患者。

2. 背景技术

[0003] 耐药性癫痫是负面影响患者的生活质量的严重状况。患有耐药性癫痫的那些患者处于癫痫猝死(SUDEP)的较高危险中。与SUDEP相关的危险因素包括频繁的全身性强直阵挛性癫痫发作、抗癫痫药物(AED)多药疗法和常见的夜间癫痫发作,也是存在于患有耐药性癫痫的那些患者中的因素(Pack AM., SUDEP, What Are the Risk Factors? Do Seizures or Antiepileptic Drugs Contribute to an Increased Risk?, *Epilepsy Currents*, 第12卷, No. 4 (7月/8月) 2012第131-132页)。在患有耐药性癫痫的那些患者中的SUDEP危险可超过5%/十年(Devinsky O. *N Engl J Med.* 2011; 365 (19): 1801-11)。尽管AED的多重组合的试验,但患有耐药性癫痫的大多数患者没有美国食品和药物管理局(Food and Drug Administration) (FDA)批准的治疗方案选项。CDKL5和SCN1A相关癫痫是通常与耐药性癫痫相关的罕见癫痫。

[0004] CDKL5是产生细胞周期蛋白依赖性激酶样5 (CDKL5) 蛋白的基因,所述CDKL5蛋白主要在脑、胸腺和睾丸中表达。该基因由24个外显子组成;外显子2-11编码催化结构域,而外显子12-18编码羧基末端。在小鼠中,表达谱提示CDKL5蛋白涉及神经元成熟(Rusconi等人, *J Biol Chem.*, 2008; 283 (44): 30101-11)。CDKL5使核内的MECP2基因的蛋白质产物磷酸化,并且可能解释了雷特综合征(Rett syndrome)和CDKL5相关癫痫之间的相似性(Mari F., Azimonti S., Bertani I., Bolognese F., Colombo E., Caselli R., Scala E., Longo I., Grosso S., Pescucci C., Ariani F., Hayek G., Balestri P., Bergo A., Badaracco G., Zappella M., Broccoli V., Renieri A., Kilstrup-Nielsen C., Landsberger N., CDKL5 Belongs to the Same Molecular Pathway of MeCP2 and it is Responsible for the Early-Onset Seizure Variant of Rett Syndrome, *Human Molecular Genetics*, 2005, 第14卷, No. 14, 1935-1946)。MECP2调节与突触功能和维持相关的基因。这种功能的丧失驱动了表型,并且负责与雷特综合征的相似性。CDKL5还使DNA甲基转移酶1 (DNMT1) 和双羧蛋白磷酸化,并且与Rac1相互作用以影响肌动蛋白重塑和神经元形态发生。

[0005] CDKL5相关癫痫是最常存在于女性的X连锁遗传性癫痫性脑病。男性比女性更严重受影响(Melani等人,Dev Med Child Neurol.2011;53(4):354-60)。发病率为在45,000个活产儿中~1。患有CDKL5相关性X连锁遗传性癫痫性脑病的患者在生命的前几个月显示出弱发育技能的早期征兆(例如弱吸吮、弱目光接触)。随后,手部运动技能的损害、语言习得的缺乏以及严重的总体发育延迟变得显而易见(Fehr等人,Eur J Hum Genet.2013;21(3):266-73;Melani等人,Dev Med Child Neurol.2011;53(4):354-60)。目光接触和社交交往通常减少。许多患者永远无法独立行走。CDKL5相关癫痫与皮质萎缩或变性无关。CDKL5缺陷引起癫痫性脑病,其中癫痫样异常促成进行性功能损害。在前四个月内,癫痫经常伴随婴儿痉挛存在(Mei等人,Epilepsia.2010 Apr;51(4):647-54)。癫痫发作的平均年龄为6周,其中超过90%在生命的前3个月内经历癫痫发作。随后,由振动强直期随后为阵挛期组成的强直阵挛性癫痫发作发生,并且经常持续2至4分钟(Melani等人,Dev Med Child Neurol.2011;53(4):354-60)。在3岁后,癫痫发作在许多儿童中减轻,而其它人继续具有耐药性癫痫,具有强直性痉挛和肌阵挛性癫痫发作(Mei等人,Epilepsia.2010Apr;51(4):647-54)。脑电图发现经常包括具有发作间广泛的局灶性或多局灶性放电的本底减慢。在较年幼的儿童中可见爆发抑制模式(Melani等人,Dev Med Child Neurol.2011;53(4):354-60)。

[0006] SCN1A(Nav1.1)是几乎唯一地在脑中表达的钠通道 $\alpha 1$ 亚基基因。SCN1A中的突变可引起各种癫痫,所述癫痫的范围从良性发热性癫痫发作到严重癫痫性脑病和Dravet综合征(婴儿严重肌阵挛性癫痫;Mulley等人,Hum Mutat.2005;25(6):535-42;Catterall等人,J Physiol.2010;588(Pt 11):1849-59)。癫痫潜在的主要机制看起来是 α -氨基丁酸(GABA)中间神经元抑制功能的损害(Catterall等人,J Physiol.2010;588(Pt 11):1849-59;Yu FH.,Mantegazza M.,Westenbroek RE.,Robbins CA.,Kalume F.,Burton KA.,Spain WJ.,McKnight GS.,Scheuer T.,Catterall WA.,Reduced Sodium Current in GABAergic Interneurons in a Mouse Model of Severe Myoclonic Epilepsy in Infancy,Nature Neuroscience,2006,9月,第9卷,No.9,1142-1149)。

[0007] Dravet综合征最初在1978年被Charlotte Dravet描述为婴儿严重肌阵挛性癫痫(SMEI)(Dravet C.Dev Med Child Neurol.2011;53(Suppl 2):1-6)。它引起发热和无热、全身性和单侧(unilateral)、阵挛性或强直阵挛性癫痫发作;它也可引起失神性、失神性肌阵挛性和复杂部分性癫痫发作。癫痫发作通常在其他方面正常的婴儿中生命的第一年内开始。最初的癫痫发作通常是热性癫痫持续状态(Dravet C.,Bureau M.,Oguni H.,Fukuyama Y.,Cokar O.,Severe Myoclonic Epilepsy in Infancy:Dravet Syndrome,Adv.Neurol.(2005),95,71-102)。随后,肌阵挛性、非典型失神性和部分性癫痫发作通常发展。癫痫发作通常是耐药的,但癫痫的严重性接近青春期趋于减小。发育在生命的第二年内延迟,并且超过95%的患者中存在智力残疾(Chieffo D.,Battaglia D.,Lettori D.,Del Re M.,Brognia C.,Dravet C.,Mercuri E.,Guzzetta F.,Chieffo,D.,Chieffo,D.,Neuropsychological Development in Children with Dravet Syndrome,Epilepsy Research,(2011),95,86-93)。大约25%的患者中诊断出自闭症谱系障碍(Genton等人,Epilepsia.2011;52(Suppl 2):44-9)。大多数患者在儿童期晚期发展小脑功能障碍,体现为共济失调步态障碍、构音障碍和意向性震颤((Genton等人,Epilepsia.2011;52(Suppl

2):44-9)。死亡率很高。大约15%的患者到青春期时死亡,并且20%到早期成年期时死亡(Genton等人,Epilepsia.2011;52(Suppl 2):44-9)。SUDEP和癫痫持续状态是最常见的死因。

[0008] 无义突变是DNA中的单点改变,在转录时,所述单点改变导致编码氨基酸的信使核糖核酸(mRNA)三联体(例如CAG)转换为被解释为终止密码子(即,提前终止密码子)的三联体(例如UAG)。mRNA内的提前终止密码子的存在导致截短的非功能性蛋白质和后续疾病的产生。无义突变尤其是大多数遗传性疾病的大约13%至40%个体病例的基础,所述遗传性疾病包括CDKL5缺陷和SCN1A缺陷(特别是Dravet综合征)(Frame Kathryn,Elibri D0.The International CDKL5 Disorder Database Newsletter 1(2013年7月))。

3. 发明内容

[0009] 本文提供了治疗、预防、改善或管理无义突变介导的癫痫疾病和/或与提前终止密码子相关的癫痫疾病的方法,所述方法包括将1,2,4-噁二唑苯甲酸(例如3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸)施用于患有无义突变介导的癫痫疾病的患者。具体地,本文提供了治疗、预防、改善或管理与无义突变或提前终止密码子相关的癫痫疾病(例如导致CDKL5和/或SCN1A缺陷(特别是Dravet综合征);或者,例如SCN2A、GABRG2、DEPDC5和/或NAPB缺陷)的方法,所述方法包括将1,2,4-噁二唑苯甲酸(例如3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸)施用于患有与无义突变或提前终止密码子相关的癫痫疾病(例如导致CDKL5和/或SCN1A缺陷(特别是Dravet综合征);或者,例如SCN2A、GABRG2、DEPDC5和/或NAPB缺陷)的患者。

4. 附图说明

[0010] 图1是显示了用于监测SCN1A无义密码子W192X的通读活性的报道构建体的示意图。显示了在报道构建体中使用的SCN1A核苷酸序列(SEQ ID NO:1),具有由灰色阴影指示的TAG无义突变(W192X)。

[0011] 图2是显示了用于监测CDKL5无义密码子R59X的通读活性的报道构建体的示意图。显示了在报道构建体中使用的CDKL5核苷酸序列(SEQ ID NO:2),具有由灰色阴影指示的TGA无义突变(R59X)。

[0012] 图3是显示了用于监测CDKL5无义密码子(R550X)的通读活性的报道构建体的示意图。显示了在报道构建体中使用的CDKL5核苷酸序列(SEQ ID NO:3),具有由灰色阴影指示的TGA无义突变(R550X)。

[0013] 图4是显示了与图1中所示的具有SCN1A报道构建体的细胞中的DMSO相比,1,2,4-噁二唑苯甲酸化合物,具体地,3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸的通读活性中的倍数增加的图。

[0014] 图5是显示了与图2(R59X)和图3(R550X)中所示的具有CDKL5报道构建体的细胞中的DMSO相比,1,2,4-噁二唑苯甲酸化合物,具体地,3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸的通读活性中的倍数增加的图。

[0015] 图6是本文实例6.2中描述的临床方案的研究设计的示意图。

5. 具体实施方式

[0016] 5.1 定义

[0017] 如本文使用的,术语“提前翻译终止”具有与本领域普通技术人员通常理解相同的含义。在某些实施例中,术语“提前翻译终止”一般是指将对应于氨基酸的密码子改变为终止密码子的突变的结果。在具体实施例中,术语“提前翻译终止”是指在翻译过程中,其中功能性蛋白的产生由于DNA中的无义突变而停止的事件,所述无义突变将对应于氨基酸的经转录的mRNA密码子改变为提前终止密码子。

[0018] 如本文使用的,术语“提前终止密码子 (premature termination codon)”和“提前终止密码子 (premature stop codon)”具有与本领域普通技术人员通常理解相同的含义。在某些实施例中,术语“提前终止密码子 (premature termination codon)”和“提前终止密码子 (premature stop codon)”是指当对应于氨基酸的密码子应该存在时终止密码子的出现。

[0019] 如本文使用的,术语“无义突变”具有与本领域普通技术人员通常理解相同的含义。在某些实施例中,术语“无义突变”是指DNA中的突变,所述突变将mRNA中对应于氨基酸的密码子改变为终止密码子。在某些实施例中,无义突变是在DNA中出现,然后作为提前终止密码子转录成mRNA的突变。

[0020] 如本文使用的,术语“无义抑制”具有与本领域普通技术人员通常理解相同的含义。在某些实施例中,术语“无义抑制”是指提前翻译终止的抑制或压制,导致功能性蛋白的产生。

[0021] 如本文使用的,术语“提前翻译终止的调节”是指在无义抑制剂的存在下,通过提前终止密码子的通读产生的功能性蛋白的量中的增加。在某些实施例中,为了治疗、预防、改善或管理无义突变介导的疾病,期望增加由具有提前终止密码子的mRNA编码的蛋白质的产生,即,使得来源于疾病基因表达的提前终止密码子能够通读,因此通过使用无义抑制剂可发生mRNA的翻译。

[0022] 如本文使用的,术语“活性剂”、“药物”和“原料药”是指本文提供的选自3-[5-(2-氟-苯基)-乙基]-[1,2,4]噁二唑-3-基]-苯甲酸(具有通用名“阿他卢仑”)的1,2,4-噁二唑苯甲酸化合物或其药学可接受的盐,并且在本文中统称为“化合物1”。

[0023] 如本文使用的,术语“剂量”意指一次施用的活性剂的数量。

[0024] 如本文使用的,术语“单位剂型”包括固体剂型例如片剂、囊片、胶囊、锭剂、分散体、粉末、颗粒或凝胶等等,或者液体剂型例如溶液、悬浮液、乳剂或酏剂等等,以及可重构以提供这种液体剂型的固体形式例如粉末或颗粒,其中此类单位剂型适合于经口或肠胃外施用于患者。

[0025] 如本文使用的,术语“给药方案”和“剂量”意指根据患者体重,经过给定时间段施用的活性剂的量。

[0026] 如本文使用的,术语“受试者”和“患者”可互换使用,以指具有感觉和随意运动能力,并且对于其存在需要氧和有机食物的动物或任何活生物。非限制性例子包括人、灵长类、马科、猪科、牛科、兔属、鼠属、鼠科、犬科和猫科动物物种的成员。在一些实施例中,受试者是哺乳动物或温血脊椎动物。在某些实施例中,受试者是非人动物。在具体实施例中,受

试者是人以及进一步的人患者。在某些实施例中,受试者是胎儿、胚胎、婴儿、儿童、青少年或成人。在一个实施例中,受试者已通过遗传预筛选确定为具有无义突变。在另一个实施例中,受试者已通过遗传预筛选确定为具有特定的提前终止密码子(即UAA、UGA或UAG)。在另一个实施例中,受试者中的提前终止密码子的背景已由遗传预筛选确定(即UAAA、UAAC、UAAU、UAAG、UGAA、UGAC、UGAU、UGAG、UAGA、UAGC、UAGU或UAGG)。

[0027] 如本文使用的,在产生功能性通读蛋白质的上下文中的术语“有效量”是指对受试者具有预防和/或治疗益处的功能性通读蛋白质的量。在具体实施例中,有效量的功能性通读蛋白质是具有下述效应中的一种、两种或更多种的蛋白质的量:(1) 预防无义突变介导的癫痫疾病的发作、发展和/或进展,(2) 预防与无义突变介导的癫痫疾病相关的一种或多种症状的发作、发展和/或进展,(3) 减少无义突变介导的癫痫疾病的持续时间和/或严重性,(4) 减少与无义突变介导的癫痫疾病相关的症状的数目,(5) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的持续时间,(6) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的严重性,和(7) 改善受试者的生活质量。

[0028] 无义突变介导的癫痫疾病的症状包括特征在于意识不清、惊厥和肌肉强直的惊厥性癫痫发作、跌落癫痫发作、全身性单侧(一侧)阵挛性癫痫发作或全身性强直阵挛性(癫痫大发作)癫痫发作;特征在于意识短暂丧失的失神性癫痫发作;特征在于通常在身体两侧上的偶发性抽搐的全身性肌阵挛性癫痫发作;特征在于同时涉及身体两侧的重复性、有节奏的抽搐的全身性阵挛性癫痫发作;特征在于肌肉僵硬的全身性强直性癫痫发作;特征在于突然和泛发的肌张力丧失(特别是在手臂和腿部中)的全身性无张力性癫痫发作,这经常导致跌倒;特征在于意识、抽搐、肌肉强直、痉挛、头部转向的简单运动性部分性癫痫发作;特征在于意识和影响视觉、听觉、嗅觉、味觉或触觉的异常感觉的简单感觉性部分性癫痫发作;特征在于意识和记忆或情绪障碍的简单心理性部分性癫痫发作;特征在于意识和自动作用的损害,例如咂唇、咀嚼、烦躁、行走和其它重复性、非自愿但协调的运动的复杂部分性癫痫发作(局部认知障碍性癫痫发作(focal dyscognitive seizures));特征在于意识保留,然后发展为意识丧失和惊厥的部分性癫痫发作伴继发性全身发作;癫痫猝死(SUDEP);和夜间癫痫发作。

[0029] 如本文使用的,在本文所述的化合物施用的上下文中,术语“有效量”是指对受试者具有预防和/或治疗益处的化合物的量。在具体实施例中,本文所述的化合物的有效量具有下述效应中的一种、两种或更多种:(1) 预防无义突变介导的癫痫疾病的发作、发展和/或进展,(2) 预防与无义突变介导的癫痫疾病相关的一种或多种症状的发作、发展和/或进展,(3) 减少无义突变介导的癫痫疾病的持续时间和/或严重性,(4) 减少与无义突变介导的癫痫疾病相关的症状的数目,(5) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的持续时间,(6) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的严重性,和/或(7) 改善受试者的生活质量。下文在第5.4节中提供了本文所述的化合物的有效量的例子。在具体实施例中,当用于治疗、预防、改善或管理本文在下文第6节中提供的症状或无义突变介导的癫痫疾病时,本文所述的化合物的有效量具有前述效应中的一种、两种或更多种。

[0030] 如本文使用的,在功能性通读蛋白质的上下文中的术语“功能性”是指这样的蛋白质,所述蛋白质以足够数量产生,以治疗、预防或改善来源于蛋白质的不存在的疾病。另外,该术语是指这样的蛋白质,所述蛋白质具有野生型蛋白质的足够功能活性,以在细胞或受

试者中具有有益效应,由于编码蛋白质的核酸序列(例如基因)中的突变(例如无义突变),所述细胞或受试者否则不产生野生型蛋白质或产生不足量的野生型蛋白质。在一个具体实施例中,功能性通读蛋白质基本上执行全长野生型蛋白质的功能,即治疗、预防、改善或管理疾病。在另一个具体实施例中,功能性通读蛋白质执行全长野生型蛋白质的功能中的一种、两种、三种或更多种。在某些实施例中,所产生的功能性通读蛋白质是功能性非野生型蛋白质。在某些实施例中,所产生的功能性通读蛋白质是功能性野生型蛋白质。在一些实施例中,所产生的功能性非野生型蛋白质是全长的。在一些实施例中,所产生的功能性野生型蛋白质是全长的。在其它实施例中,功能性非野生型蛋白质不是全长的。在其它实施例中,所产生的功能性野生型蛋白质不是全长的。

[0031] 如本文使用的,在功能性通读蛋白质的上下文中,术语“基本上执行全长野生型蛋白质的功能”意指功能性通读蛋白质执行全长野生型蛋白质的至少一种、两种、三种或更多种功能。

[0032] 如本文使用的,术语“无义突变介导的癫痫疾病”是指直接或间接来源于基因中的无义突变的癫痫疾病或状况或癫痫类型,其中无义突变阻止了受影响细胞中野生型蛋白质的产生。例如,CDKL5基因中的无义突变阻止野生型CDKL5蛋白的产生,并且导致CDKL5无义突变介导的癫痫疾病。另外,例如,SCN1A基因中的无义突变阻止野生型SCN1A蛋白的产生,并且导致SCN1A无义突变介导的癫痫疾病(特别是Dravet综合征)。无义突变介导的癫痫疾病的例子包括但不限于Dravet综合征、婴儿严重肌阵挛性癫痫(SMEI)、CDKL5、SCN1A、全面性癫痫伴热性惊厥附加症(GEFS+)、颞叶癫痫、难治性儿童期癫痫、良性家族性新生儿-婴儿癫痫发作(BFNIS)、良性家族性新生儿癫痫发作(BFNIS)、青少年肌阵挛性癫痫(JME)、儿童失神性癫痫(CAE)、常染色体显性夜间额叶癫痫(ADNFLE)、隐源性全身性癫痫(CGE)、隐源性局灶性癫痫(CFE)、肌阵挛站立不能性癫痫(MAE)、婴儿严重特发性全身性癫痫(SIGEI)、婴儿痉挛(IS)和早发性癫痫性脑病(EOEE)。

[0033] 如本文使用的,在疗法施用的上下文中的“组合”是指超过一种疗法的使用。术语“组合”的使用不限制其中将疗法施用于患有疾病的受试者的次序。在某些实施例中,向患有疾病的受试者施用一种或多种疗法包括但不限于可在第二疗法施用于已患有疾病、患有疾病或易受疾病影响的受试者之前(例如前1分钟、5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周或12周)、同时或之后(例如后1分钟、5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周或12周)施用的第一疗法。将疗法以一定顺序和在时间间隔内施用于受试者,使得本文所述的单位剂型可连同另一种疗法一起发挥作用,以提供比疗法单独施用增加的益处。

[0034] 如本文使用的,术语“管理(manage)”、“管理(managing)”和“管理(management)”是指患者源自本文提供的药物组合物施用的有益效应,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐,其不导致治疗、预防或改善无义突变介导的疾病。

[0035] 如本文使用的,术语“预防(prevent)”、“预防(preventing)”和“预防(prevention)”是指由于向患有此类疾病的患者施用本文提供的包含化合物1或其盐的药物组合物,预防(例如避免)患者中无义突变介导的疾病或其症状的发作、复发、扩散或恶化

(并且因此治疗或至少改善此类疾病)。因为与无义突变相关的疾病具有遗传或躯体基础,所以需要在患者中筛选无义突变的存在。当通过筛选确定患者具有无义突变时,有效量的药物组合物可施用于患者以预防疾病或其症状的发作、复发、扩散或恶化,所述药物组合物包含有效量的本文提供的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐。

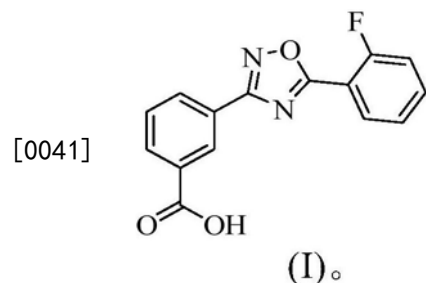
[0036] 如本文使用的,术语“治疗(treat)”、“治疗(treating)”和“治疗(treatment)”是指疾病或与疾病相关的症状的根除或改善。在某些实施例中,此类术语是指由于向患有此类疾病的患者施用本文提供的药物组合物,最小化患者中疾病的扩散或恶化,所述药物组合物包含本文提供的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐。当确定患者患有与遗传或体细胞无义突变相关的疾病时,有效量的药物组合物可施用于患者以根除、改善或最小化疾病或其症状的扩散或恶化,所述药物组合物包含有效量的本文提供的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐。

[0037] 如本文使用的,术语“约”或“大约”意指如由本领域普通技术人员确定的关于特定值的可接受误差,其部分取决于如何测量或测定该值。在某些实施例中,术语“约”或“大约”意指在1、2、3或4个标准差内。在某些实施例中,术语“约”或“大约”意指在给定值或范围的50%、20%、15%、10%、9%、8%、7%、6%、5%、4%、3%、2%、1%、0.5%或0.05%内。

[0038] 如本文使用的,在蛋白质的上下文中的术语“野生型”是指这样的蛋白质,所述蛋白质在自然界中发现(通常但不一定,该蛋白质是其不存在负责疾病的占优势蛋白质),并且指定为标准蛋白质或参考蛋白质。

[0039] 5.2. 化合物

[0040] 用于制备本文提供的药物组合物和盐的化合物是3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸(一般称为阿他卢仑),具有式(I)的结构:



[0042] 式(I)化合物可根据美国专利号6,992,096、美国专利号7,678,922和美国专利号8,367,841中所述的方法制备,所述专利各自的公开内容以引用的方式全文并入本文。可替代地,式(I)化合物也可根据基于本文教导对于本领域技术人员显而易见的其它方法制备。所有这些替代方法都预期包括在本文描述的方法的范围内。本文提供的式(I)化合物和盐统称为“化合物1”。

[0043] 在一个实施例中,用于本文提供的药物组合物、过程和方法中的式(I)化合物是游离酸。在一个实施例中,游离酸是固体。在又一个实施例中,固体游离酸是美国专利7,863,456中所述的方法制备,所述美国专利的公开内容以引用的方式全文并入本文。在又一个实施例中,固体游离酸是结晶形式A。在又一个实施例中,固体游离酸是结晶形式B。式(I)化合物的这些固体形式也可根据美国专利号7,863,456中所述的方法制备,所述美国专利的公开内容以引用的方式全文并入本文。可替代地,式(I)化合物的固体形式也可根据基于本文教导对于本领域技术人员显而易见的其它方法制备。

[0044] 在另一个实施例中,式(I)化合物的游离酸是药学可接受的溶剂化物。在一个实施例中,游离酸是水合物。在另一个实施例中,式(I)化合物是药学可接受的无水形式。

[0045] 在另一个实施例中,用于本文提供的药物组合物、过程和方法中的化合物1是式(I)化合物的药学可接受的游离酸。在另一个实施例中,用于本文提供的药物组合物、过程和方法中的化合物1是式(I)化合物的药学可接受的盐。在另一个实施例中,用于本文提供的药物组合物、过程和方法中的化合物1是式(I)化合物的药学可接受的无水游离酸或盐。

[0046] 5.3. 盐形式

[0047] 在某些实施例中,本文提供的方法包括使用式(I)的盐形式,包括选自L-精氨酸、L-组氨酸、L-赖氨酸、N-甲基葡糖胺、甲醇镁、氢氧化钾、氢氧化钠或氨丁三醇的盐(于2015年3月5日提交、作为国际专利申请号WO 2015/134711公开的PCT申请号PCT/US2015/018889,所述专利以引用的方式全文并入本文)。更具体地,本文提供的方法包括使用选自L-赖氨酸、钠和氨丁三醇的式(I)的盐形式。

[0048] 5.4. 药物组合物

[0049] 包含有效量的化合物1的药物组合物和单个单位剂型可用于本文提供的方法中。各个剂型可适合于经口、皮肤、粘膜(包括但不限于舌下、颊、直肠、鼻或阴道)、或肠胃外(包括但不限于皮下、肌内、动脉内、腹膜内、鞘内、心室内、尿道内、胸骨内、颅内、滑膜内、膀胱内或静脉内)或眼部施用。优选的药物组合物和单个单位剂型适合于经口施用。

[0050] 在某些实施例中,药物组合物包含按重量计约0.1%至约99%、约5%至约90%、约5%至约50%、约10%至约40%、约20%至约30%、约0.1%至约5%、约0.1%至约2.5%、约0.1%至约1%、或约0.25%至约0.5%的化合物1。在某些实施例中,药物组合物包含按重量计约0.1%、约0.25%、约0.5%、约1%、约2%、约5%、约10%、约15%、约20%、约25%、约30%、约35%、约40%、约50%、约60%、约70%、约80%或约90%的化合物1。在某些实施例中,药物组合物包含按重量计约0.25%、约0.5%或约1%的化合物1。

[0051] 在某些实施例中,本文提供的药物组合物包含约1mg至约5,000mg、约10mg至约2,000mg、约50mg至约1,000mg、约100mg至约1,000mg、或约100mg至约500mg化合物1。在某些实施例中,本文提供的药物组合物包含约125mg、约200mg、约325mg、约400mg或约500mg化合物1。在某些实施例中,本文提供的药物组合物包含约120mg至约130、约195mg至约205mg、约320mg至约330mg、约395mg至约405mg、或约495mg至约505mg化合物1。

[0052] 在某些实施例中,如本文提供的,本文提供的药物组合物中的化合物1是3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸的游离酸或3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸的盐。

[0053] 本文提供的药物组合物可以单位剂型或双重剂型提供。如本文使用的,单位剂型是指适合于使用本领域已知的包装施用于人或动物受试者的物理离散单位。每个单位剂量含有与所需的药物载体或赋形剂结合、足以产生所需疗效的预定数量的活性成分。单位剂型的例子包括但不限于个别包装的小包、小袋或瓶或滴管。单位剂型可以其一部分或多份施用。多重剂型是包装在单个容器中的多个相同的单位剂型,以作为分开或组合的单位剂型施用。多重剂型的例子包括颗粒或粉末的小包或小袋,片剂或胶囊的小瓶或瓶,或以流体盎司、品脱或加仑的液体溶液瓶,用于肠胃外、经口或经由滴管眼部施用。

[0054] 本文提供的药物组合物可经过一段时间作为分份剂量施用。应理解,治疗的精确

剂量和持续时间可随着待治疗的患者的年龄、重量和状况而变化,并且可使用已知的测试方案凭经验、或者通过从体内或体外测试或诊断数据外推、或者通过观察某些临床因素来确定。还应理解对于任何特定的个体,可根据个体需要和施用或监督药物组合物施用的个人的专业判断随着时间过去调整具体的剂量方案。

[0055] 5.4.1. 局部用制剂

[0056] 在某些实施例中,本文提供的药物组合物在共溶剂中配制为局部用制剂,所述共溶剂例如但不限于二甲基亚砷、丙二醇等等。

[0057] 5.4.2. 经口制剂

[0058] 在某些实施例中,本文提供的药物组合物配制用于经口施用。在某些实施例中,本文提供的用于经口施用的药物组合物以用于经口施用的固体、半固体或液体剂型提供。如本文使用的,经口施用还包括颊、舌和舌下施用。合适的经口剂型包括但不限于片剂、舌下或颊膜剂(即“速溶”)、咀嚼片、泡腾片、分散片、小片、胶囊、丸剂、条、糖锭、锭剂、软锭剂、经口膜剂、扁囊剂、丸剂、含药口香糖、散装粉末或颗粒、泡腾或非泡腾粉末或颗粒、口腔薄雾剂(oral mist)、溶液、乳剂、悬浮液、糯米纸囊剂(wafer)、喷洒剂(sprinkle)、酞剂和糖浆剂。除活性成分之外,药物组合物可含有一种或多种药学可接受的载体或赋形剂,包括但不限于粘结剂、填料、稀释剂、崩解剂、润湿剂、表面活性剂、润滑剂、助流剂、pH调节剂、着色剂、染料迁移抑制剂、甜味剂、调味剂、乳化剂、悬浮剂和分散剂、防腐剂、溶剂、溶解剂、非水性液体、有机酸和二氧化碳源。

[0059] 粘结剂或造粒剂对片剂赋予粘结性,以确保片剂在压制后保持完整。合适的粘结剂或造粒剂包括但不限于淀粉如玉米淀粉、马铃薯淀粉和预胶化淀粉(例如STARCH 1500);明胶;糖如蔗糖、葡萄糖、右旋糖、糖蜜和乳糖;天然和合成树胶如阿拉伯胶、海藻酸、海藻酸盐、鹿角菜提取物、潘瓦尔胶(panwar gum)、茄替胶、洋车前子壳(isabgol husk)粘液、羧甲基纤维素、甲基纤维素、聚乙烯吡咯烷酮(PVP)、硅酸镁铝(Veegum)、落叶松阿拉伯半乳聚糖、黄蓍胶粉和瓜尔胶;纤维素如乙基纤维素、乙酸纤维素、羧甲基纤维素(CMC)、羧甲基纤维素钙、羧甲基纤维素钠、甲基纤维素、羟乙基纤维素(HEC)、羟丙基纤维素(HPC)、羟丙基甲基纤维素(HPMC);微晶纤维素如AVICEL®-PH-101、AVICEL®-PH-103、AVICEL®RC-581、AVICEL®-PH-105(FMC Corp., Marcus Hook, PA);及其混合物。合适的填料包括但不限于滑石、碳酸钙、微晶纤维素、粉末状纤维素、葡萄糖结合剂、高岭土、甘露醇、硅酸、山梨糖醇、淀粉、预胶化淀粉及其混合物。

[0060] 合适的稀释剂包括但不限于磷酸二钙、硫酸钙、乳糖、山梨糖醇、蔗糖、肌醇、纤维素、高岭土、甘露醇、氯化钠、干淀粉和糖粉。当以足够数量存在时,某些稀释剂如甘露醇、乳糖、山梨糖醇、蔗糖和肌醇可对一些压制片赋予允许通过咀嚼在口中崩解的性质。这种压制片可用作咀嚼片。

[0061] 合适的崩解剂包括但不限于琼脂;膨润土;纤维素如甲基纤维素和羧甲基纤维素;木制品;天然海绵;阳离子交换树脂;海藻酸;树胶如瓜尔胶和VEEGUM®HV;柑橘渣;交联纤维素如交联羧甲基纤维素;交联聚合物如交聚维酮;交联淀粉;碳酸钙;微晶纤维素如淀粉羟乙酸钠;波拉克林钾;淀粉如玉米淀粉、马铃薯淀粉、木薯淀粉和预胶化淀粉;粘土;align;及其混合物。本文提供的药物组合物可含有按重量计约0.5至约15%或约1至约5%的崩解剂。

[0062] 合适的润滑剂包括但不限于硬脂酸钙；硬脂酸镁；矿物油；轻矿物油；甘油；山梨糖醇；甘露醇；二醇如山萼酸甘油酯和聚乙二醇 (PEG)；硬脂酸；月桂基硫酸钠；滑石；氢化植物油，包括花生油、棉籽油、葵花油、芝麻油、橄榄油、玉米油和大豆油；硬脂酸锌；油酸乙酯；月桂酸乙酯；琼脂；淀粉；石松；二氧化硅或硅胶，例如 **AEROSIL®** 200 (W.R.Grace Co., Baltimore, MD) 和 **CAB-O-SIL®** (Cabot Co. of Boston, MA)；及其混合物。本文提供的药物组合物可含有按重量计约0.1至约5%的润滑剂。

[0063] 合适的助流剂包括但不限于胶体二氧化硅、**CAB-O-SIL®** (Cabot Co. of Boston, MA) 和无石棉滑石。合适的着色剂包括但不限于任何经批准的、认证的水溶性FD&C染料和悬浮在氧化铝水合物上的水不溶性FD&C染料，以及色淀及其混合物。色淀是通过将水溶性染料吸附到重金属的水合氧化物的组合，导致不溶性形式的染料。合适的调味剂包括但不限于从植物如水果中提取的天然香料，以及产生愉快味觉的化合物的合成共混物如薄荷和水杨酸甲酯。合适的甜味剂包括但不限于蔗糖、乳糖、甘露醇、糖浆、甘油和人工甜味剂如糖精和阿斯巴甜。合适的乳化剂包括但不限于明胶、阿拉伯胶、黄蓍胶、膨润土和表面活性剂如聚氧乙烯脱水山梨糖醇单油酸酯 (**TWEEN®** 20)、聚氧乙烯脱水山梨糖醇单油酸酯80 (**TWEEN®** 80) 和三乙醇胺油酸酯。合适的悬浮剂和分散剂包括但不限于羧甲基纤维素钠、果胶、黄蓍胶、硅酸镁铝、阿拉伯胶、羧甲基纤维素钠、羟丙基甲基纤维素和聚乙烯吡咯烷酮。合适的防腐剂包括但不限于甘油、对羟基苯甲酸甲酯和对羟基苯甲酸丙酯、苯甲酸、苯甲酸钠和醇。合适的润湿剂包括但不限于单硬脂酸丙二醇酯、脱水山梨糖醇单油酸酯、二甘醇单月桂酸酯和聚氧乙烯月桂基醚。合适的溶剂包括但不限于甘油、山梨糖醇、乙醇和糖浆。乳液中利用的合适的非水性液体包括但不限于矿物油和棉籽油。合适的有机酸包括但不限于柠檬酸、富马酸、抗坏血酸和酒石酸。合适的二氧化碳源包括但不限于碳酸氢钠和碳酸钠。

[0064] 应该理解即使在同一制剂内，许多载体和赋形剂也可发挥多种功能。

[0065] 本文提供的作为用于经口施用的片剂的药物组合物可作为压制片、模印片、咀嚼锭剂、快速溶解片剂、泡腾片剂、小片、珠、经包衣的珠、多重压制片或者肠溶包衣片、糖衣片或薄膜衣片提供。肠溶衣片是用物质包衣的压制片，所述物质抵抗胃酸的作用但在肠中溶解或崩解，因此使活性成分免于胃的酸性环境。肠溶包衣包括但不限于脂肪酸、脂肪、水杨酸苯酯、蜡、虫胶、氨化虫胶和邻苯二甲酸乙酸纤维素。糖衣片是被糖包衣包裹的压制片，所述糖包衣可有益于掩盖令人讨厌的味道或气味并且使片剂免于氧化。薄膜衣片是用水溶性材料的薄层或薄膜覆盖的压制片。薄膜包衣包括但不限于羟乙基纤维素、羧甲基纤维素钠、聚乙二醇4000和邻苯二甲酸乙酸纤维素。薄膜包衣赋予与糖包衣相同的一般特性。多重压制片是由超过一个压制循环制成的压制片，包括分层片剂和压制包衣片或干包衣片。

[0066] 片剂剂型可由单独或者与本文所述的一种或多种载体或赋形剂组合的粉状、结晶或颗粒形式的活性成分制备，所述载体或赋形剂包括粘结剂、崩解剂、控制释放聚合物、润滑剂、稀释剂和/或着色剂。调味剂和甜味剂在咀嚼片和锭剂的形成中尤其有用。

[0067] 本文提供的用于经口施用的药物组合物可作为软胶囊或硬胶囊提供，所述胶囊可由明胶、甲基纤维素、淀粉或海藻酸钙制成。硬胶囊也称为干填胶囊 (DFC)，由两区段组成，一区段在另一区段上滑过，因此完全封闭活性成分。软弹性胶囊 (SEC) 是柔软的球形壳如明胶壳，其通过添加甘油、山梨糖醇或类似的多元醇而增塑。软明胶壳可含有防腐剂以防止微

生物的生长。合适的防腐剂是如本文所述的那些,包括对羟苯甲酸甲酯和对羟苯甲酸丙酯以及山梨酸。本文提供的液体、半固体和固体剂型可包封在胶囊中。合适的液体和半固体剂型包括在碳酸丙烯酯、植物油或甘油三酯中的溶液和悬浮液。胶囊也可如本领域技术人员已知的进行包被,以便修改或维持活性成分的溶解。

[0068] 本文提供的用于经口施用的药物组合物可以液体和半固体剂型提供,包括乳剂、溶液、悬浮液、酏剂和糖浆剂。乳剂是两相体系,其中一种液体以小球的形式分散在另一种液体各处,所述乳剂可为水包油或油包水的。乳剂可包括药学可接受的非水性液体或溶剂、溶解剂或乳化剂、以及防腐剂。悬浮液可包括药学可接受的悬浮剂和防腐剂。水性醇溶液可包括药学可接受的缩醛,例如低级烷基醛的二(低级烷基)缩醛,例如乙醛二乙缩醛;以及具有一个或多个羟基的水混溶性溶剂,例如丙二醇和乙醇。酏剂是澄清、增甜的和水醇溶液。糖浆剂是糖例如蔗糖的浓缩水溶液,并且还可含有防腐剂。对于液体剂型,例如,聚乙二醇中的溶液可用足够数量的药学可接受的液体载体例如水稀释,以方便地测量用于施用。

[0069] 其它有用的液体和半固体剂型包括但不限于含有本文提供的活性成分和二烷基化的单亚烷基二醇或聚亚烷基二醇的那些,所述单亚烷基二醇或聚亚烷基二醇包括1,2-二甲氧基甲烷、二甘醇二甲醚、三甘醇二甲醚、四甘醇二甲醚、聚乙二醇-350-二甲醚、聚乙二醇-550-二甲醚、聚乙二醇-750-二甲醚,其中350、550和750是指聚乙二醇的近似平均分子量。这些制剂还可包含一种或多种抗氧化剂,例如丁基羟基甲苯(BHT)、丁基羟基茴香醚(BHA)、没食子酸丙酯、维生素E、乙二胺四乙酸(EDTA)、氢醌、羟基香豆素、乙醇胺、卵磷脂、脑磷脂、抗坏血酸、苹果酸、山梨糖醇、磷酸、亚硫酸氢盐、偏亚硫酸氢钠、硫代二丙酸及其酯和二硫代氨基甲酸酯。

[0070] 本文提供的用于经口施用的药物组合物还可以脂质体、胶束、微球体或纳米系统的形式提供。

[0071] 本文提供的用于经口施用的药物组合物可作为非泡腾或泡腾片剂或颗粒和粉末提供,以重构成液体剂型。用于非泡腾颗粒或粉末中的药学可接受的载体和赋形剂可包括稀释剂、甜味剂和润湿剂。用于泡腾颗粒或粉末中的药学可接受的载体和赋形剂可包括有机酸和二氧化碳源。

[0072] 在某些实施例中,药物组合物配制为固体经口剂型。在某些实施例中,药物组合物配制为液体经口剂型。在某些实施例中,单位剂型在药学可接受的液体或半固体溶剂中混合后作为悬浮液提供,所述药学可接受的液体或半固体溶剂包括但不限于水、牛奶、碳酸饮料、果汁、水果果汁、水果宾治(fruit punch)、苹果酱、酸奶、布丁、冰淇淋、婴儿食品、婴儿配方食品或者基于大豆或谷物的产品。

[0073] 在某些实施例中,本文提供了药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其药学可接受的盐和一种或多种另外的药学可接受的赋形剂。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。在另一个实施例中,一种或多种赋形剂选自聚右旋糖、甘露醇、泊洛沙姆、聚乙二醇、羟乙基纤维素、交聚维酮、人工调味料和硬脂酸镁。在某些实施例中,人工调味料是人工香草调味料。

[0074] 本文另外提供了药物组合物,所述药物组合物包含约按重量计25%的3-[5-(2-

氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐;按重量计约1%的胶体二氧化硅;和一种或多种另外的药学可接受的赋形剂。在某些实施例中,本文提供的药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐和选自下述的一种或多种赋形剂:聚右旋糖、泊洛沙姆(例如泊洛沙姆407)、聚乙二醇(例如聚乙二醇3350)、甘露醇、羟乙基纤维素、人工香草调味料、交聚维酮、胶体二氧化硅和硬脂酸镁(例如具有植物起源)。在某些实施例中,本文提供的药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐,并且可存在选自下述的一种或多种赋形剂:悬浮剂、也可提供味道掩蔽的粘结剂、表面活性剂、崩解剂和其它赋形剂。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。在另一个实施例中,3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐以例如按重量计约25%的量存在)。在另一个实施例中,一种或多种赋形剂选自聚右旋糖、甘露醇、泊洛沙姆、聚乙二醇、羟乙基纤维素、交聚维酮、人工香草香料和硬脂酸镁。在另一个实施例中,一种或多种赋形剂(及其在总制剂重量中的比例)选自悬浮剂如以按重量计约26%的 **Litesse®Ultra**[精制聚右旋糖],粘结剂如以按重量计约26%的甘露醇,表面活性剂如以按重量计约10.0%的聚乙二醇3350和以按重量计约4%的 **Lutrol®micro F127**[泊洛沙姆407粉末],崩解剂如以按重量计约5%的交聚维酮,以及各自按重量计小于约2%的其他赋形剂如以按重量计约1%的 **cab-o-sil**、羟乙基纤维素、硬脂酸镁[非牛的]和以按重量计约1%的胶体二氧化硅。

[0075] 本文还提供了药物组合物,所述药物组合物包含按重量计约25%的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、按重量计约26%的聚右旋糖、按重量计约26%的甘露醇、按重量计约3%的泊洛沙姆、按重量计约10%的聚乙二醇、按重量计约2%的羟乙基纤维素、按重量计约5%的交聚维酮、按重量计约1%的人工香草香料、按重量计约1%的胶体二氧化硅和按重量计约1%的硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0076] 本文还提供了药物组合物,所述药物组合物包含在约120mg至约1005mg范围内的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、在约133mg至约1030mg范围内的聚右旋糖、在约137mg至约901mg范围内的甘露醇、在约19mg至约147mg范围内的泊洛沙姆、在约52mg至约402mg范围内的聚乙二醇、在约7mg至约59mg范围内的羟乙基纤维素、在约26mg至约201mg范围内的交聚维酮、在约3mg至约29mg范围内的人工香草香料、在约5mg至约39mg范围内的胶体二氧化硅、以及在约5mg至约39mg范围内的硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0077] 本文还提供了药物组合物,所述药物组合物包含约130mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约133mg聚右旋糖、约137mg甘露醇、约19mg泊洛沙姆、约52mg聚乙二醇、约7mg羟乙基纤维素、约26mg交聚维酮、约3mg人工香草香料、约5mg胶体二氧化硅和约5mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一

个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0078] 本文还提供了药物组合物,所述药物组合物包含约205mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约210mg聚右旋糖、约216mg甘露醇、约30mg泊洛沙姆、约82mg聚乙二醇、约12mg羟乙基纤维素、约41mg交聚维酮、约6mg人工香草香料、约8mg胶体二氧化硅和约8mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0079] 本文还提供了药物组合物,所述药物组合物包含约330mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约338mg聚右旋糖、约348mg甘露醇、约48mg泊洛沙姆、约132mg聚乙二醇、约19mg羟乙基纤维素、约66mg交聚维酮、约9mg人工香草香料、约13mg胶体二氧化硅和约13mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0080] 本文还提供了药物组合物,所述药物组合物包含约405mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约415mg聚右旋糖、约427mg甘露醇、约59mg泊洛沙姆、约162mg聚乙二醇、约24mg羟乙基纤维素、约81mg交聚维酮、约12mg人工香草香料、约16mg胶体二氧化硅和约16mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0081] 本文还提供了药物组合物,所述药物组合物包含约505mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约518mg聚右旋糖、约453mg甘露醇、约74mg泊洛沙姆、约202mg聚乙二醇、约30mg羟乙基纤维素、约101mg交聚维酮、约15mg人工香草香料、约20mg胶体二氧化硅和约20mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0082] 本文还提供了药物组合物,所述药物组合物包含约1005mg 3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]-苯甲酸或其药学可接受的盐、约1030mg聚右旋糖、约901mg甘露醇、约147mg泊洛沙姆、约402mg聚乙二醇、约59mg羟乙基纤维素、约201mg交聚维酮、约29mg人工香草香料、约39mg胶体二氧化硅和约39mg硬脂酸镁。在一个实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在一个实施例中,药物组合物配制为颗粒。

[0083] 在某些实施例中,单位剂型包含约35mg至约5,600mg化合物1、约35mg至约2800mg化合物1、约35mg至约1,400mg化合物1、约125mg至约1,000mg化合物1、约250mg至约1,000mg化合物1、约325mg至约1,000mg化合物1、或约500mg至约1,000mg化合物1。

[0084] 在某些实施例中,单位剂型包含约35mg、约50mg、约70mg、约100mg、约125mg、约140mg、约175mg、约200mg、约250mg、约280mg、约325mg、约350mg、约400mg、约450mg、约500mg、约560mg、约700mg、约750mg、约1,000mg、约1,400mg、约2800mg或约5600mg化合物1。

[0085] 在一个特定实施例中,单位剂型包含约125mg、约250mg或约1,000mg化合物1。

[0086] 在一个更特定的实施例中,单位剂型包含125mg、250mg或1,000mg化合物1。

[0087] 在某些实施例中,药物组合物配制为粉末。在一个实施例中,药物组合物配制为微粒化粉末。在一个实施例中,药物组合物配制为纳米颗粒。在另一个实施例中,本文提供的药物组合物配制为颗粒。在某些实施例中,本文提供的药物组合物包装在小包或小袋中。在某些实施例中,本文提供的药物组合物包装在热封层压铝小包或小袋中。在某些实施例中,本文提供的药物组合物包装在儿童防护小包或小袋中。在某些实施例中,本文提供的药物组合物包装在小包或小袋中,所述小包或小袋包含聚对苯二甲酸乙二醇酯、聚乙烯、铝箔、粘合剂和密封膜的层。在某些实施例中,药物组合物可在瓶包括但不限于高密度聚乙烯(HDPE)瓶中提供。

[0088] 在某些实施例中,本文提供的药物组合物配制为用于重构的颗粒。在某些实施例中,本文提供的药物组合物配制为用于重构为经口悬浮液的颗粒。

[0089] 在某些实施例中,本文提供的药物组合物在施用之前通过与药学可接受的液体或半固体溶解剂混合为悬浮液进行重构,所述药学可接受的液体或半固体溶解剂包括但不限于水、牛奶、碳酸饮料、果汁、水果果汁、水果宾治、苹果酱、酸奶、布丁、冰淇淋、婴儿食品、婴儿配方食品或者基于大豆或谷物的产品。

[0090] 在某些实施例中,本文提供的药物组合物在施用之前通过与水混合为悬浮液进行重构。在一个实施例中,化合物1的125mg单位剂量制剂的重构通过在含有化合物1的瓶中直接添加至少约5mL的水来进行,以达到在悬浮液的总体积中至少约25mg/mL的标称浓度。在另一个实施例中,250mg单位剂量制剂化合物1的重构通过在含有化合物1的瓶中直接添加至少约10mL的水来进行,以达到在悬浮液的总体积中至少约25mg/mL的标称浓度。在另一个实施例中,500mg单位剂量制剂化合物1的重构通过在含有化合物1的瓶中直接添加至少约20mL的水来进行,以达到在悬浮液的总体积中至少约25mg/mL的标称浓度。在另一个实施例中,1000mg单位剂量制剂化合物1的重构通过在含有化合物1的瓶中直接添加至少约40mL的水来进行,以达到在悬浮液的总体积中至少约25mg/mL的标称浓度。

[0091] 在其它实施例中,含有本文提供的药物组合物的单位剂型仅在剂量制备时打开。将每个单位剂型的全部内容物与液体或半固体溶解剂混合为悬浮液,其中液体为至少30mL(1盎司)或半固体为至少3汤匙。制备的剂量应该在施用前充分混合。基于患者偏好,可增加液体或半固体溶解剂的量。

[0092] 在某些实施例中,本文提供的药物组合物包含作为游离酸或药学可接受的盐的化合物1,其中药学可接受的盐为镁盐、钾盐、钠盐、氨丁三醇盐、L-赖氨酸盐、L-精氨酸盐、N-甲基葡糖胺盐或L-组氨酸盐。

[0093] 5.4.3. 肠胃外制剂和施用

[0094] 本文提供的包含化合物1的药物组合物可通过注射、输注或植入进行肠胃外施用,用于局部或全身施用。如本文使用的肠胃外施用包括但不限于静脉内、动脉内、腹膜内、鞘内、心室内、尿道内、胸骨内、颅内、肌内、滑膜内、膀胱内和皮下施用。

[0095] 本文提供的用于肠胃外施用的药物组合物可配制为适合于肠胃外施用的任何剂型,包括但不限于溶液、悬浮液、乳剂、胶束、脂质体、微球体、纳米系统和适合于在注射前在液体中的溶液或悬浮液的固体形式。这样的剂型可根据药学科学领域技术人员已知的常规方法制备(参见,Remington:The Science and Practice of Pharmacy,同上)。

[0096] 预期用于肠胃外施用的药物组合物可包括一种或多种药学可接受的载体和赋形剂,包括但不限于水性媒介物、水混溶性媒介物、非水性媒介物、对抗微生物生长的抗微生物剂或防腐剂、稳定剂、溶解度增强剂、等渗剂、缓冲剂、抗氧化剂、局部麻醉剂、悬浮剂和分散剂、润湿剂或乳化剂、络合剂、多价螯合剂或螯合剂、冷冻保护剂、冻干保护剂、增稠剂、pH调节剂和惰性气体。

[0097] 合适的水性媒介物包括但不限于水、盐水、生理盐水或磷酸盐缓冲盐水(PBS)、氯化钠注射液、林格氏注射液、等渗右旋糖注射液、无菌水注射液、右旋糖和乳酸林格氏注射液。合适的非水性媒介物包括但不限于植物起源的不挥发性油、蓖麻油、玉米油、棉籽油、橄榄油、花生油、薄荷油、红花油、芝麻油、大豆油、氢化植物油、氢化大豆油和椰子油的中链甘油三酯、以及棕榈籽油。合适的水混溶性媒介物包括但不限于乙醇、1,3-丁二醇、液体聚乙二醇(例如聚乙二醇300和聚乙二醇400)、丙二醇、甘油、N-甲基-2-吡咯烷酮、N,N-二甲基乙酰胺和二甲基亚砷。

[0098] 合适的抗微生物剂或防腐剂包括但不限于苯酚、甲酚、汞制剂、苯甲醇、氯丁醇、对羟基苯甲酸甲酯和对羟基苯甲酸丙酯、硫柳汞、苯扎氯铵(例如苄索氯铵)、对羟基苯甲酸甲酯和对羟基苯甲酸丙酯以及山梨酸。合适的等渗剂包括但不限于氯化钠、甘油和右旋糖。合适的缓冲剂包括但不限于磷酸盐和柠檬酸盐。合适的抗氧化剂是如本文所述的那些,包括亚硫酸氢盐和偏亚硫酸氢钠。合适的局部麻醉剂包括但不限于盐酸普鲁卡因。合适的悬浮剂和分散剂是如本文所述的那些,包括羧甲基纤维素钠、羟丙基甲基纤维素和聚乙烯吡咯烷酮。合适的乳化剂是本文所述的那些,包括聚氧乙烯脱水山梨糖醇单月桂酸酯、聚氧乙烯脱水山梨糖醇单油酸酯80和三乙醇胺油酸酯。合适的多价螯合剂或螯合剂包括但不限于EDTA。合适的pH调节剂包括但不限于氢氧化钠、盐酸、柠檬酸和乳酸。合适的络合剂包括但不限于环糊精,包括 α -环糊精、 β -环糊精、羟丙基- β -环糊精、磺基丁基醚- β -环糊精和磺基丁基醚7- β -环糊精(CAPTISOL[®], CyDex, Lenexa, KS)。

[0099] 当本文提供的药物组合物配制用于多剂量施用,多剂量肠胃外制剂必须含有以抑菌或抑真菌浓度的抗微生物剂。所有肠胃外制剂都必须是无菌的,如本领域已知和实践的。

[0100] 在一个实施例中,用于肠胃外施用的药物组合物作为即用型无菌溶液提供。在另一个实施例中,药物组合物作为无菌干燥可溶性产品提供,包括冻干粉末和皮下注射片剂,以在使用前用媒介物重构。在又一个实施例中,药物组合物作为即用型无菌悬浮液提供。在又一个实施例中,药物组合物作为无菌干燥不溶性产品提供,以在使用前用媒介物重构。在另外一个实施例中,药物组合物作为即用型无菌乳剂提供。

[0101] 本文提供的用于肠胃外施用的药物组合物可配制为立即释放剂型或修饰释放剂型,包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放和按程序工作释放形式。

[0102] 本文提供的用于肠胃外施用的药物组合物可配制为悬浮液、固体、半固体或触变性液体,用于作为植入储库施用。在一个实施例中,本文提供的药物组合物分散在固体内部基质中,所述固体内部基质由外部聚合物膜包围,所述外部聚合物膜在体内不溶解,但允许药物组合物中的活性成分渗透或离子扩散。

[0103] 合适的内部基质包括但不限于聚甲基丙烯酸甲酯、聚甲基丙烯酸丁酯、增塑或未增塑聚氯乙烯、增塑尼龙、增塑聚对苯二甲酸乙二醇酯、天然橡胶、聚异戊二烯、聚异丁烯、

聚丁二烯、聚乙烯、乙烯-乙酸乙烯酯共聚物、硅橡胶、聚二甲基硅氧烷、硅酮碳酸酯共聚物、亲水性聚合物如丙烯酸和甲基丙烯酸酯的水凝胶、胶原、交联聚乙烯醇和交联的部分水解的聚乙酸乙烯酯。

[0104] 合适的外部聚合物膜包括但不限于聚乙烯、聚丙烯、乙烯/丙烯共聚物、乙烯/丙烯酸乙酯共聚物、乙烯/乙酸乙烯酯共聚物、硅橡胶、聚二甲基硅氧烷、氯丁橡胶、氯化聚乙烯、聚氯乙烯、具有乙酸乙烯酯、偏二氯乙烯、乙烯和丙烯的氯乙烯共聚物、离聚物聚对苯二甲酸乙二醇酯、丁基橡胶表氯醇橡胶、乙烯/乙烯醇共聚物、乙烯/乙酸乙烯酯/乙烯醇三元共聚物和乙烯/乙烯氧基乙醇共聚物。

[0105] 5.4.4. 粒度

[0106] 在某些实施例中，本文提供的药物组合物包含具有增强的溶解度的化合物1的微粒化形式。在某些实施例中，本文提供的药物组合物包含具有增强的溶解度和/或溶解速率的化合物1的纳米颗粒形式。

[0107] 在具体实施例中，本文提供的药物组合物包含化合物1的微粒化形式，其中化合物1的>90%颗粒具有增强的溶解度、具有在约1-10微米之间的直径(D₉₀值)。在某些实施例中，本文提供的药物组合物包含具有增强的溶解度，具有约10微米、约9微米、约8微米、约7微米、约6微米、约5微米、约4微米、约3微米、约2微米或约1微米的D₉₀值的化合物1的微粒化形式。在某些实施例中，本文提供的药物组合物包含具有增强的溶解度和/或溶解速率、具有约1-5微米的D₉₀值的化合物1的微粒化形式。在某些实施例中，本文提供的药物组合物包含具有增强的溶解度和/或溶解速率，具有约5微米、约4微米、约3微米、约2微米或约1微米的D₉₀值的化合物1的微粒化形式。在某些实施例中，本文提供的药物组合物包含具有增强的溶解度的化合物1的纳米颗粒形式。在具体实施例中，本文提供的药物组合物包含化合物1的纳米颗粒形式，其中化合物1的>90%颗粒具有约0.1微米、约0.09微米、约0.08微米、约0.07微米、约0.06微米、约0.05微米、约0.04微米、约0.03微米、约0.02微米或约0.01微米的D₉₀值。

[0108] 本文提供了具有约2μm至约12μm的体积加权平均直径D[4,3]的化合物1的微粒化形式。本文还提供了具有约1μm至约3μm的表面加权平均直径D[3,2]的化合物1的微粒化形式。本文还提供了D₉₀粒度在约5μm至约26μm范围内、D₅₀粒度在约1μm至约6μm范围内、或D₁₀粒度在约0.1μm至约1.5μm范围内的化合物1形式。

[0109] 5.4.5. 试剂盒

[0110] 本文提供的药物组合物可使用本领域技术人员众所周知的包装材料作为制造物品提供。药物包装材料的例子包括但不限于泡罩包装、瓶、小包、小袋、管、吸入器、泵、袋、小瓶、容器、注射器、滴管、以及适合于所选择的制剂以及预期施用模式和治疗模式的任何包装材料。

[0111] 本文提供了试剂盒，当由医学从业者使用时，所述试剂盒可简化适当量的活性成分对受试者的施用。在某些实施例中，本文提供的试剂盒包括容器和本文提供的药物制剂的剂型及其使用说明书。在某些实施例中，与试剂盒一起包括的说明书提供了关于化合物1施用的剂量和/或给药方案的指导。

[0112] 在某些实施例中，试剂盒包括容器，所述容器包含本文提供的药物制剂的剂型，在容器中包含本文描述的一种或多种其它治疗剂。在某些实施例中，药物制剂作为用于经口

悬浮液的白色至灰白色粉末提供。在某些实施例中,药物制剂包含基质和/或悬浮剂、表面活性剂和/或赋形剂。在某些实施例中,药物制剂作为用于经口悬浮液的颗粒提供。在某些实施例中,用于经口悬浮液的药物制剂以包含125、250或1000mg活性原料药的剂量强度包装在铝箔、儿童防护小袋(小包)中。在某些实施例中,试剂盒包含小包或小袋,所述小包或小袋包含用于经口悬浮液的药物制剂的一种或多种剂量强度(125、250或1000mg或匹配安慰剂)。

[0113] 本文提供的试剂盒还可包括用于施用活性成分的装置。这种装置的例子包括但不限于注射器、无针注射器、滴注袋、贴剂、滴管和吸入器。

[0114] 本文提供的试剂盒还可包括可用于施用活性成分的药学可接受的媒介物。例如,如果活性成分以必须重构用于肠胃外施用的固体形式提供,则该试剂盒可包含合适媒介物的密封容器,活性成分可溶解于所述合适媒介物中以形成适合于肠胃外施用的无微粒的无菌溶液,或可重构为用于经口施用的悬浮液。药学可接受的媒介物的例子包括但不限于:水性媒介物,包括但不限于注射用水USP、氯化钠注射液、林格氏注射液、右旋糖注射液、右旋糖和氯化钠注射液以及乳酸林格氏注射液;水混溶性媒介物,包括但不限于乙醇、聚乙二醇和聚丙二醇;和非水性媒介物,包括但不限于玉米油、棉籽油、花生油、芝麻油、油酸乙酯、肉豆蔻酸异丙酯和苯甲酸苄酯。

[0115] 5.5. 使用方法

[0116] 本文提供了用于治疗、预防、改善或管理无义突变介导的癫痫疾病的方法,所述方法包括将1,2,4-噁二唑苯甲酸施用于患有无义突变介导的癫痫疾病的患者。具体地,本文提供了用于治疗、预防、改善或管理无义突变介导的癫痫疾病的方法,所述方法包括将有效量的1,2,4-噁二唑苯甲酸施用于患有无义突变介导的癫痫疾病的患者。本文另外提供了治疗、预防、改善或管理与无义突变或提前终止密码子相关的癫痫疾病的方法,所述方法包括将有效量的1,2,4-噁二唑苯甲酸施用于患有与无义突变或提前终止密码子相关的癫痫疾病的患者。

[0117] 本文还提供了通过调节提前翻译终止来治疗、预防、改善或管理无义突变介导的癫痫疾病的方法,所述方法包括向患有能够通过调节提前翻译终止改善的一类无义突变介导的癫痫疾病的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。

[0118] 在某些实施例中,向受试者施用有效量的1,2,4-噁二唑苯甲酸在患有无义突变介导的癫痫疾病的患者中导致下述效应中的一种、两种或更多种:(1) 预防无义突变介导的癫痫疾病的发作、发展和/或进展,(2) 预防与无义突变介导的癫痫疾病相关的一种或多种症状的发作、发展和/或进展,(3) 减少无义突变介导的癫痫疾病的持续时间和/或严重性,(4) 减少与无义突变介导的癫痫疾病相关的症状的数目,(5) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的持续时间,(6) 减少与无义突变介导的癫痫疾病相关的一种或多种症状的严重性,和(7) 改善所述受试者的生活质量。

[0119] 在某些实施例中,如本文下文在第6节中所述,向受试者施用有效量的1,2,4-噁二唑苯甲酸在患有无义突变介导的癫痫疾病的患者中导致下述效应中的一种、两种或更多种:(1) 减少从基线的癫痫发作的频率,所述癫痫发作例如惊厥性癫痫发作、跌落癫痫发作、

运动性癫痫发作、强直阵挛性癫痫发作、半惊厥性癫痫发作、跌落发作、强直性癫痫发作、局灶性运动性癫痫发作和肌阵挛癫痫发作；(2)减少小癫痫发作类型的频率，所述小癫痫发作类型例如肌阵挛性癫痫发作和瞪眼性(失神性或复杂部分性)癫痫发作；(3)改善认知、运动、行为功能和/或生活质量；(4)减少癫痫持续状态发作的次数，所述癫痫持续状态定义为持续超过10分钟的惊厥；(5)减少救援用药的使用次数；和(6)减少急诊室就诊/住院次数。

[0120] 根据本文所述方法待治疗的无义突变介导的癫痫疾病包括但不限于Dravet综合征也称为婴儿严重肌阵挛性癫痫(SMEI)、CDKL5、发热性癫痫发作(FS)、全面性癫痫伴热性惊厥附加症(GEFS+)、家族性颞叶癫痫、难治性儿童期癫痫、良性家族性新生儿-婴儿癫痫发作(BFNIS)、良性家族性新生儿癫痫发作(BFNIS)、青少年肌阵挛性癫痫(JME)、儿童失神性癫痫(CAE)、常染色体显性夜间额叶癫痫(ADNFLE)、隐源性全身性癫痫(CGE)、隐源性局灶性癫痫(CFE)、家族性局灶性癫痫、具有不同病灶的家族性局灶性癫痫(FFEVF)、家族性颞叶内侧癫痫(FMTLE)、常染色体显性颞叶外侧癫痫(ADLTE)、肌阵挛站立不能性癫痫(MAE)、婴儿严重特发性全身性癫痫(SIGEI)、婴儿痉挛(IS)和早发性癫痫性脑病(EOEE)。在某些实施例中，根据本文所述的方法待治疗的患者具有耐药性癫痫。

[0121] 无义突变介导的癫痫疾病的症状包括特征在于意识不清、惊厥和肌肉强直的惊厥性癫痫发作、跌落癫痫发作、全身性单侧(一侧)阵挛性癫痫发作或全身性强直阵挛性(癫痫大发作)癫痫发作；特征在于意识短暂丧失的失神性癫痫发作；特征在于通常在身体两侧上的偶发性抽搐的全身性肌阵挛性癫痫发作；特征在于同时涉及身体两侧的重复性、有节奏的抽搐的全身性阵挛性癫痫发作；特征在于肌肉僵硬的全身性强直性癫痫发作；特征在于突然和泛发的肌张力丧失(特别是在手臂和腿部中)的全身性无张力性癫痫发作，这经常导致跌倒；特征在于意识、抽搐、肌肉强直、痉挛、头部转向的简单运动性部分性癫痫发作；特征在于意识和影响视觉、听觉、嗅觉、味觉或触觉的异常感觉的简单感觉性部分性癫痫发作；特征在于意识和记忆或情绪障碍的简单心理性部分性癫痫发作；特征在于意识和自动作用的损害，例如咂唇、咀嚼、烦躁、行走和其它重复性、非自愿但协调的运动的复杂部分性癫痫发作(局部认知障碍性癫痫发作)；特征在于意识保留，然后发展为意识丧失和惊厥的部分性癫痫发作伴继发性全身发作；癫痫猝死(SUDEP)；和夜间癫痫发作。

[0122] 在一些实施例中，根据本文所述方法治疗的无义突变介导的癫痫疾病来源于一种或多种基因的一个或两个等位基因中的无义突变，所述一种或多种基因包括但不限于SCN1A、CDKL5、SCN2A、GABRG2、DEPDC5和NAPB。

[0123] 在一些实施例中，根据本文所述方法治疗的无义突变介导的癫痫疾病来源于SCN1A基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中，SCN1A基因的一个或两个等位基因中的一个或多个无义突变是W192X、R222X、R568X、R701X、R854X、K1017X、W1261X、R1213X、W1408X、W952X、W1284X、S219fsX275、K1100fsX1107、L1670fsX1107和/或S1846fsX1856。在某些实施例中，来源于SCN1A的一个或两个等位基因中的无义突变，并且根据本发明的方法治疗的无义突变介导的癫痫疾病是Dravet综合征，也称为婴儿严重肌阵挛性癫痫(SMEI)。在一些实施例中，根据本发明的方法治疗患有Dravet综合征的患者，所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的W192X无义突变。在一些实施例中，根据本发明的方法治疗患有Dravet综合征的患者，所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的R222X无义突变。在一些实施例中，根据本发明的方法治疗

患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的R568X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的R701X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的R854X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的L1017X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的W1261X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的R1213X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的W1408X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的W952X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的W1284X无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的S219fsX275无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的K1100fsX1107无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的L1670fsX1107无义突变。在一些实施例中,根据本发明的方法治疗患有Dravet综合征的患者,所述Dravet综合征来源于SCN1A基因的一个或两个等位基因中的S1846fsX1856无义突变。

[0124] 在一些实施例中,根据本文所述方法治疗的无义突变介导的癫痫疾病来源于CDKL5基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中,CDKL5基因的一个或两个等位基因中的一个或多个无义突变是R59X、R550X、Q834X、R79X、Q118X、R134X、L142X、Q347X、R559X和/或R970X。在某些实施例中,来源于CDKL5的一个或两个等位基因中的无义突变,并且根据本发明的方法治疗的无义突变介导的癫痫疾病是CDKL5。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R59X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R550X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的Q834X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R79X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的Q118X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R134X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的L142X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的Q347X无义突变的CDKL5

是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R559X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,来源于CDKL5基因的一个或两个等位基因中的R970X无义突变的CDKL5是根据本发明的方法治疗的无义突变介导的癫痫疾病。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R59X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R550X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的Q834X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R79X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的Q118X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R134X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的L142X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的Q347X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R559X无义突变。在一些实施例中,根据本发明的方法治疗患有CDKL5的患者,所述CDKL5来源于CDKL5基因的一个或两个等位基因中的R970X无义突变。

[0125] 在一些实施例中,根据本文所述方法治疗的无义突变介导的癫痫疾病来源于SCN2A基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中,SCN2A基因的一个或两个等位基因中的一个或多个无义突变是R102X。在某些实施例中,来源于SCN2A的一个或两个等位基因中的无义突变,并且根据本发明的方法治疗的无义突变介导的癫痫疾病是难治性儿童期癫痫。在一些实施例中,根据本发明的方法治疗患有难治性儿童期癫痫的患者,所述难治性儿童期癫痫来源于SCN2A基因的一个或两个等位基因中的R102X无义突变。

[0126] 在一些实施例中,根据本文所述方法治疗的无义突变介导的癫痫疾病来源于GABRG2基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中,GABRG2基因的一个或两个等位基因中的一个或多个无义突变是R136X、W429X、Q40X、Q390X、Q1X、Q351X、W390X和/或Y444Mfs51X。在某些实施例中,来源于GABRG2的一个或两个等位基因中的无义突变,并且根据本发明的方法治疗的无义突变介导的癫痫疾病是全面性癫痫伴热性惊厥附加症(GEFS+)、Dravet综合征或发热性癫痫发作(FS)。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的R136X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的W429X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的Q40X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的Q390X无义突变。在一些实施例中,根据本发明

的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的Q1X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的Q351X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的W390X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于GABRG2基因的一个或两个等位基因中的Y444Mfs51X无义突变。

[0127] 在一些实施例中,根据本文所述方法治疗的无义突变介导的癫痫疾病来源于DEPDC5基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中,DEPDC5基因的一个或两个等位基因中的一个或多个无义突变是R555X和/或Y306X。在某些实施例中,来源于DEPDC5的一个或两个等位基因中的无义突变,并且根据本发明的方法治疗的无义突变介导的癫痫疾病为家族性局灶性癫痫、具有不同病灶的家族性局灶性癫痫 (FFEVF)、家族性颞叶内侧癫痫 (FMTLE)、或常染色体显性颞叶外侧癫痫 (ADLTE)。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于DEPDC5基因的一个或两个等位基因中的R555X无义突变。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于DEPDC5基因的一个或两个等位基因中的Y306X无义突变。

[0128] 在一些实施例中,根据本文所述方法治疗的无义突变介导的癫痫疾病来源于NAPB基因的一个或两个等位基因中的一个或多个无义突变。在某些实施例中,NAPB基因的一个或两个等位基因中的一个或多个无义突变是S160X。在某些实施例中,来源于NAPB的一个或两个等位基因中的无义突变,并且根据本发明的方法治疗的无义突变介导的癫痫疾病是早发性癫痫性脑病 (EOEE)。在一些实施例中,根据本发明的方法治疗患有无义突变介导的癫痫疾病的患者,所述癫痫疾病来源于NAPB基因的一个或两个等位基因中的S160X无义突变。

[0129] 本文还提供了通过调节提前翻译终止用于治疗、预防、改善或管理无义突变介导的癫痫疾病症状的方法,所述方法包括向具有能够通过调节提前翻译终止改善的无义突变介导的癫痫疾病症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。

[0130] 本文还提供了用于治疗、预防、改善或管理CDKL5相关癫痫的方法,所述方法包括向患有CDKL5相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理CDKL5相关癫痫的症状的方法,所述方法包括向具有CDKL5相关癫痫的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的某些突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的R59X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的R550X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的Q834X无义突变。在某些实施例中,CDKL5相关癫痫来源于

CDKL5基因的一个或两个等位基因上的R79X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的Q118X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的R134X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的L142X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的Q347X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的R559X无义突变。在某些实施例中,CDKL5相关癫痫来源于CDKL5基因的一个或两个等位基因上的R970X无义突变。

[0131] 本文还提供了用于治疗、预防、改善或管理SCN1A相关癫痫的方法,所述方法包括向患有SCN1A相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理SCN1A相关癫痫的症状的方法,所述方法包括向具有SCN1A相关癫痫的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,SCN1A相关癫痫来源于SCN1A基因的一个或两个等位基因上的某些突变。

[0132] 本文还提供了用于治疗、预防、改善或管理SCN1A相关癫痫如Dravet综合征的方法。本文还提供了用于治疗、预防、改善或管理Dravet综合征的方法,所述方法包括向患有Dravet综合征的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理Dravet综合征的症状的方法,所述方法包括向具有Dravet综合征的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,Dravet综合征来源于SCN1A基因的一个或两个等位基因上的某些突变。在某些实施例中,Dravet综合征来源于SCN1A基因的一个或两个等位基因上的W192X无义突变。

[0133] 本文还提供了用于治疗、预防、改善或管理SCN2A相关癫痫的方法,所述方法包括向患有SCN2A相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理SCN2A相关癫痫的症状的方法,所述方法包括向具有SCN2A相关癫痫的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,SCN2A相关癫痫来源于SCN2A基因的一个或两个等位基因上的某些突变。在某些实施例中,SCN2A相关癫痫来源于SCN2A基因的一个或两个等位基因上的R102X无义突变。

[0134] 本文还提供了用于治疗、预防、改善或管理GABRG2相关癫痫的方法,所述方法包括向患有GABRG2相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理GABRG2相关癫痫的症状的方法,所述方法包括向具有GABRG2相关癫痫的症状的患者施用有效量的药物组合物,所述药

物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的某些突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的R136X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的W429X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的Q40X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的Q390X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的Q1X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的Q351X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的W390X无义突变。在某些实施例中,GABRG2相关癫痫来源于GABRG2基因的一个或两个等位基因上的Y444Mfs51X无义突变。

[0135] 本文还提供了用于治疗、预防、改善或管理DEPDC5相关癫痫的方法,所述方法包括向患有DEPDC5相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理DEPDC5相关癫痫的症状的方法,所述方法包括向具有DEPDC5相关癫痫的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,DEPDC5相关癫痫来源于DEPDC5基因的一个或两个等位基因上的某些突变。在某些实施例中,DEPDC5相关癫痫来源于DEPDC5基因的一个或两个等位基因上的R555X无义突变。在某些实施例中,DEPDC5相关癫痫来源于DEPDC5基因的一个或两个等位基因上的Y306X无义突变。

[0136] 本文还提供了用于治疗、预防、改善或管理NAPB相关癫痫的方法,所述方法包括向患有NAPB相关癫痫的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。本文还提供了用于治疗、预防、改善或管理NAPB相关癫痫的症状的方法,所述方法包括向具有NAPB相关癫痫的症状的患者施用有效量的药物组合物,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的。在某些实施例中,NAPB相关癫痫来源于NAPB基因的一个或两个等位基因上的某些突变。在某些实施例中,NAPB相关癫痫来源于NAPB基因的一个或两个等位基因上的S160X无义突变。

[0137] 本文还提供了在患有无义突变介导的癫痫疾病或者具有无义突变介导的癫痫疾病的一种或多种症状的受试者中筛选无义突变的存在的方法,并且当鉴定无义突变时,有效量的药物组合物可施用于患者以预防疾病或其症状的发作、复发、扩散或恶化,所述药物组合物包含有效量的本文提供的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐。在受试者中筛选无义突变的存在的方法包括从患者获得的样品的全外显子组测序。在某些实施例中,通过筛选已确定受试者具有无义突变。在某些实施例中,通过筛选已确定患者具有哪个提前终止密码子(即UAA、UGA或UAG)。

[0138] 在某些实施例中,根据本文提供的方法治疗的患者如本文下文在第6节处所述。

[0139] 在某些实施例中,根据本文提供的方法治疗的患者是两岁。在某些实施例中,根据本文提供的方法治疗的患者超过两岁。在某些实施例中,根据本文提供的方法治疗的患者小于十二岁。在某些实施例中,根据本文提供的方法治疗的患者是十二岁。在某些实施例中,根据本文提供的方法治疗的患者是二十二岁。

[0140] 在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于SCN1A缺陷(特别是Dravet综合征)的无义突变。在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于CDKL5缺陷的无义突变。在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于SCN2A缺陷的无义突变。在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于GABRG2缺陷的无义突变。在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于DEPDC5缺陷的无义突变。在某些实施例中,根据本文提供的方法治疗的患者已诊断为在一个或多个等位基因中具有关于NAPB缺陷的无义突变。

[0141] 在某些实施例中,根据本文提供的方法治疗的患者具有耐药性癫痫。在某些实施例中,根据本文提供的方法治疗的患者抗拒用或多种抗癫痫药的治疗。在某些实施例中,根据本文提供的方法治疗的患者抗拒用下述抗癫痫药物中的一种或多种的治疗:丙戊酸、双丙戊酸钠、苯妥英、扑米酮、苯巴比妥、卡马西平、地西洋、氯硝西洋、乙琥胺、艾司利卡西平、非氨酯、吡仑帕奈、噻加宾、托吡酯、左乙拉西坦和/或拉莫三嗪。

[0142] 在某些实施例中,本文提供的方法包括根据下式在24小时时期内以三个剂量施用药物组合物,如本文提供的,所述药物组合物包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂:1X、1X、2X,其中X是活性剂的特定剂量(例如2mg/kg、5mg/kg、8mg/kg、10mg/kg、15mg/kg或20mg/kg)。在一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以下述剂量对于多个24小时时期连续施用三次/24小时时期:约1mg/kg至约3mg/kg(例如约2mg/kg)、约3mg/kg至约7mg/kg(例如约5mg/kg)、约6mg/kg至约10mg/kg(例如约8mg/kg)、约7mg/kg至约13mg/kg(例如约10mg/kg)、约13mg/kg至约17mg/kg(例如约15mg/kg)、或约18mg/kg至约22mg/kg(例如约20mg/kg)的3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂,如本文提供的,共多个24小时时期包括但不限于数天、数周、数月或数年。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以下述剂量连续施用三次/24小时时期:约5mg/kg至约9mg/kg(例如约7mg/kg)、约5mg/kg至约9mg/kg(例如约7mg/kg)、以及12mg/kg至约16mg/kg(例如约14mg/kg)的活性剂,共数周、数月或数年。在一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以下述剂量连续施用三次/24小时时期:约8mg/kg至约12mg/kg(例如约10mg/kg)、约8mg/kg至约12mg/kg(例如约10mg/kg)、以及约18mg/kg至约22mg/kg(例如约20mg/kg)的活性剂,共数天、数周、数月或数年。在一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以下述剂量连续施

用三次/24小时时期:约18mg/kg至约22mg/kg (例如约20mg/kg)、约18mg/kg至约22mg/kg (例如约20mg/kg)、以及约38mg/kg至约42mg/kg (例如约40mg/kg) 的活性剂,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔 (例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM) 施用三次。

[0143] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以2mg/kg、2mg/kg和4mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔 (例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM) 施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨2mg/kg、在中午2mg/kg以及在晚上4mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨2mg/kg、在中午2mg/kg以及在晚上4mg/kg的剂量连续施用三次/24小时时期,共12周。

[0144] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以5mg/kg、5mg/kg和10mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔 (例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM) 施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨5mg/kg、在中午5mg/kg以及在晚上10mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨5mg/kg、在中午5mg/kg以及在晚上10mg/kg的剂量连续施用三次/24小时时期,共12周。

[0145] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以8mg/kg、8mg/kg和16mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔 (例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM) 施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨8mg/kg、在中午8mg/kg以及在晚上16mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨8mg/kg、在中午8mg/kg以及在晚上16mg/kg的剂量连续施用三次/24小时时期,共12周。

[0146] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以10mg/

kg、10mg/kg和20mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔(例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM)施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨10mg/kg、在中午10mg/kg以及在晚上20mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨10mg/kg、在中午10mg/kg以及在晚上20mg/kg的剂量连续施用三次/24小时时期,共12周。

[0147] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以15mg/kg、15mg/kg和30mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔(例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM)施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨15mg/kg、在中午15mg/kg以及在晚上30mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨15mg/kg、在中午15mg/kg以及在晚上30mg/kg的剂量连续施用三次/24小时时期,共12周。

[0148] 在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以20mg/kg、20mg/kg和40mg/kg活性剂的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在施用活性剂的每个24小时期间,它优选以大约6、6和12小时的间隔(例如在早餐后~7:00AM、在午餐后~1:00PM、以及在晚餐后~7:00PM)施用三次。在另一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨20mg/kg、在中午20mg/kg以及在晚上40mg/kg的剂量连续施用三次/24小时时期,共数天、数周、数月或数年。在又一个具体实施例中,如本文提供的,包含3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸或其盐以及一种或多种药学可接受的载体和赋形剂的药物组合物,以在早晨20mg/kg、在中午20mg/kg以及在晚上40mg/kg的剂量连续施用三次/24小时时期,共12周。

[0149] 在具体实施例中,根据本文下文在第6节处提供的治疗方案,将本文提供的药物组合物施用于患者。

[0150] 化合物1治疗功效遵循钟形剂量-响应曲线,其中达到且维持在特定范围内的某一稳态血浆浓度导致最大活性。因此,认为个别患者可能需要特定的剂量(即1X、1X、2X,其中X是特定剂量如2mg/kg、5mg/kg、8mg/kg、10mg/kg、15mg/kg或20mg/kg),以便达到化合物1的治疗有效血浆浓度。

[0151] 在某些实施例中,本文提供的方法包括维持患者中的化合物1的血浆浓度大于:约0.1μg/mL、约0.5μg/mL、约2μg/mL、约5μg/mL、约10μg/mL、约20μg/mL、约25μg/mL、约40μg/

mL、约50 μ g/mL、约100 μ g/mL、约150 μ g/mL、约200 μ g/mL、约250 μ g/mL或约500 μ g/mL至少约2、2.5、3、3.5、4、4.5、5、6、8、12或24小时或更长时间。例如,可通过高效液相色谱(HPLC)测量血浆中的化合物1水平。

[0152] 在另一个实施例中,本文提供的方法包括维持患者中约0.1 μ g/mL至约500 μ g/mL、约2 μ g/mL至约40 μ g/mL、约2 μ g/mL至约20 μ g/mL、约2 μ g/mL至约10 μ g/mL、或约10 μ g/mL至约20 μ g/mL的化合物1的血浆浓度至少约2、2.5、3、3.5、4、4.5、5、6、8、12或24小时或更长时间。

[0153] 在一些实施例中,化合物1与至少一种另外的治疗剂组合施用。在一些实施例中,在化合物1施用之前、在化合物1施用之后、与化合物1施用同时或其组合,施用另外的治疗剂。在一些实施例中,另外的治疗剂是拉罗尼酶(更具体而言, α -L-艾杜糖苷酶)和/或一种或多种抗组胺药。

[0154] 在某些实施例中,化合物1与一种或多种疗法组合使用,以治疗无义突变介导的癫痫疾病。在一个具体实施例中,与本文提供的化合物1或药物组合物组合用于治疗、预防、改善或管理无义突变介导的癫痫疾病的一种或多种疗法是抗惊厥药。在一个具体实施例中,与本文提供的化合物1或药物组合物组合用于治疗、预防、改善或管理无义突变介导的癫痫疾病的一种或多种疗法是丙戊酸、双丙戊酸钠、苯妥英、扑米酮、苯巴比妥、卡马西平、地西泮、氯硝西泮、乙琥胺、艾司利卡西平、非氨酯、吡仑帕奈、噻加宾、托吡酯、左乙拉西坦和/或拉莫三嗪。

[0155] 应理解施用于有此需要的患者的药物组合物或活性剂的量是或可基于所讨论的患者的实际重量或所讨论的患者群体(例如男性或女性,包括成人和儿童)的平均重量来计算。

[0156] 6.实例

[0157] 6.1.阿他卢仑促进在SCN1A和CDKL5 mRNA序列中的浓度依赖性通读提前终止密码子。

[0158] 生成萤光素酶报道构建体,以评估存在于SCN1A和CDKL5 mRNA序列中的提前终止密码子处的化合物的通读活性。图1是用于监测SCN1A无义突变W192X(UAG提前终止)的通读活性的报道构建体的示意图。图2是用于监测CDKL5无义突变R59X(UGA提前终止)的通读活性的报道构建体的示意图。图3是用于监测CDKL5无义突变R550X(UGA提前终止)的通读活性的报道构建体的示意图。在每个构建体中,萤光素酶报道分子在氨基末端处侧面为3XHA附加表位,并且在C末端处侧面为FLAG附加表位。来自TPI基因的内含子插入萤光素酶基因中。具有疾病相关的无义突变的来自SCN1A(参见图1)和CDKL5(参见图2和3)的序列与报道序列一起在框内引入,使得在提前终止密码子处的通读导致功能性萤光素酶蛋白的产生。

[0159] 用构建体SCN1A-Trp192x(图1)、构建体CDKL5-R59X(图2)或构建体CDKL5-R550X(图3)转染293H细胞。细胞用溶剂(DMSO)或3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸(阿他卢仑)(递减浓度,从3 μ M开始)处理24小时。测量阿他卢仑促进每个构建体中的提前终止密码子处的通读的能力,并且报告为相对光单位(y轴)。结果显示于图4(SCN1A)和图5(CDKL5)中。结果证实阿他卢仑促进来自SCN1A和CDKL5 mRNA的序列中插入的提前终止密码子的浓度依赖性通读。

[0160] 6.2.阿他卢仑对于患有无义突变CDKL5或Dravet综合征的患者中的耐药性癫痫的第2阶段随机化、双盲安慰剂对照交叉安全性和耐受性研究的方案

[0161] 该实例描述了用于人调查研究的临床研究方案。本研究根据方案、美国 (US) 政府研究条例、和适用的良好临床实践 (GCP) 国际标准、以及机构研究政策和程序进行。关于临床方案的概要参见下表1。关于缩写列表参见下表2。

[0162] 表1:临床方案概要

[0163]

阶段:	第 2 阶段
方法:	介入研究
研究持续时间:	32 周伴随可用延期

[0164]

目标:	本研究的主要目标是: • 表征患有来源于无义突变的 CDKL5 相关癫痫或 SCN1A 相关癫痫如 Dravet 综合征的患者中的阿他卢仑的安全性概况 本研究的次要目标是: • 在患有来源于无义突变的 CDKL5 相关癫痫或 SCN1A 相关癫痫如 Dravet 综合征的患者中的阿他卢仑治疗后, 评估从基线的惊厥和/或跌落癫痫发作频率中的变化 • 在患有来源于无义突变的 CDKL5 相关癫痫或 SCN1A 相关癫痫如 Dravet 综合征的患者中的阿他卢仑治疗后, 确定小癫痫发作类型中的变化。(癫痫发作类型如国际抗癫痫联盟[ILAE]标准定义(International League Against Epilepsy. Seizure Classification. 2014. EpilepsyDiagnosis.org)) 本研究的探索目标是: • 在患有来源于无义突变的 CDKL5 相关癫痫或 SCN1A 相关癫痫如 Dravet 综合征的患者中的阿他卢仑治疗后, 评估在认知、运动和行为功能以及生活质量(QOL)中从基线的变化
患者数目:	16 个可评估的 (8 个具有 CDKL5 无义突变, 8 个具有 SCN1A 无义突变 (Dravet 综合征))
诊断和主要纳入标准:	在第 0 周时 (在签署知情同意书/同意书时) 年龄≥ 2 岁且≤ 12 岁, 男性或女性 如通过医疗记录、基因测试和下述临床特点证明的, 在 1 个等位基因中关于 SCN1A 缺陷 (特别是 Dravet 综合征) 或 CDKL5 缺陷的无义突变的诊断证明文件: • 尽管以治疗剂量的 2 种或更多种抗癫痫药(AED)的适当试验, 但未能控制癫痫发作 • 在入选 (即随机化/基线就诊) 前, 以稳定剂量的 1 至 3 种基线 AED 的当前方案最少 4 周。(迷走神经刺激剂[VNS]、生酮饮食和改良的阿特金斯饮食不计入该限制, 但在入选前 3 个月必须保持不变。) • 在随机化之前, 经过 4 周的日记筛选, 最少 6 次惊厥或跌落癫痫发作, 其持续时间> 3 秒

[0165]

研究产品、剂量、途径、方案：	阿他卢仑（用于悬浮的经口粉末/颗粒） 剂量：每天3次（早晨、中午和晚上分别为10 mg、10 mg和20 mg/kg） 剂量逐步增加：无 最大剂量：每天3次（早晨、中午和晚上分别为10 mg、10 mg和20 mg/kg）
施用持续时间：	每个患者以盲法方式接受总共12周的活性药物（阿他卢仑）和12周的安慰剂

[0166] 表2:缩写列表

[0167]

缩写	定义
BUN	血尿素氮
CBC	全血细胞计数
CI	置信区间
CMP	综合代谢实验对象组
EOS	研究结束
IB	研究者手册
ILAE	国际抗癫痫联盟
ITT	意向治疗
IVRS/IWRS	交互式语音应答系统/交互式网络应答系统
LFT	肝功能测试
LOAEL	观察到不良作用水平的最低剂量
mRNA	信使核糖核酸
PI	主要研究者
PK	药代动力学
QOL	生活质量
QOLCE	儿童期癫痫生活质量
SAE	严重不良事件
SMEI	婴儿严重肌阵挛性癫痫
SUDEP	癫痫猝死
TEAE	治疗紧急不良事件
TID	每天三(3)次
VNS	迷走神经刺激剂

[0168] 6.2.1.阿他卢仑

[0169] 用于本研究中的阿他卢仑 (3-[5-(2-氟-苯基)-[1,2,4]噁二唑-3-基]苯甲酸) 为在儿童防护铝箔小包或小袋中包装的用于悬浮的白色至灰白色粉末/颗粒形式。每个小包或小袋含有125、250或1000mg原料药,所述原料药为制剂总重量的25%。

[0170] 6.2.1.1. 安慰剂

[0171] 用于安慰剂对照的临床研究的安慰剂作为用于悬浮的白色至灰白色粉末/颗粒提供。安慰剂粉末/颗粒在匹配活性药物产品的填充重量的小包或小袋中供应,所述小包或小袋含有125、250或1000mg原料药。安慰剂类似于活性产品,除了通过加入填料(微晶纤维素)和增加量的甘露醇来替换阿他卢仑之外,所述填料和甘露醇共同构成粉末/颗粒的约50%。

[0172] 6.2.2. 研究设计

[0173] 交叉设计通常是统计上有效的并且因此需要更少的受试者。另外,混杂协变量的影响也减少,因为每个交叉患者充当他或她自己的对照。12周治疗期提供了足够的时间来评价患者的癫痫发作活动和QOL中的变化,同时仍然允许患者的适当监测。因为用于该患者群体的治疗选项是最少的,所以该交叉研究中的中途退出率预期很低。

[0174] 本研究是包括下述的第2阶段介入研究:筛选(第-4周至第0周/第1天)、治疗期1(第0周/第1天-第12周)、清除期(第12周-第16周)、交叉至治疗期2(第16周-第28周)和随访(第28周-第32周)。

[0175] 研究设计显示于图6中。事件的时间表在表3中提供。

[0176] 6.2.2.1. 药物施用计划

[0177] 患者在每个治疗期过程中接受12周的阿他卢仑或安慰剂。治疗期1随后为4周清除期。基于阿他卢仑PK和药效学数据,4周清除期视为消除任何阿他卢仑药物效应的适当时间长度。清除期后,患者交叉以在治疗期2过程中接受相反的治疗。

[0178] ●在治疗期1过程中接受阿他卢仑的患者在治疗期2过程中接受安慰剂。

[0179] ●在治疗期1过程中接受安慰剂的患者在治疗期2过程中接受阿他卢仑。

[0180] 研究药物每天施用3次(TID)。待施用的剂量水平是:在早晨10mg/kg、在中午10mg/kg和在晚上20mg/kg。

[0181] 给药基于患者在基线时的体重。在每次诊所就诊时评价重量。如果患者的体重从基线变化 $\geq 10\%$,则可重新计算实际剂量。

[0182] 第一个研究药物剂量在诊所中施用并且记录施用日期和时间。在每个治疗期结束时,在诊所就诊前一晚(即就诊6/第12周[治疗期1结束]前一晚和就诊18/第28周[治疗期2结束]前一晚)时服用最后一个研究药物剂量。

[0183] 6.2.2.2. 研究风险和利益

[0184] 6.2.2.2.1. 研究药物的风险

[0185] 在研究自始至终就不良事件密切监测所有患者。

[0186] 阿他卢仑是CYP2C9和CYP2C8的弱抑制剂。阿他卢仑与CYP2C8和CYP2C9底物之间的临床药物相互作用研究仍未得出结论。阿他卢仑具有增加主要由CYP2C8或CYP2C9代谢的药物的血浆浓度的潜力,在所述药物中包括其为CYP2C8或CYP2C9的底物、具有窄治疗指数的药物。其它伴随AED和由这些酶系统代谢的其它药物水平的效应是未知的,但它可增加其水平,导致潜在的毒性。因此,在基线和在每个治疗期的第一个阿他卢仑剂量后4周(即就诊4/第4周和就诊14/第20周)测量AED血浆水平。AED可根据需要基于毒性的体征和症状和/或药物水平中的变化进行调整。

[0187] 6.2.3. 研究目标

[0188] 本研究的主要目标是:

[0189] ●表征患有来源于无义突变的CDKL5相关癫痫或SCN1A相关癫痫如Dravet综合征的患者中的阿他卢仑的安全性概况。

[0190] 本研究的次要目标是：

[0191] ●在患有来源于无义突变的CDKL5相关癫痫或SCN1A相关癫痫如Dravet综合征的患者中的阿他卢仑治疗后，评估从基线的惊厥和/或跌落癫痫发作频率中的变化。

[0192] ●在患有来源于无义突变的CDKL5相关癫痫或SCN1A相关癫痫如Dravet综合征的患者中的阿他卢仑治疗后，确定小癫痫发作类型（失神性、肌阵挛性、复杂部分性/局部认知障碍性）中的变化。

[0193] 本研究的探索目标是：

[0194] ●在患有来源于无义突变的CDKL5相关癫痫或SCN1A相关癫痫如Dravet综合征的患者中的阿他卢仑治疗后，评估在认知、运动和行为功能以及QOL中从基线的变化。

[0195] 6.2.4. 终点

[0196] 6.2.4.1. 主要终点

[0197] 本研究的主要研究终点包括：

[0198] ●阿他卢仑的总体安全性概况，特征在于任何不良事件或严重不良事件（SAE）的类型、频率、严重性、时机和与研究药物的关系；在体检、实验室测试结果和由于不良事件或SAE的药物停用中的变化。

[0199] 6.2.4.2. 次要终点主要终点

[0200] 本研究的次要终点如下：

[0201] ●癫痫发作频率从基线的变化。要计数的运动性癫痫发作是强直-阵挛性癫痫发作、半惊厥性癫痫发作、跌落癫痫发作、强直性癫痫发作和局灶性运动性癫痫发作。

[0202] ●还评估了对肌阵挛性癫痫发作（即持续或消失）的作用。

[0203] ●数据在基线期间和在基线后每4周时进行收集，以鉴定下述中的变化：

[0204] ○定义为持续>10分钟的惊厥的癫痫持续状态的发作次数

[0205] ○救援用药的使用次数

[0206] ○急诊室就诊/住院次数

[0207] 6.2.4.3. 探索性终点

[0208] 探索性终点包括：

[0209] ●小癫痫发作类型中的变化：

[0210] ○肌阵挛性癫痫发作的次数

[0211] ○瞪眼性（失神性或复杂部分性）癫痫发作的次数

[0212] 另外，使用下述仪器评价癫痫疾病的严重性、认知和运动量表、QOL、以及安全性和耐受性：

[0213] 1. 使用儿童行为评价系统：第三版（Sabaz等人Epilepsy Behav. 2003, 4 (6) :680-91）评价人格和行为的临床和适应性量度。

[0214] 2. 如通过学前儿童语言发展量表，第四版（PSL-4）（Zimmerman等人2002）测量的语言技能

[0215] 3. 如通过文兰适应行为量表（Vineland Adaptive Behavior Scales），第二版（VABS-II）（Sparrow等人2005）测量的行为功能的适应水平

[0216] 4.如通过儿童期癫痫的生活质量(QOLCE) (Sabaz等人Epilepsy Behav.2003,4(6):680-91)评价的生活质量

[0217] 6.2.4.4.纳入撤出

[0218] 选择用于本研究的患者必须符合下述标准:

[0219] 1.在第0周时(在签署知情同意书/同意书时)年龄 ≥ 2 岁 ≤ 12 岁,男性或女性

[0220] 2.如通过医疗记录、基因测试和下述临床特点证明的,在1个等位基因中关于SCN1A缺陷(特别是Dravet综合征)或CDKL5缺陷的无义突变的诊断证明文件:

[0221] a.尽管以治疗剂量的2种或更多种AED的适当试验,但未能控制癫痫发作

[0222] 3.在筛选就诊前,以稳定剂量的1至3种基线AED最少4周

[0223] a.迷走神经刺激剂(VNS)、生酮饮食和改良的阿特金斯饮食不计入该限制,但在入选前3个月必须保持不变。

[0224] 4.在筛选就诊前,VNS必须保持稳定的设置最少3个月

[0225] 5.如果是生酮或改良的阿特金斯饮食,则在筛选就诊前,必须保持稳定比率最少3个月

[0226] 6.在执行任何研究程序前,必须从患者或患者的法定代理人获得的书面同意书

[0227] 7.在随机化之前,经过4周的日记筛选,最少6次惊厥或跌落癫痫发作,其持续时间 >3 秒

[0228] 6.2.4.5.排除标准

[0229] 如果符合下述排除标准中的任一种,则不能将患者纳入研究中:

[0230] 1.患者小于2岁或超过12岁

[0231] 2.与除SCN1A缺陷(特别是Dravet综合征)或CDKL5缺陷外的遗传病症相关的癫痫

[0232] 3.患者具有并非无义突变的SCN1A(Dravet)或CDKL5基因突变

[0233] 4.非氨酯已在入选(基线就诊)之前的过去12个月内起始

[0234] 5.患者目前或已在入选(基线随访)之前的过去30天内参与过临床试验

[0235] 6.在研究者看来,可不利地影响患者的安全、使得研究药物施用或随访过程不太可能完成、或可损害研究结果的评价的先前或进行中的医疗状况(例如伴随疾病、精神病状况)、病史、物理发现或实验室异常。

[0236] 6.2.4.6.患者招募和筛选

[0237] 从主要研究者(PI)或助理研究者的临床实践招募八个无义突变SCN1A(Dravet综合征)患者和8个无义突变CDKL5患者用于研究。在例行就诊期间,询问符合研究标准的患者/父母/法定监护人他们是否愿意参与研究。就纳入评价在2岁至12岁之间的任何种族的男性和女性患者。在例行就诊期间,研究者通知每个潜在的患者/家长/法定监护人研究的性质,解释潜在的风险和研究有关程序。如果患者/家长/法定监护人同意,则在开始任何研究程序之前向他们给予知情同意书文件以阅读并签署。仅研究中列出的PI、助理研究者和其它研究人员才能获得患者信息。一旦研究患者/家长/法定监护人已签署了知情同意书,就可开始筛选程序。

[0238] 6.2.4.7.随机化

[0239] 在患者已完成必要的筛选评价并且已被研究者确认为合格之后,可将患者随机化到研究内。

[0240] 入选十六个患者 (8个具有CDKL5无义突变和8个具有SCN1A无义突变)。在每个病症组内,患者在治疗期1过程中以1:1的比率随机化至2个可能的治疗指定的1个中:

[0241] ●安慰剂

[0242] ●阿他卢仑 (10、10、20mg/kg/天)

[0243] 6.2.4.8.盲法

[0244] 通过使用在外观、味道、气味、包装、标签和施用时间表方面与活性药物匹配的安慰剂来隐藏治疗的身份。解盲仅在研究完成前患者急症的情况下,在临时DMC审查时由DMC要求,以及在研究结束时发生。除了急症解盲之外,各个患者、父母/护理人员和现场人员不被告知随机化治疗指定,直到由研究者决定揭示这些数据用于整体阿他卢仑临床开发项目的意义时。

[0245] 6.2.5.患者的提早撤出

[0246] 6.2.5.1.何时和如何撤出患者

[0247] 如果患者或患者的法定监护人,或者研究者认为继续不是患者的最佳利益,则患者可随时停用研究药物。下述是研究药物停用的可能原因列表:

[0248] 1.父母/监护人撤回同意书。

[0249] 2.患者不依从研究程序。

[0250] 3.要求研究药物停用的方案违反。

[0251] 4.严重不良事件,包括显著的毒性,如严重的认知或行为毒性、肝功能和肾功能受损、或造血作用受损。

[0252] 5.不可归因于其它已知的激发因素的癫痫发作恶化。

[0253] 6.与导致不可接受的毒性的伴随AED方案的相互作用。如果可能的话,避免用药调整,并且可能需要受试者退出研究,由研究者自行决定。

[0254] 如果患者必须停用研究药物,则基于反应类型和/或撤出原因来确定停用研究药物的方法。例如,如果患者经历快速进行性皮炎,则它导致研究药物的突然停止,但如果患者经历过度疲劳,则研究药物可逐渐减量。关于停止方法的讨论在患者和/或患者的父母/法定监护人与医生之间发生。

[0255] 6.2.5.2.撤出患者的数据收集和随访

[0256] 对于从研究撤出的所有患者,存在最后一个研究药物剂量后4周的一次最终就诊。如果在给患者/家长/法定监护人打过4次电话后无法联系患者/家长/法定监护人,则向患者/家长/法定监护人发送保证邮件(certified letter)。

[0257] 6.2.6.研究药物

[0258] 6.2.6.1.阿他卢仑

[0259] 阿他卢仑作为用于经口悬浮液的白色至灰白色粉末/颗粒形式提供。原料药和药物产品在现行良好生产规范(cGMP)条件下制造。该制剂包括基质和悬浮剂、表面活性剂和辅助制造过程的各种赋形剂。用于经口悬浮液的粉末/颗粒包装在铝箔、儿童防护小袋(小包)中,并且以含有125、250或1000mg活性原料药的剂量强度供应。所有赋形剂都已测试至药物或食品级别,并且一般视为安全的。

[0260] 6.2.6.2.安慰剂

[0261] 白色至灰白色粉末/颗粒安慰剂制剂提供用于经口悬浮液。安慰剂制剂已在cGMP

条件下制造。药物的干粉/颗粒和液体悬浮液在外观、气味和味道方面匹配活性制剂。安慰剂制剂含有类似于活性产品中使用的赋形剂。安慰剂包装在相同的铝箔、儿童防护小袋(小包)中,匹配活性药物小袋的125、250和1000mg剂量强度各自。

[0262] 6.2.6.3. 药物试剂盒

[0263] 提供了药物试剂盒,所述药物试剂盒各自含有剂量强度(125、250或1000mg或匹配安慰剂)之一的65个小包或小袋。

[0264] 6.2.6.4. 治疗方案

[0265] 患者在每个治疗期过程中接受12周的盲法阿他卢仑或安慰剂。每个患者以基于其以千克计的体重的剂量开始。研究药物以10mg/kg、10mg/kg和20mg/kg(分别为早晨、中午和晚上)的TID方式施用。剂量从125、250和1000mg箔小包或小袋施用。

[0266] 给药基于患者在基线时的体重。在每次诊所就诊时评价重量。如果患者的体重从基线变化 $\geq 10\%$,则可重新计算实际剂量。

[0267] 第一个研究药物剂量在诊所中施用并且记录施用日期和时间。在每个治疗期结束时,在诊所就诊前一晚(即就诊6/第12周[治疗期1结束]前一晚和就诊18/第28周[治疗期2结束]前一晚)时服用最后一个研究药物剂量。

[0268] 每个剂量应该在餐前或餐后 ~ 30 分钟内服用。给药间隔应该为在早晨和中午剂量之间 ~ 6 小时(± 1 小时)、在中午和晚上剂量之间 ~ 6 小时(± 1 小时)、以及在晚上剂量和第二天的早晨剂量之间 ~ 12 小时(± 1 小时)。

[0269] 6.2.6.5. 给药延迟的说明

[0270] 研究药物(盲法阿他卢仑或安慰剂)施用中的给药延迟应该坚持下述指导:

[0271] ●如果研究药物的给药延迟 ≤ 1 小时,则应该服用计划的剂量而无需改变后续剂量方案;

[0272] ●如果研究药物给药延迟 > 1 小时但 ≤ 4 小时,则应该服用计划的剂量;然而,当天的所有未来剂量都应该稍后移动大约相应的量;

[0273] ●如果研究药物剂量延迟 > 4 小时,则不应该服用剂量。研究药物施用可继续,但不应该服用错过的剂量,并且后续研究药物给药的计划时机不应该改变。

[0274] 6.2.6.6. 研究药物制备和贮存

[0275] 研究药物小袋应该在室温下贮存,远离儿童接触直到重构时,并且应该仅在剂量制备时打开。每个小袋的全部内容物应该与至少30mL(1盎司)液体(水、牛奶、果汁宾治)、或3汤匙半固体食品(酸奶或苹果酱)混合。小袋的全部内容物应该与至少30mL(1盎司)液体(例如水、牛奶)、或3汤匙半固体食品(酸奶、布丁或苹果酱)混合。制备的剂量应该在施用前充分混合。基于患者偏好,可增加液体或半固体食品的量。

[0276] 每个制备的剂量最好在制备后立即施用。如果在制备的24小时(如果保持冷藏(2 至 8°C))或3小时(在室温(15 至 30°C)下)内不消耗,则应该丢弃制备的剂量。诊所工作人员指导每个患者或家长/护理人员关于每个剂量从每个试剂盒中服用的小袋的具体数目,并且提供关于药物制备的详细口头指导。另外,当分配药物供应时,向患者或家长/护理人员提供详细的书面药物混合和给药说明书。

[0277] 6.2.6.7. 用于将患者分配至治疗组的方法

[0278] 该介入研究含有安慰剂部分,其中患者不接受超出现有背景AED方案的活性药物

疗法。按照盲法随机化时间表完成阿他卢仑和安慰剂对治疗次数的分配。

[0279] 随机化是减少偏差并且允许记录治疗效应的最高证据标准的公认手段。使用置换区组随机化技术。这种方法允许治疗臂关于预先限定的分层因子以及每个臂中的患者数目达到平衡。该过程由经验丰富的临床研究组织 (CRO) 通过交互式语音应答系统/交互式网络应答系统 (IVRS/IWRS) 系统建立且执行,以最大化随机化的完整性和安全性,并且确保通过研究场所的适当访问和使用便利性。该方法应该足以阻止场所人员基于已知区组大小做出关于治疗分配的推断。计划1:1的阿他卢仑:安慰剂随机化,以便避免与不平衡随机化相关的统计功效损失。

[0280] 为了最小化研究药物盲法的潜在妥协,并且减少将活性药物和安慰剂在家庭内混合的非故意给药错误或有意尝试的机会,如果发生所述情况,则随机化系统将随后入选的家庭成员(例如兄弟姐妹)分配至与入选的第一名家庭成员相同的治疗组。这种方法存在过去的优先[Ballard 2006]。

[0281] 当患者在研究中被随机化并且准备开始研究药物时,PI或合格的指定人员分配适当数量的盲法研究用药,并且将其分发给患者和/或患者的父母/法定监护人。正确的剂量施用和时间表的详细说明在离开预约之前已进行讨论且得到充分理解。

[0282] 6.2.6.8. 患者依从性监测

[0283] 研究团队经由临床评估和随访电子邮件或打电话评价且追踪患者对研究药物方案的依从性。患者每个月都要接受关于研究药物治疗方案的临床评估,直至接下来的10个月,在第一个研究用药剂量后的前两周过程中具有就诊。严重不依从研究药物方案(<80%或>120%)的任何患者都根据PI从研究中撤出。

[0284] 6.2.6.9. 先前疗法和伴随疗法

[0285] 在研究自始至终,包括在具有研究药物施用的治疗期过程中,患者在基线就诊前继续其目前的AED方案,所述AED方案由以稳定剂量的1至3种药物组成,共至少4周。在基线就诊时和在研究期间收集伴随的AED浓度,以评价潜在的相互作用。如果患者具有VNS,则在基线就诊前,设置必须保持稳定比率最少4周。另外,如果患者使用生酮饮食,则在基线就诊前,稳定比率必须已存在至少3个月。在研究期间允许所有伴随AED;如果在入选(基线)前给药已具有稳定剂量 ≥ 12 个月,则允许非氨酯。如果可能的话,避免用药调整,并且可能需要受试者退出研究,由研究者自行决定。

[0286] 6.2.6.10. 贮存

[0287] 含有研究药物的小袋在控制室温(~ 15 至 30°C)下贮存在仅研究人员可接近的锁定房间中。来自代表性样品的可用稳定性数据支持在室温下贮存48个月时的药物产品的使用。适当时,可监测临床研究样品或代表性样品的稳定性,以支持临床研究。

[0288] 6.2.6.11. 研究药物的分配

[0289] 阿他卢仑的给药基于患者体重的mg/kg,并且调整以允许用高达3个可用小袋剂量强度(125mg、250mg和/或1000mg)的给药。该小袋的全部内容物由构造介质构造且施用。研究药物的供应基于患者重量进行计算,并且由PI或合格的指定人员提供。分发给每个研究患者的研究药物小袋的数量在分配后在研究日志中注明。执行定期研究药物核对(reconciliation),以记录分配的药物和剩余的药物。该核对录入药物核对表格中,并且由研究团队签字且注明日期。

[0290] 6.2.6.12. 用药过量注意事项

[0291] 对于经历用药过量的任何患者(对于本方案施用阿他卢仑剂量>4倍预期的总日剂量水平[即>160mg/kg/天]),应该进行对于任何症状性副作用的观察,并且应该密切跟踪生命体征以及生物化学和血液学参数(与方案一致或根据需要更频繁)。应该启动适当的支持管理来减轻不利效应。在获得关于药物足够的人体经验之前,不特别推荐也不禁止洗胃或呕吐诱导的使用。

[0292] 6.2.7. 事件时间表

[0293] 要记录的数据类型和时机在表3中概括。

[0294] 表3: 事件时间表

[0295]

方案活动	筛选 ^a	治疗期 1 ^b					4 周清除/ 交叉	治疗期 2 ^{b,c}				EOS 就诊 ^d	随访 ^e
周 (±7 天)	-4 (第-4周至 第0周; 第28天至 第-1天)	0	2	4	8	12		16	18	20	24	28	32
就诊	1	2 ^f	3	4	6	8		10	12	14	16	18	20
知情同意书/同意书	X												
病史	X												
血清病毒筛选	X												
体检	X	X				X		X				X	X
高度和重量	X	X	X	X	X	X	X	X	X	X	X	X	X
生命体征	X	X	X	X	X	X	X	X	X	X	X	X	X
提供的癫痫发作数据日记	X	X	X	X	X	X		X	X	X	X	X	
收集的癫痫发作数据日记		X	X	X	X	X		X	X	X	X	X	
分配的研究药物		X ^g	X	X	X			X ^g	X	X	X		
研究药物施用		X ^h						X ^h					
研究药物依从性和归还			X	X	X	X			X	X	X	X	
不良事件	X	X	X	X	X	X		X	X	X	X	X	X
伴随用药	X	X	X	X	X	X		X	X	X	X	X	X
用于 CBC、CMP、LFT、BUN、肌酸酐水平、血清 HCG 的血液 ⁱ	X	X						X				X	X
用于 AED 评价的血浆 PK 的血液 ^j		X		X				X		X			
尿分析	X	X				X		X				X	X

[0296]

方案活动	筛选 ^a	治疗期 1 ^b					4 周清除/ 交叉	治疗期 2 ^{b,c}				EOS 就诊 ^d	随访 ^e
儿童行为评价系统		X				X		X				X	X
学前儿童语言发展量表		X				X		X				X	X
文兰适应行为量表		X				X		X				X	X
儿童期癫痫生活质量		X				X		X				X	X

[0297] 缩写: AED=抗癫痫药; BUN=血尿素氮; CBC=全血细胞计数; CMP=综合代谢实验对象组; EOS=研究结束; HCG=人绒毛膜促性腺激素; LFT=肝功能测试; PK=药代动力学

[0298] a. 筛选从第-4周到第0周(即28天)发生。 ± 7 天就诊窗口不适用于筛选期。

[0299] b. 未显示的奇数编号就诊通过电话和/或电子邮件评估进行

[0300] c. 在治疗期2过程中, 患者交叉并且开始接受与他们在治疗期1过程中接受的相反的盲法研究药物(即, 先前接受盲法阿他卢仑的患者现在接受安慰剂, 并且先前接受安慰剂的患者现在接受阿他卢仑。

[0301] d. 对于完成研究的所有患者和提早停止研究的任何患者完成EOS就诊。

[0302] e. 随访就诊将在EOS就诊或最后一个研究药物剂量后4周发生。

[0303] f. 就诊2视为基线就诊。就诊2必须在就诊1后不早于28天和至多42天发生。所有的研究和实验室评价都必须在第一个研究药物剂量施用之前完成。

[0304] g. 在就诊2(基线)和就诊10(第16周)时的第一个研究药物剂量应该在诊所中给予。

[0305] h. 在就诊8/第12周(治疗期1)和就诊18/第28周(EOS就诊)之前的最后一个研究药物剂量应该在前一晚在家中服用。在诊所就诊前不应该服用早晨剂量。

[0306] i. 血清HCG样品仅对于有生育潜力的女性患者获取

[0307] j. 样品在研究药物的早晨剂量之前立即获得(仅谷水平)。

[0308] 6.2.7.1. 筛选、治疗和随访期

[0309] 研究的筛选评估在临床研究设施处执行。研究参与者在每次预定的现场就诊的早晨向诊所报道, 并且留在诊所直到所有研究有关程序已完成, 并且患者已接受了关于药物贮存、重构和施用的指导后由研究者释放。

[0310] 在知情同意书的时间开始直到随访期结束评价不良事件。

[0311] 在最后一个剂量后4周时, 患者必须返回诊所用于随访评价。

[0312] 6.2.7.1.1. 就诊1(筛选, 在基线就诊2前4周)

[0313] 筛选就诊(就诊1)在例行就诊期间的基线就诊2之前4周发生。筛选程序如下进行:

[0314] ●获得书面知情同意书/同意书。

[0315] ●确定患者是否符合初步合格标准:

[0316] o收集人口统计信息

[0317] o收集当前病史和相关病史

[0318] o鉴定使用的伴随用药

[0319] o鉴定并确认稳定使用AED用药

[0320] 如果患者符合初步合格标准, 则执行下述评价:

- [0321] ●生命体征 (包括收缩压和舒张压、桡动脉脉搏率和体温) :在坐姿时执行
- [0322] ●体检
- [0323] ●高度和重量
- [0324] ●血液抽取用于临床实验室评估:
- [0325] ○血尿素氮 (BUN)、全血细胞计数 (CBC)、综合代谢实验对象组 (CMP)、肝功能测试 (LFT)
- [0326] ○适用时的血清HCG (样品仅对于有生育潜力的女性患者获取)
- [0327] ○血清病毒筛选
- [0328] ●尿分析
- [0329] ●指示患者或患者的家长/法定监护人在接下来的4周内保持癫痫发作日记,包括下述信息:
 - [0330] ○癫痫发作类型、持续时间、强度
 - [0331] ○发绀的存在或不存在
 - [0332] ○救援用药的使用
- [0333] 6.2.7.1.2. 就诊2 (基线, 第0周)
- [0334] 在4周筛选期后, 审查在筛选就诊时提供的日记卡, 并且确认所有纳入/排除标准。合格患者如下完成基线就诊 (就诊2/第0周):
 - [0335] ●体检
 - [0336] ●高度和重量
 - [0337] ●生命体征 (包括收缩压和舒张压、桡动脉脉搏率和体温) :在患者已处于坐姿3-5分钟后执行
 - [0338] ●收集癫痫发作日记并且查看条目
 - [0339] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
 - [0340] ●记录伴随用药中的任何变化
 - [0341] ●完成下述QOL评价:
 - [0342] ○儿童行为评价系统
 - [0343] ○学前儿童语言发展量表
 - [0344] ○文兰适应行为量表
 - [0345] ○ QOLCE
 - [0346] ●血液抽取用于临床实验室评估
 - [0347] ○ CBC、CMP、LFT、BUN、肌酸酐、血清HCG
 - [0348] ○用于AED水平评价的血浆PK
 - [0349] ●尿分析
- [0350] ●分发新的癫痫发作日记和审查完成说明书
- [0351] ●分发盲法研究药物和审查施用说明书
 - [0352] ○ T1D给药10mg/kg、10mg/kg、20mg/kg (早晨、中午、晚上)
 - [0353] ○第一个研究药物剂量应该在这次就诊时所需的所有其它评价和程序完成后在诊所中施用。

[0354] 6.2.7.1.3.就诊3 (第2周)

[0355] 患者返回场所进行就诊3。在就诊3时的程序如下进行：

[0356] ●高度和重量

[0357] ●生命体征 (包括收缩压和舒张压、桡动脉脉搏率和体温)：在患者已处于坐姿3-5分钟后执行

[0358] ●收集癫痫发作日记并且查看条目

[0359] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件

[0360] ●记录伴随用药中的任何变化

[0361] ●分发新的癫痫发作日记和审查完成说明书

[0362] ●分发盲法研究药物和审查施用说明书

[0363] TID给药10mg/kg、10mg/kg、20mg/kg (早晨、中午、晚上)

[0364] 6.2.7.1.4.就诊4 (第4周)

[0365] 患者返回场所进行就诊4。在就诊4时的程序如下进行：

[0366] ●高度和重量

[0367] ●生命体征 (包括收缩压和舒张压、桡动脉脉搏率和体温)：在患者已处于坐姿3-5分钟后执行

[0368] ●收集癫痫发作日记并且查看条目

[0369] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件

[0370] ●记录伴随用药中的任何变化

[0371] ●血液抽取血浆PK用于AED水平评价

[0372] ●分发新的癫痫发作日记和审查完成说明书

[0373] ●分发盲法研究药物和审查施用说明书

[0374] TID给药10mg/kg、10mg/kg、20mg/kg (早晨、中午、晚上)

[0375] 6.2.7.1.5.就诊6 (第8周)

[0376] 患者返回场所进行就诊6。在就诊6时的程序如下进行：

[0377] ●高度和重量

[0378] ●生命体征 (包括收缩压和舒张压、桡动脉脉搏率和体温)：在患者已处于坐姿3-5分钟后执行

[0379] ●收集癫痫发作日记并且查看条目

[0380] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件

[0381] ●记录伴随用药中的任何变化

[0382] ●分发新的癫痫发作日记和审查完成说明书

[0383] ●分发盲法研究药物和审查施用说明书

[0384] ●TID给药10mg/kg、10mg/kg、20mg/kg (早晨、中午、晚上)

[0385] ●提醒患者/家长/法定监护人，在下次诊所就诊 (就诊8) 前，患者应该在就诊前一晚服用其最后一个研究药物剂量。

- [0386] 6.2.7.1.6.就诊8(第12周[4周清洗开始])
- [0387] 患者返回场所进行就诊8。就诊8如下进行：
- [0388] ●体检
- [0389] ●高度和重量
- [0390] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温)：在患者已处于坐姿3-5分钟后执行
- [0391] ●收集癫痫发作日记并且查看条目
- [0392] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
- [0393] ●记录伴随用药中的任何变化
- [0394] ●完成下述QOL评价：
- [0395] 儿童行为评价系统
- [0396] 学前儿童语言发展量表
- [0397] 文兰适应行为量表
- [0398] QOLCE
- [0399] ●分发新的癫痫发作日记和审查完成说明书
- [0400] ●在这次就诊时不分发研究药物。
- [0401] 6.2.7.1.7.治疗期2-就诊10(第16周[交叉就诊])
- [0402] 患者返回场所进行就诊10。患者交叉并且开始接受与他们在治疗期1过程中接受的相反的盲法研究药物(即,先前接受盲法阿他卢仑的患者现在接受安慰剂,并且先前接受安慰剂的患者现在接受阿他卢仑)。就诊10如下进行：
- [0403] ●体检
- [0404] ●高度和重量
- [0405] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温)：在患者已处于坐姿3-5分钟后执行
- [0406] ●收集癫痫发作日记并且查看条目
- [0407] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
- [0408] ●记录伴随用药中的任何变化
- [0409] ●血液抽取用于临床实验室评估
- [0410] CBC、CMP、LFT、BUN、肌酸酐、血清HCG
- [0411] ●尿分析
- [0412] ●分发新的癫痫发作日记和审查完成说明书
- [0413] ●分发盲法研究药物和审查施用说明书
- [0414] TID给药10mg/kg、10mg/kg、20mg/kg(早晨、中午、晚上)
- [0415] 第一个研究药物剂量应该在这次就诊时所需的所有其它评价和程序完成后在诊所中施用。
- [0416] 6.2.7.1.8.就诊12(第18周)
- [0417] 患者返回场所进行就诊12。就诊12如下进行：

- [0418] ●高度和重量
- [0419] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温):在患者已处于坐姿3-5分钟后执行
- [0420] ●收集癫痫发作日记并且查看条目
- [0421] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
- [0422] ●记录伴随用药中的任何变化
- [0423] ●分发新的癫痫发作日记和审查完成说明书
- [0424] ●分发盲法研究药物和审查施用说明书
- [0425] TID给药10mg/kg、10mg/kg、20mg/kg(早晨、中午、晚上)
- [0426] 6.2.7.1.9.就诊14(第20周)
- [0427] 患者返回场所进行就诊14。就诊14如下进行:
- [0428] ●高度和重量
- [0429] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温):在患者已处于坐姿3-5分钟后执行
- [0430] ●收集癫痫发作日记并且查看条目
- [0431] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
- [0432] ●血液抽取血浆PK用于AED水平评价
- [0433] ●记录伴随用药中的任何变化
- [0434] ●分发新的癫痫发作日记和审查完成说明书
- [0435] ●分发盲法研究药物和审查施用说明书
- [0436] TID给药10mg/kg、10mg/kg、20mg/kg(早晨、中午、晚上)
- [0437] 6.2.7.1.10.就诊16(第24周)
- [0438] 患者返回场所进行就诊16。就诊16如下进行:
- [0439] ●高度和重量
- [0440] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温):在患者已处于坐姿3-5分钟后执行
- [0441] ●收集癫痫发作日记并且查看条目
- [0442] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件
- [0443] ●记录伴随用药中的任何变化
- [0444] ●分发新的癫痫发作日记和审查完成说明书
- [0445] ●分发盲法研究药物和审查施用说明书
- [0446] TID给药10mg/kg、10mg/kg、20mg/kg(早晨、中午、晚上)
- [0447] ●提醒患者/家长/法定监护人,在下次诊所就诊(就诊18)前,患者应该在就诊前一晚服用其最后一个研究药物剂量。
- [0448] 6.2.7.1.11.就诊18(第28周-研究结束就诊[或提早终止就诊])
- [0449] 患者返回场所进行就诊18。这次就诊视为研究结束(EOS)就诊并且应该对于所有

患者完成。患者应该在诊所就诊前一晚服用其最后一个研究药物剂量。

[0450] 另外,提早停止研究的任何患者都应该完成这次就诊。

[0451] 就诊18如下进行:

[0452] ●体检

[0453] ●高度和重量

[0454] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温):在患者已处于坐姿3-5分钟后执行

[0455] ●收集癫痫发作日记并且查看条目

[0456] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件

[0457] ●记录伴随用药中的任何变化

[0458] ●完成下述QOL评价:

[0459] 儿童行为评价系统

[0460] 学前儿童语言发展量表

[0461] 文兰适应行为量表

[0462] QOLCE

[0463] ●血液抽取用于临床实验室评估

[0464] CBC、CMP、LFT、BUN、肌酸酐、血清HCG

[0465] ●尿分析

[0466] ●在这次就诊时不分发研究药物。

[0467] 6.2.7.1.12.就诊20(第32周[随访就诊])

[0468] 患者返回场所进行就诊20。这次就诊应该在最后一个研究药物剂量和EOS就诊后4周发生。就诊20如下进行:

[0469] ●体检

[0470] ●高度和重量

[0471] ●生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温):在患者已处于坐姿3-5分钟后执行

[0472] ●记录自最后一次就诊以后发生的任何不良事件和在这次就诊期间发生的任何不良事件

[0473] ●记录伴随用药中的任何变化

[0474] ●完成下述QOL评价:

[0475] 儿童行为评价系统

[0476] 学前儿童语言发展量表

[0477] 文兰适应行为量表

[0478] QOLCE

[0479] ●血液抽取用于临床实验室评估

[0480] CBC、CMP、LFT、BUN、肌酸酐、血清HCG

[0481] ●尿分析

[0482] 6.2.7.1.13.电话/电子邮件:就诊5、7、9、11、13、15、17和19

[0483] 询问患者关于他们的研究药物剂量,以检查依从性以及他们如何耐受它。评价不良事件并且解决患者可能遇到的任何问题。

[0484] 在就诊7和就诊17的联系期间,应该提醒患者/家长/法定监护人应该在下次诊所就诊前一晚服用最后一个研究药物剂量,并且在诊所就诊(即就诊8或就诊18)的早晨不应该服用研究药物。

[0485] 6.2.7.1.14.血清病毒筛选

[0486] 在筛选时进行的测试包括乙型肝炎表面抗原、丙型肝炎抗体和人免疫缺陷病毒(HIV)。关于收集、加工和运输信息参考研究手册。

[0487] 6.2.7.1.15.体检

[0488] 体检(包括一般外观、头、眼、耳、鼻、口、咽喉、心脏、甲状腺、胸部和肺部、腹部、四肢、神经肌肉系统、皮肤和淋巴结)在筛选、就诊2(基线)、就诊8、就诊10、第18周(EOS或提早终止)和随访时进行。

[0489] 如临床指示的,体检也可在研究期间的任何时间执行。

[0490] 6.2.7.1.16.生命体征

[0491] 在每次诊所就诊时监测生命体征(包括收缩压和舒张压、桡动脉脉搏率和体温)。

[0492] 6.2.7.1.17.高度和重量

[0493] 在每次诊所就诊时测量高度(以cm计)。在每次诊所就诊时测量重量(以kg计)。

[0494] 6.2.7.1.18.不良事件

[0495] 在筛选时开始,在每次预定的诊所就诊时评价且记录不良事件。如果患者未在预定日就诊诊所,则需要由合格的场所人员给患者打电话以评价不良事件。另外,鼓励受试者/护理人员在就诊之间的间隔内的任何时间报告所关注的不良事件。

[0496] 当临床指示时,获得确定异常结果的意义或病因学或者监测不良事件的过程所需的另外测试和其它评估。就不良事件跟踪患者共最后一个研究药物剂量施用后至少28天,或者直到任何药物有关不良事件和/或进行中的SAE已解决或变得稳定,无论哪个较晚。

[0497] 6.2.7.1.19.伴随用药

[0498] 在每次预定的诊所就诊时收集且记录伴随用药信息。记录在研究过程期间使用的任何伴随用药(处方药或非处方药)和使用原因。关于时机、类型和量的信息记录在CRF中。

[0499] 6.2.8.统计学

[0500] 6.2.8.1.样品量确定

[0501] 由于主要目标是表征患有来源于无义突变的CDKL5或SCN1A(Dravet综合征)癫痫疾病的患者中阿他卢仑的安全性概况,因此本研究不支持统计检验。本研究中纳入十六(16)个患者(8个具有CDKL5无义突变和8个具有SCN1A无义突变[Dravet综合征])

[0502] 6.2.8.2.随机化

[0503] 入选十六个患者(8个具有CDKL5无义突变和8个具有SCN1A无义突变[Dravet综合征])。在每个病症组内,患者在治疗期1过程中以1:1的比率随机化至2个可能的治疗指定的1个中:

[0504] ●安慰剂

[0505] ●阿他卢仑(10、10、20mg/kg/天)

[0506] 在治疗期1和4周清除期完成之后,患者交叉并且开始接受与他们在治疗期1过程

中接受的相反的盲法研究药物(即,先前接受盲法阿他卢仑的患者现在接受安慰剂,并且先前接受安慰剂的患者现在接受阿他卢仑)。

[0507] 6.2.8.3.用于分析的群体

[0508] 意向治疗(ITT)群体-ITT群体含有所有随机化患者。

[0509] 6.2.8.4.功效终点定义

[0510] 6.2.8.4.1.癫痫发作

[0511] 基于ILAE标准就下述评价癫痫发作活动:

[0512] ●运动性癫痫发作,包括强直阵挛性癫痫发作、半惊厥性癫痫发作、跌落癫痫发作、强直性癫痫发作、局灶性运动性癫痫发作。

[0513] ●瞪眼性癫痫发作是失神性癫痫发作或复杂部分性癫痫发作。

[0514] ●肌阵挛性癫痫发作是癫痫发作持续或消失。

[0515] ●癫痫持续状态发作:持续长于10分钟的惊厥状态。

[0516] 基线癫痫发作/ER就诊/住院总次数定义为在4周筛选期(第-4周至第0周(第1天))时的癫痫发作/ER就诊/住院总次数。

[0517] 6.2.8.4.2.人格和行为的临床和适应性测量

[0518] 使用儿童行为评价系统(第3版)进行人格和行为的临床和适应性测量的评价。这是通过PI或临床研究护士/协调者进行的用于测量行为和情绪优势与劣势的筛选系统。

[0519] 6.2.8.4.2.1.语言技能

[0520] 语言技能通过学前儿童语言发展量表,第四版(PSL-4)(Zimmerman等人2002)进行测量。该评价用于评估幼儿的基本交流和语言技能,并且通过PI或临床研究护士/协调者进行。

[0521] 6.2.8.4.2.2.行为功能的适应水平

[0522] 行为功能的适应水平通过文兰适应行为量表,第二版(VABS-II)(Sparrow等人2005)进行测量。该评价用于评估儿童适应实际的日常技能的能力,所述日常技能是运行和满足环境要求所必需的。该评价通过PI或临床研究护士/协调者进行。

[0523] 6.2.8.4.2.3.生活质量

[0524] 生活质量通过QOLCE(Sabaz等人Epilepsy Behav.2003,4(6):680-91)进行评价。该调查问卷用于评估这些患有癫痫的儿童的生活质量,并且分发给家长来完成。

[0525] 6.2.8.5.统计分析

[0526] 如果存在的话,则该比例的置信区间(CI)使用正态近似来计算,如果事件的数目为至少5。否则,提供使用精确方法的CI。对于安全性概括,除非另有说明,否则不呈现CI。概括统计数据在每个病症组内进行分析。所有分析都使用统计分析系统(Statistical Analysis System)(SAS®)(版本9.0或更高)来执行。

[0527] 6.2.8.5.1.研究进行

[0528] 列出且概括所有方案偏差。

[0529] 6.2.8.5.2.研究群体

[0530] 制表与患者处置、人口统计学、基线特征和病史相关的数据的频率分布或概括统计。

[0531] 6.2.8.5.2.1.患者处置

[0532] 制表患者的处置,包括筛选患者的数目、随机化患者的数目、接受至少一个研究药物剂量的随机化患者的数目、以及过早停用研究药物的患者的数目。

[0533] 6.2.8.5.2.2.人口统计学和基线特征

[0534] 通过连续变量的平均值和标准差以及分类变量的频率分布来描述性地概括患者的人口统计学和基线特征。概括基于所有随机化患者(即ITT群体)来执行。

[0535] 6.2.8.5.2.3.病史和先前用药

[0536] 概括了病史和先前用药信息。

[0537] 6.2.8.6.暴露程度

[0538] 对阿他卢仑治疗的暴露程度定义为最后一个剂量日期减去第一个剂量日期+1天。频率根据持续时间范围(以天计)呈现: ≤ 28 (≤ 4 周)、29至56(4至8周)、57至84(8至12周)和 >84 (>12 周)。还展示了每个类别中的患者数目以及平均持续时间。

[0539] 6.2.8.6.1.研究疗法的停用

[0540] ITT群体用于概括研究药物的停用以及研究药物过早终止的原因。使用点估计值和95%CI来概括停用研究药物的患者比例。

[0541] 6.2.8.6.2.治疗依从性

[0542] 通过分析报道的未使用的研究药物来评价研究药物依从性。这些信息用于通过病症组和治疗臂来描述且概括依从性。按照实际服用药物相对于在研究期间应该已服用的量的百分比来评价依从性。

[0543] 6.2.8.7.安全性分析

[0544] 所有安全性呈现都基于ITT群体,并且仅基于包括在目的分析期内的数据。所有不良事件的列表也基于在预定的分析时间点时的所有可用数据。SAE和AE概括代表下述时期:

[0545] ●直到就诊8(第12周)结束时

[0546] ●直到就诊18(第28周,EOS就诊)结束时

[0547] ●在第13周开始到第28周结束之间。

[0548] 还提供了概括在目的分析期结束后的AE和SAE发生的另外频率表。所有AE和SAE都通过治疗组概括。还描述性地概括了标记的实验室异常。对于AE或实验室标记的异常没有执行统计检验。

[0549] 6.2.8.7.1.不良事件

[0550] 概括信息(通过治疗的患者数目和百分比)对于下述进行制表:

[0551] ●TEAE,包括临床和实验室不良事件

[0552] ●治疗有关的不良事件

[0553] ●通过严重性的TEAE

[0554] ●通过严重性的治疗有关的不良事件

[0555] ●严重不良事件

[0556] ●导致停用的不良事件

[0557] 概括通过治疗组呈现并且通过系统器官分类和优选项进行分类。所展示的不良事件的频率是代表经历不良事件的患者数目除以患者总数目的粗比率。

[0558] 6.2.8.7.2.不良事件实验室参数

[0559] 描述性地概括了从基线(随机化前的最后一次测量)的临床实验室测试中的变化

和使用预先限定的异常标准的实验室标记的异常(实验室不良事件)。在按患者的分析中,基于所观察到的最差严重性等级,具有相同异常超过一次的患者仅计数一次。

[0560] 6.2.8.7.3.其它参数

[0561] 描述性地概括了高度、重量、生命体征和体检数据。概括了到第12周和第28周的伴随用药。

[0562] 6.2.8.8.功效分析

[0563] 在每个病症组(Dravet或CDKL5)内和通过治疗组概括所有功效终点。

[0564] 对于自第1天以后的每4周期间过程中(第0周至第4周、第4周至第8周等,定义为在“第4xX周”时,X=1、2、…、6)的下述测量总次数的概括统计,连同从基线的变化对于下述进行制表:

[0565] ●运动性癫痫发作

[0566] ●瞪眼性癫痫发作

[0567] ●肌阵挛性癫痫发作

[0568] ●救援用药的使用

[0569] ●ER就诊/住院

[0570] 为了评价每个治疗期(治疗期1[从基线到第12周]和治疗期2[从就诊10到EOS就诊])中的运动性癫痫发作总次数中的变化,可使用ANCOVA模型,具有在基线时的运动性癫痫发作总次数、体重和年龄作为协变量,以及治疗组作为因子。在高度不平衡的情况下,考虑混合效应模型。适当时,用于分析重复测量数据的统计方法也可探索从基线的运动性癫痫发作总次数中的变化。

[0571] 在每个测量时间点时的概括统计连同从基线的变化一起对于下述进行制表:

[0572] ●儿童行为评价系统

[0573] ●学前儿童语言发展量表

[0574] ●文兰适应行为量表

[0575] ●QOLCE

[0576] 6.2.9.安全性和不良事件

[0577] 6.2.9.1.定义

[0578] 6.2.9.1.1.涉及对患者或其它人的风险的未预料到的问题

[0579] 符合所有下述标准的任何事故、经历或结果:

[0580] ●在性质、严重性或频率中出乎意料的(即在研究有关的文件如机构审查委员会(Institutional Review Board)(IRB)-批准的方案或同意书、IB等中没有描述的)

[0581] ●与研究参与有关或可能有关(即可能有关意指存在事故经历或结果可能通过研究涉及的程序引起的合理可能性)

[0582] ●研究将患者或其它人置于更大的伤害(包括身体、心理、经济或社会伤害)危险中的提示。

[0583] 6.2.9.1.2.不良事件

[0584] 不良事件是在研究过程期间发展或在严重性中恶化的任何症状、体征、疾病或经历。并发疾病或伤害应该视为不良事件。如果异常处于下述情况,则诊断程序的异常结果被视为不良事件:

- [0585] ●导致研究撤出
- [0586] ●与严重不良事件相关
- [0587] ●与临床体征或症状相关
- [0588] ●导致另外的治疗或进一步的诊断测试
- [0589] ●由研究者视为具有临床意义
- [0590] 对于该方案,应该报告为不良事件的不利医疗事故包括下述:
- [0591] ●怀疑或未怀疑是由于研究药物的所有不良事件。
- [0592] ●用药过量(对于研究药物的本方案施用研究药物剂量>4倍最高预期的总日剂量水平[>160mg/kg/天])。
- [0593] ●来自药物误用、滥用、戒断、敏感性或毒性的所有反应。
- [0594] ●来源于用药错误或超出方案中所述的研究药物使用的所有反应。
- [0595] ●明显无关的疾病,包括先前存在的疾病的恶化。
- [0596] ●伤害或意外。注意如果医学状况已知已引起伤害或意外(头晕继发的跌倒),则医学状况(头晕)和意外(跌倒)应该报告为2个分开的不良事件。意外的结果(跌倒继发的髌部骨折)应该记录在源文件中。
- [0597] ●需要临床干预或进一步调查(除了订购重复[确认]测试以外)的生理测试或体检发现中的异常。
- [0598] ●预先存在的状况(例如过敏性鼻炎)必须在关于就诊1的适当CRF上注明,但不应该报告为不良事件,除非该状况在不良事件报告期过程中恶化或发作频率增加。诊断性和治疗性非侵入性和侵入性程序如手术不应该报告为不良事件。然而,如果对于其执行程序医学状况满足不良事件的定义,则应该报告该医疗状况。例如,在不良事件报告期过程中开始的急性阑尾炎应该报告为不良事件,并且所导致的阑尾切除术应该记录在源文件中。如果在进入研究之前计划手术程序,并且由于基线状况恶化而不执行手术,则这不应该报告为不良事件。注意如下文SAE段落中所述,由于在研究期过程中的不良事件的结果而发生的任何入院患者住院治疗应该报告为SAE。
- [0599] 每个不良事件由研究者使用医学和科学判断分类为严重或不严重的。
- [0600] 6.2.9.1.3.严重不良事件
- [0601] 不良事件被分类为严重或不严重的。严重不良事件是其为下述的任何AE:
- [0602] ●致命的
- [0603] ●危及生命的
- [0604] ●需要住院时间或延长住院时间
- [0605] ●导致持续或显著的残疾或无能力
- [0606] ●先天性异常或出生缺陷
- [0607] ●重要的医疗事件
- [0608] 重要的医疗事件是可能不立即危及生命,但显然具有重大临床意义的那些事件。它们可危及患者,并且可能需要干预以防止上述其它严重后果之一。例如,研究药物或其它药物用药过量或滥用、并未导致入院患者住院治疗的癫痫发作、或急诊室中的支气管痉挛的强化治疗通常被视为严重的。
- [0609] 研究药物的用药过量被视为对于本方案施用研究药物剂量>4倍预期的总日剂量

水平(>160mg/kg/天)。不符合任何严重标准的所有不良事件都应该视为不严重的不良事件。注意在最后一个剂量日期的4周内发生的任何SAE都应该报告给研究者。

[0610] 应了解,虽然本发明的具体实施例已在本文中描述用于说明性目的,但本文所述的发明在范围上不受本文公开的具体实施例的限制。这些实施例预期作为本发明的几个方面的说明。任何等价实施例都预期在本发明的范围内。事实上,除本文显示和描述的那些之外,本发明的各种修改根据前述说明书对于本领域技术人员将变得显而易见,所述修改也预期在本发明的范围内。

序列表

<110> PTC医疗公司

<120> 用于治疗癫痫的方法

<130> 10589-239-228

<140> TBA

<141> 2010-10-28

<150> US 62/248,891

<151> 2015-10-30

<160> 3

<170> PatentIn version 3.5

<210> 1

<211> 49

<212> DNA

<213> 人工序列

<220>

<223> 具有TAG无义突变(Trp192X无义密码子)的SCN1A序列

<400> 1

aagattttac tttccttcgg gatccatgga actagctcga tttcactgt 49

<210> 2

<211> 82

<212> DNA

<213> 人工序列

<220>

<223> 具有TAG无义突变(T59X无义密码子)的CDKL5序列

<400> 2

cgtacgaaga aaatgaagaa gtcaaagaaa cgactttatg agagcttaaa atgcttcgga 60
ctctcaagca ggaaaacgta cg 82

<210> 3

<211> 88

<212> DNA

<213> 人工序列

<220>

<223> 具有TAG无义突变(R550X无义密码子)的CDKL5序列

<400> 3

cgtacgacac gagaactttg ctgagccctt ctggaagaaa taactgaaat gagggaacgc 60
tggactcacg tcgaaccaca accgtacg 88

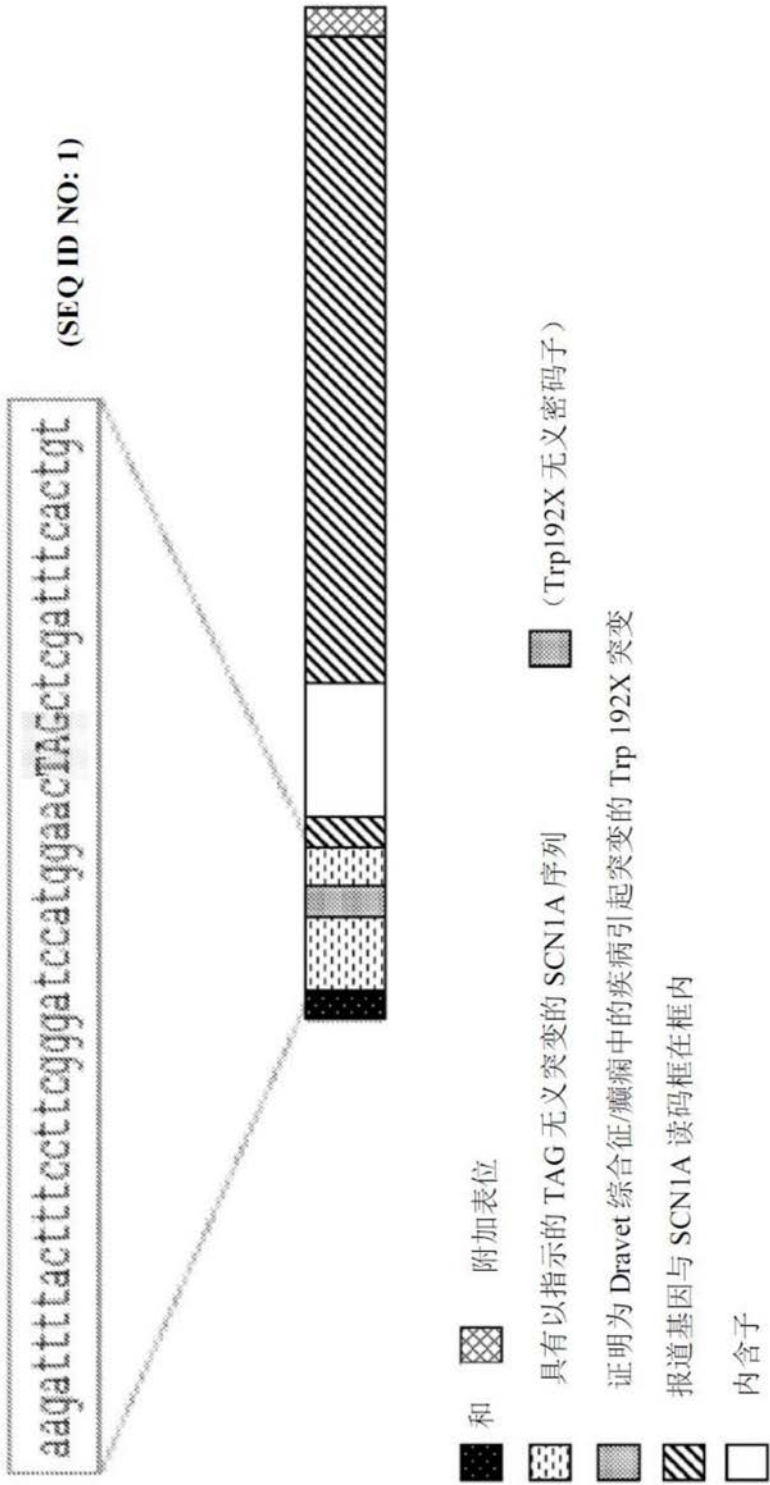


图1

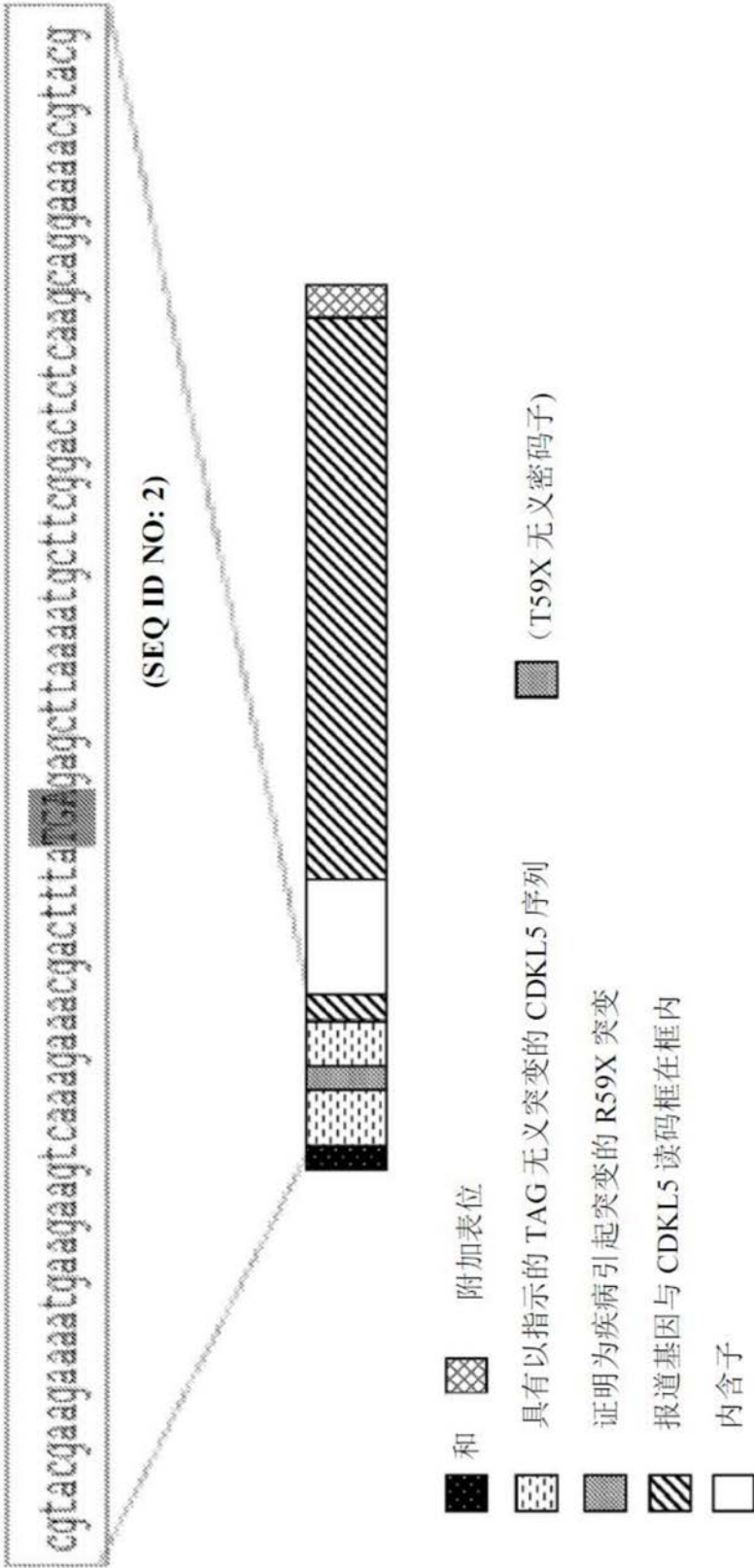


图2

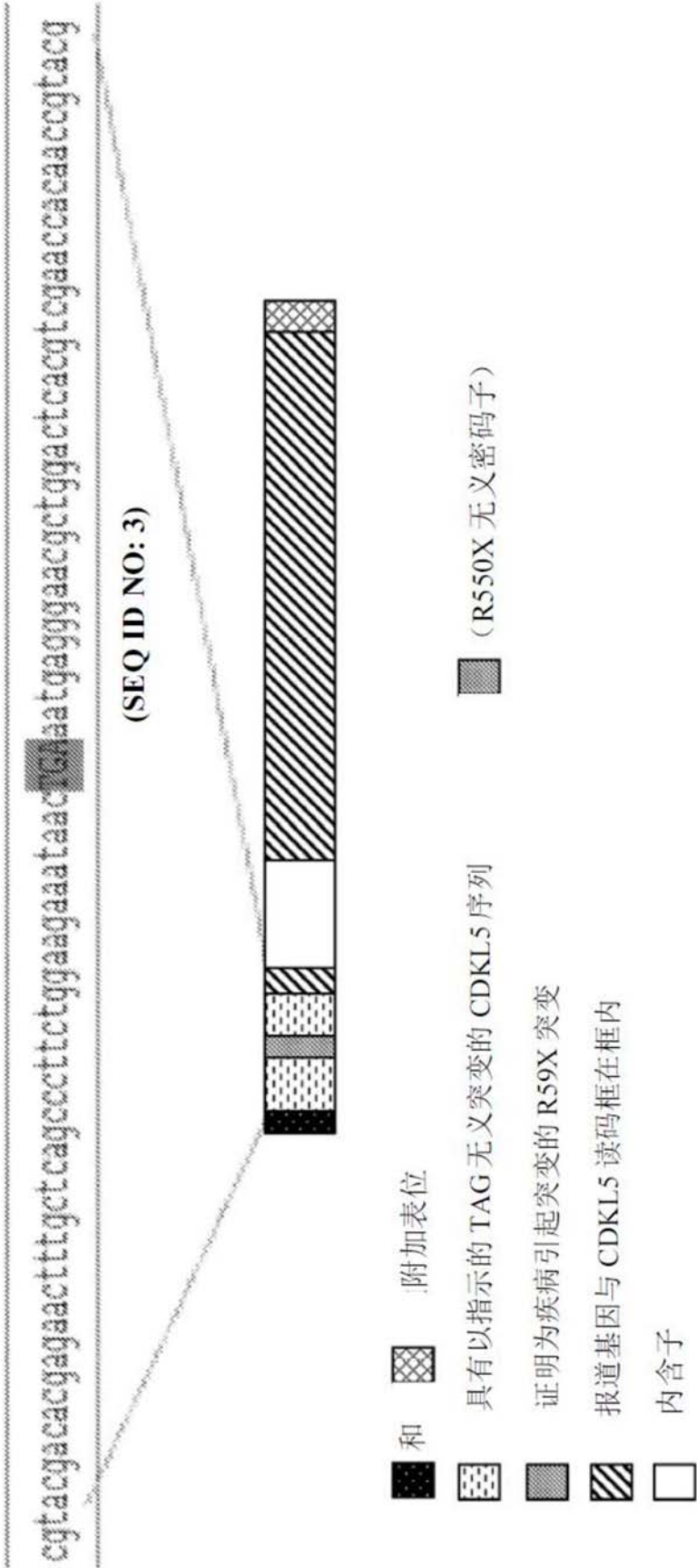


图3

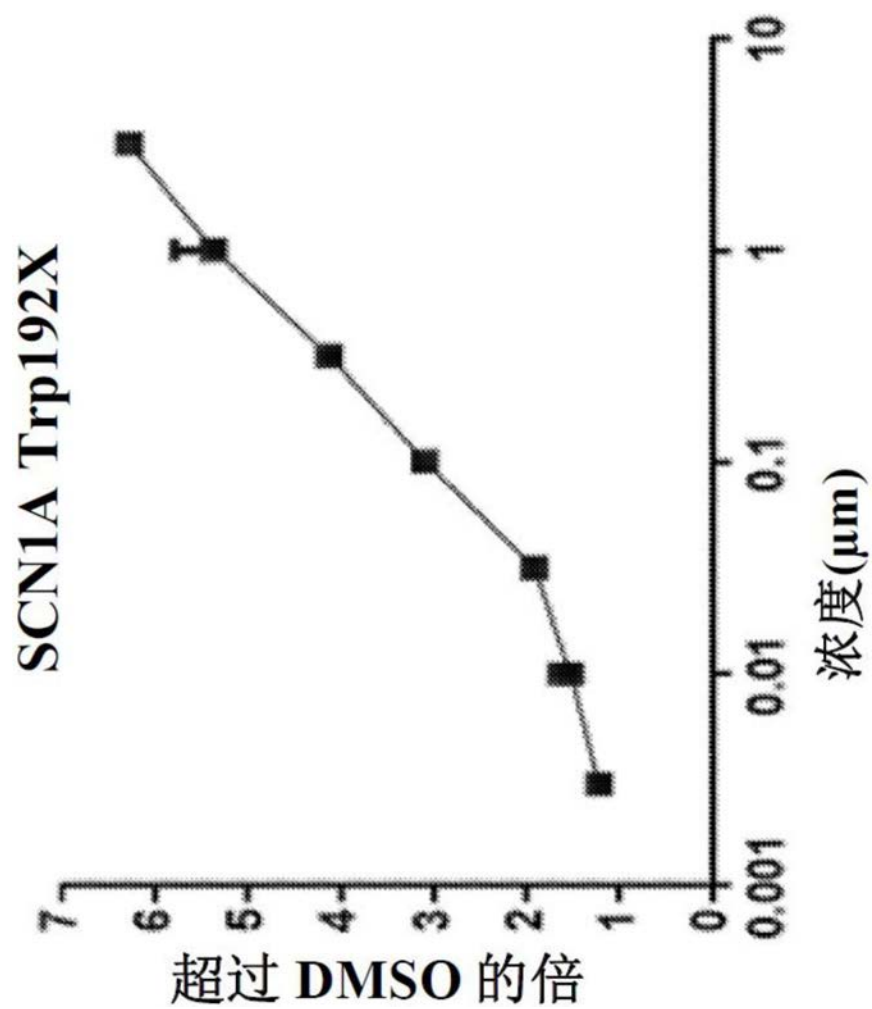


图4

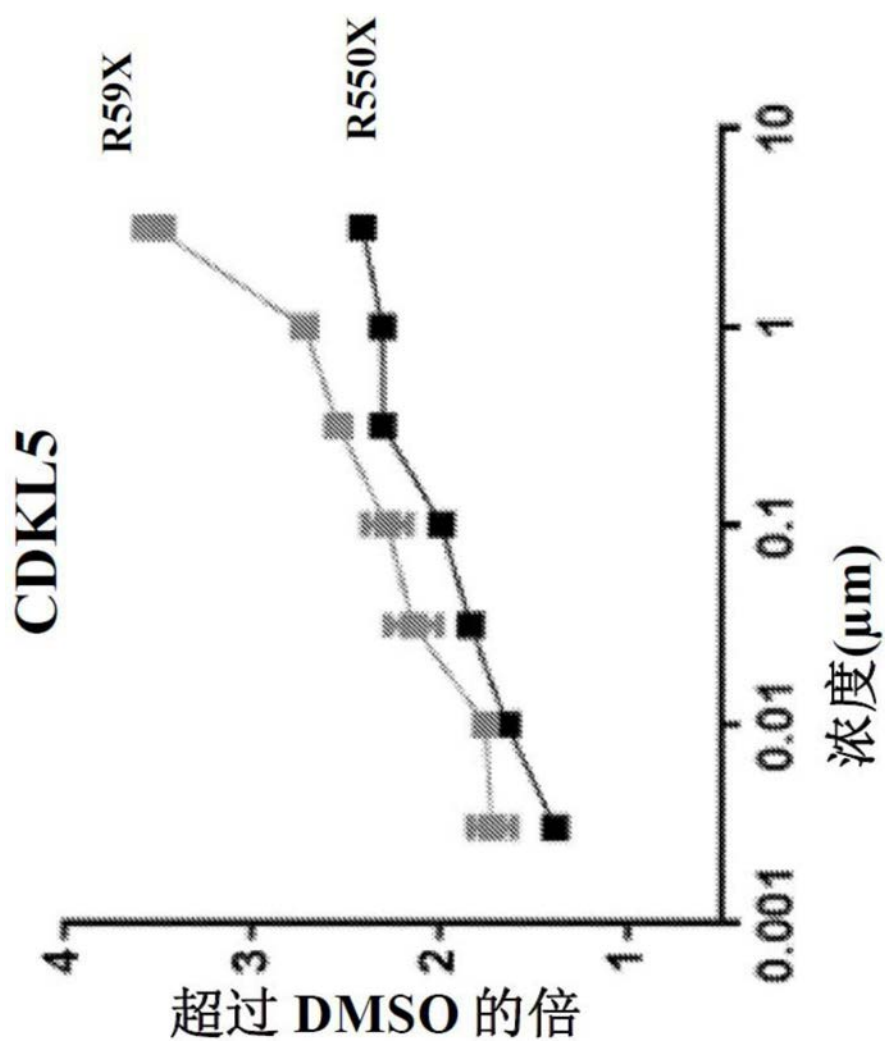


图5

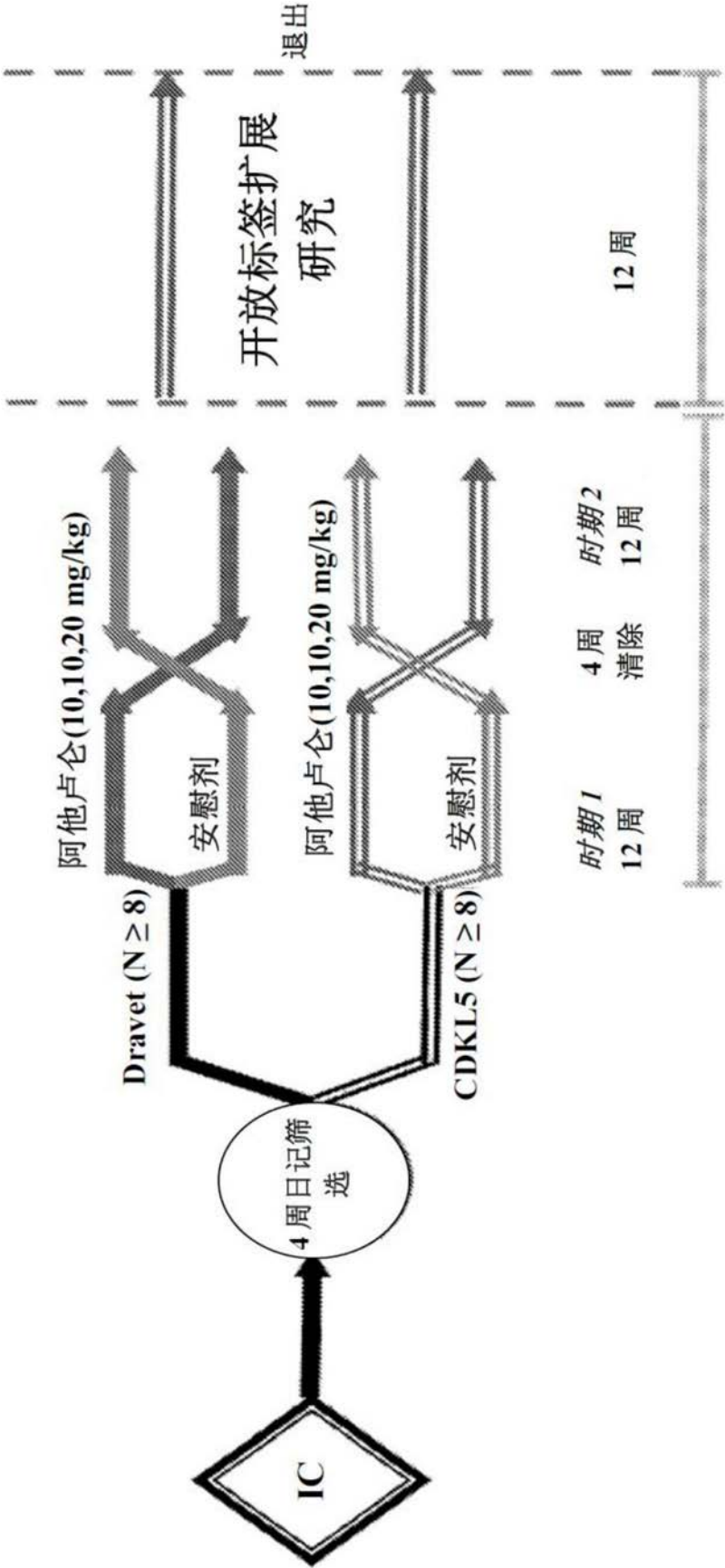


图6