

AZETUKALNER FOR USE IN THE TREATMENT OF DEPRESSION,
ANHEDONIA OR A SEIZURE DISORDER SUCH AS
EPILEPSY IN PEDIATRIC SUBJECTS

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Applications, U.S.S.N. 63/556,681, filed February 22, 2024, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Epilepsy is a common neurological disorder, with a worldwide estimated prevalence of 0.7% of the population (50 million people) (see Hirtz, D. *et al.*, *Neurology*. (2007), 68:326-337). Epilepsy prevalence is highest in young children and older adults and was estimated to be 6.2/1,000 people globally in 2016 (see Aeby *et al.*, *Front Neurol*. (2022), 13:842276; GBD 2016 Epilepsy Collaborators, *Lancet Neurol*. (2019), 18(4):357-75).

[0003] Epilepsy is characterized by abnormal electrical activities in the brain leading to seizures. The pathophysiology of most forms of epilepsy remains poorly understood, but it is known that epileptic seizures arise from an excessively synchronous and sustained firing of a group of neurons. Persistent increase in neuronal excitability is common to all epileptic syndromes. Seizures are classified by the location of onset in the brain (Fisher *et al.* *Epilepsia*. (2017), 58(4):522-30). Focal-onset seizures start in one area or group of cells on one side of the brain, while generalized-onset seizures start on both sides of the brain at the same time. Idiopathic generalized epilepsy (IGE) is a subset of generalized epilepsy, and primary generalized tonic-clonic seizure (PGTCS) is the most common seizure type encountered in IGE. PGTCS may begin in patients as young as 4 years as part of their generalized epilepsy syndrome (Hirsch *et al.* *Epilepsia*. (2022), 63(6):1475-99). A study of the Norwegian pediatric database found 19% of children with epilepsy had PGTCS (Aaberg *et al.* *Epilepsia*. (2017), 58(11):1880-91.).

[0004] Therapeutic strategies in treating epilepsy involve reducing neuronal excitability through various mechanistic pathways. Over the past 2 decades, several new ASMs were developed and marketed to expand the therapeutic spectrum by targeting different mechanisms of action and to improve the benefit-risk profile. However, up to 30% of patients remain refractory to conventional treatment and continue to have uncontrolled seizures (Brown and Adams *Nature*, (1980), 283(5748):673-6; Chen *et al.* *Neurol*, (2018), 75(3):279-86.; Elger and Schmidt, *Epilepsy Behav*. (2008), 12(4):501-39.).

[0005] Another prevalent and difficult to treat disorder, including in pediatric patients, is depression. Approximately 3% of individual ages of 3 and 17 have depression, with about 1 in 5 teens being diagnosed with major depression (Cleveland Clinic, *Depression in Children*, <https://my.clevelandclinic.org/health/diseases/14938-depression-in-children>). However, the study of

investigational medicines for the treatment of pediatric major depressive disorder remains challenging as almost all of industry-sponsored major depressive disorder pediatric trials have failed and no new products have been approved for pediatric patients since 2009.

[0006] Thus, there remains a need for effective treatments of both seizure disorders and depressive disorders in pediatric patients.

SUMMARY

[0007] Azetukalner, having the chemical name *N*-[4-(6-Fluoro-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide, is a small molecule pharmaceutical whose use as a potassium channel modulator is disclosed in U.S. Patent No. 8,293,911 and U.S. Patent No. 8,993,593. Disclosed herein are uses of azetukalner, or a pharmaceutically acceptable salt thereof, for treating seizure disorders, depressive disorders, and anhedonia in pediatric subjects.

[0008] In one aspect, provided herein are methods of treating a seizure disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, azetukalner, or pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject. In some embodiments, the seizure disorder is focal onset epilepsy, photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen's syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, Rett syndrome, multiple sclerosis, Alzheimer's disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures. In certain embodiments, the seizure disorder is generalized epilepsy. In some embodiments, azetukalner is administered. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is administered under fed conditions.

[0009] In another aspect, provided herein are methods of treating a depressive disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, the azetukalner, or pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject. In some embodiments, the depressive disorder is major depressive disorder (MDD), disruptive mood

dysregulation disorder, persistent depressive disorder, bipolar depression, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, or prolonged depressive reaction, or a combination thereof. In certain embodiments, the depressive disorder is major depressive disorder (MDD). In some embodiments, azetukalner is administered. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is administered under fed conditions.

[0010] In another aspect, provided herein are methods of treating anhedonia in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, azetukalner is administered. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is administered under fed conditions.

[0011] These and other aspects of this disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information and procedures and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION

[0012] The present disclosure provides methods of therapy comprising administering azetukalner, or a pharmaceutically acceptable salt thereof, to pediatric subjects, including for treating seizure disorders, depressive disorders, and anhedonia in pediatric subjects.

Definitions

[0013] The following definitions are more general terms used throughout the present application.

[0014] For convenience, certain terms employed herein, in the specification, examples and appended claims are collected herein.

[0015] Unless otherwise required by context, singular terms shall include pluralities, and plural terms shall include the singular.

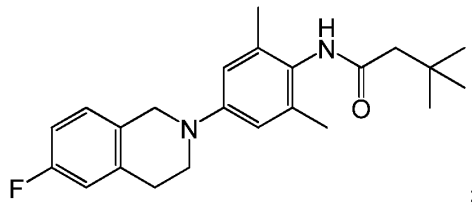
[0016] The language “in some embodiments” and the language “in certain embodiments” are used interchangeably.

[0017] The singular terms “a,” “an,” and “the” include plural references unless the context clearly indicates otherwise. Similarly, the word “or” is intended to include “and” unless the context clearly indicates otherwise.

[0018] “About” and “approximately” shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are

within 20 percent (%), typically, within 10%, or more typically, within 5%, 4%, 3%, 2% or 1% of a given value or range of values.

[0019] “Azetukalner” refers to the compound having the following formula:



and having a chemical name of *N*-[4-(6-fluoro-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide. Preparation of azetukalner and its use as a Kv7.2/Kv7.3 (KCNQ2/3) opener is disclosed in U.S. Patent No. 8,293,911 and U.S. Patent No. 8,993,593. The mechanism of action of azetukalner is different from most known AED's in that it involves potentiation or enhanced opening of the voltage-gated potassium channels Kv7.2 and Kv7.3 (Kv7.2/Kv7.3), which are important in controlling neuronal excitability. azetukalner is used in the methods described herein. azetukalner may be provided as a solid amorphous form or in one or more crystalline forms described in U.S. Patent No. 11,091,441, which is incorporated herein by reference in its entirety. azetukalner may also be provided as the neutral form (depicted above), or a salt thereof, preferably a pharmaceutically acceptable salt thereof.

[0020] As used herein, the term “salt” refers to any and all salts, and encompasses pharmaceutically acceptable salts. Salts include ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of the present disclosure include those derived from inorganic and organic acids and bases. Examples of acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid, or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts

include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0021] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of the present disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0022] “High-fat meal” refers to any food product, solid or liquid, with approximately 50 percent of the total caloric content of the food product coming from fat.

[0023] “High-calorie meal” refers to any meal having approximately 800 to 1000 calories. A representative high-fat, high-calorie meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively.

[0024] “Seizure disorders” refers to seizures and disorders associated with seizures such as focal onset epilepsy, photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy,

Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen's syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures +, Rett syndrome, multiple sclerosis, Alzheimer's disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof. In certain embodiments, the seizure disorder is focal onset epilepsy, also known as partial onset (focal) epilepsy. In some embodiments, the seizure disorder is focal onset seizures, also known as partial onset seizures. In certain embodiments, the seizure disorder is primary generalized tonic-clonic seizures.

[0025] “Depressive disorders” are mood disorders characterized by depressed mood. In certain embodiments, the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar depression, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

[0026] An “effective amount” of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount.

[0027] “Therapeutically effective amount” as used herein refers to an amount of azetukalner, or a pharmaceutically acceptable salt thereof, herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. The therapeutically effective amount is sufficient to treat the indicated disease, disorder, or condition or have the desired stated effect, including ameliorating or preventing the disease, disorder, or condition or one or more mechanisms underlying the disease, disorder, or condition. In certain embodiments, when azetukalner, or a pharmaceutically acceptable salt thereof, is administered for the treatment of a seizure disorder, therapeutically effective amount refers to a range of amounts of azetukalner, or a pharmaceutically acceptable salt thereof, which, upon administration to the subject, treats, ameliorates or prevents a seizure disorder in the subject, or exhibits a detectable therapeutic or

preventative effect in the subject having a seizure disorder. The effect is detected by, for example, a reduction in seizures (frequency) or by the severity of seizures (quality). The precise therapeutically effective amount for a given subject will depend upon the subject's size and health, the nature and extent of the seizure disorder, the presence of any concomitant medications, and other variables known to those of skill in the art. The therapeutically effective amount for a given situation can be determined by routine experimentation and is within the capabilities of the clinician.

[0028] “Treatment” as used herein refers to therapeutic applications associated with administering azetukalner, or a pharmaceutically acceptable salt thereof, that ameliorate the indicated disease, disorder, or condition or one or more underlying mechanisms of said disease, disorder, or condition, including slowing or stopping progression of the disease, disorder or condition or one or more of the underlying mechanisms. Thus, “treatment,” “treating,” and “treat” refer to reversing, alleviating, or inhibiting the progress of a disease, disorder, or condition described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease, disorder, or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence. In certain embodiments, when azetukalner, or a pharmaceutically acceptable salt thereof, is administered for the treatment of a seizure disorder, treatment refers to therapeutic applications to slow or stop progression of a seizure disorder, and/or reversal of a seizure disorder. In certain embodiments, when azetukalner, or a pharmaceutically acceptable salt thereof, is administered for the treatment of a depressive disorder, treatment refers to therapeutic applications to slow or stop progression of a depressive disorder, and/or reversal of a depressive disorder. In certain embodiments, when azetukalner, or a pharmaceutically acceptable salt thereof, is administered for the treatment of anhedonia, treatment refers to therapeutic applications to slow or stop progression of anhedonia, and/or reversal of anhedonia. Reversal of a disorder differs from a therapeutic application which slows or stops a seizure disorder in that with a method of reversing, not only is progression of a seizure disorder completely stopped, cellular behavior is moved to some degree toward a normal state that would be observed in the absence of the seizure disorder.

[0029] “Under fed conditions” refers to the condition of having consumed food during the time period between from about 4 hours prior to the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, to about 4 hours after the administration of azetukalner. The food may be a solid, liquid, or mixture of solid and liquid food with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. In some instances, the food is a meal, such as breakfast, lunch, dinner or, alternatively, baby food (*e.g.*, formula or breast milk). The azetukalner, or a pharmaceutically acceptable salt thereof, may be orally administered to the subject, for example, between about 30 minutes prior to about 2 hours after eating a meal, most

advantageously, the azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered during a meal or within 15 minutes after eating a meal.

[0030] “Under fasted conditions” refers to the condition of not having consumed food during the time period between from at least 4 hours prior to the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, to about 4 hours after administration of azetukalner.

Embodiments

[0031] As provided herein are methods of treating pediatric disorders, including pediatric seizure, depressive disorders, and anhedonia.

[0032] In one aspect, provided herein are methods of treating a seizure disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, an effective amount of azetukalner is administered. In some embodiments, an effective amount of a pharmaceutically acceptable salt thereof of azetukalner is administered.

[0033] In certain embodiments, the disease, disorder, or condition is a seizure disorder. In certain embodiments, the seizure disorder are seizures associated with a disease, disorder, or condition (*e.g.*, wherein seizures/epileptic episodes are symptoms of a disease, disorder, or condition). In some embodiments, the seizure disorder is focal onset epilepsy, photosensitive epilepsy, intractable epilepsy, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, infantile spasms/West’s syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, primary generalized tonic-clonic seizures, seizures associated with self-induced syncope, seizures associated with Angelman syndrome, seizures associated with hypothalamic hamartoma, seizures associated with Rasmussen’s syndrome, seizures associated with neurocutaneous syndromes, seizures associated with tuberous sclerosis complex, seizures associated with Rett syndrome, seizures associated with multiple sclerosis, seizures associated with Alzheimer’s disease, seizures associated with autism, seizures associated with ataxia, seizures associated with hypotonia, or a combination thereof. In some embodiments, the seizure disorder is focal onset epilepsy, photosensitive epilepsy, intractable epilepsy, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, infantile spasms/West’s syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences,

Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, primary generalized tonic-clonic seizures, or a combination thereof. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, may be used to treat seizures associated with self-induced syncope, seizures associated with Angelman syndrome, seizures associated with hypothalamic hamartoma, seizures associated with Rasmussen's syndrome, seizures associated with neurocutaneous syndromes, seizures associated with tuberous sclerosis complex, seizures associated with Rett syndrome, seizures associated with multiple sclerosis, seizures associated with Alzheimer's disease, seizures associated with autism, seizures associated with ataxia, or seizures associated with hypotonia, or a combination thereof. In some embodiments, the seizure disorder is focal onset epilepsy, photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen's syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, Rett syndrome, multiple sclerosis, Alzheimer's disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, or combination thereof. In some embodiments, the seizure disorder is focal onset epilepsy, photosensitive epilepsy, intractable epilepsy, benign rolandic epilepsy, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof.

[0034] In some embodiments, the seizure disorder is focal onset epilepsy, also known as partial onset epilepsy. In some embodiments, the seizure disorder is focal onset seizures, also known as partial onset seizures. In some embodiments, the seizure disorder is photosensitive epilepsy. In some embodiments, the seizure disorder is seizures associated with self-induced syncope. In some

embodiments, the seizure disorder is intractable epilepsy. In some embodiments, the seizure disorder is seizures associated with Angelman syndrome. In some embodiments, the seizure disorder is benign rolandic epilepsy. In some embodiments, the seizure disorder is CDKL5 disorder. In some embodiments, the seizure disorder is childhood and juvenile absence epilepsy. In some embodiments, the seizure disorder is Dravet syndrome. In some embodiments, the seizure disorder is frontal lobe epilepsy. In some embodiments, the seizure disorder is Glut1 deficiency syndrome. In some embodiments, the seizure disorder is seizures associated with hypothalamic hamartoma. In some embodiments, the seizure disorder is infantile spasms/West's syndrome. In some embodiments, the seizure disorder is juvenile myoclonic epilepsy. In some embodiments, the seizure disorder is Landau-Kleffner syndrome. In some embodiments, the seizure disorder is Lennox-Gastaut syndrome (LGS). In some embodiments, the seizure disorder is epilepsy with myoclonic-absences. In some embodiments, the seizure disorder is Ohtahara syndrome. In some embodiments, the seizure disorder is Panayiotopoulos syndrome. In some embodiments, the seizure disorder is PCDH19 epilepsy. In some embodiments, the seizure disorder is progressive myoclonic epilepsies. In some embodiments, the seizure disorder is seizures associated with Rasmussen's syndrome. In some embodiments, the seizure disorder is ring chromosome 20 syndrome. In some embodiments, the seizure disorder is reflex epilepsies. In some embodiments, the seizure disorder is temporal lobe epilepsy. In some embodiments, the seizure disorder is Lafora progressive myoclonus epilepsy. In some embodiments, the seizure disorder is seizures associated with neurocutaneous syndromes. In some embodiments, the seizure disorder is seizures associated with tuberous sclerosis complex. In some embodiments, the seizure disorder is early infantile epileptic encephalopathy. In some embodiments, the seizure disorder is early onset epileptic encephalopathy. In some embodiments, the seizure disorder is generalized epilepsy. In some embodiments, the seizure disorder is generalized epilepsy with febrile seizures. In some embodiments, the seizure disorder is seizures associated with Rett syndrome. In some embodiments, the seizure disorder is seizures associated with multiple sclerosis. In some embodiments, the seizure disorder is seizures associated with Alzheimer's disease. In some embodiments, the seizure disorder is seizures associated with autism. In some embodiments, the seizure disorder is seizures associated with ataxia. In some embodiments, the seizure disorder is seizures associated with hypotonia. In some embodiments, the seizure disorder is paroxysmal dyskinesia. In some embodiments, the seizure disorder is generalized onset seizures. In some embodiments, the seizure disorder is focal onset seizures. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures or focal onset epilepsy. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures, generalized epilepsy, or focal onset epilepsy. In some embodiments, the generalized onset seizures are primary generalized tonic-clonic seizures. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures or focal onset epilepsy.

In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures, focal onset seizures, or focal onset epilepsy.

[0035] In another aspect, provided herein are methods of treating a depressive disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, an effective amount of azetukalner is administered. In some embodiments, an effective amount of a pharmaceutically acceptable salt thereof of azetukalner is administered.

[0036] In some embodiments, the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar depression, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, or prolonged depressive reaction, or a combination thereof. In some embodiments, the depressive disorder is major depressive disorder (MDD). In some embodiments, the depressive disorder is disruptive mood dysregulation disorder. In some embodiments, the depressive disorder is persistent depressive disorder. In some embodiments, the depressive disorder is bipolar depression. In some embodiments, the depressive disorder is postpartum depression. In some embodiments, the depressive disorder is premenstrual dysphoric disorder (PMDD). In some embodiments, the depressive disorder is seasonal affective disorder (SAD). In some embodiments, the depressive disorder is atypical depression. In some embodiments, the depressive disorder is treatment-resistant depression (TRD). In some embodiments, the depressive disorder is depression associated with agitation or anxiety. In some embodiments, the depressive disorder is adjustment disorder with depressed mood. In some embodiments, the depressive disorder is prolonged depressive reaction. In some embodiments, the depressive disorder is major depressive disorder (MDD) or bipolar depression.

[0037] In some embodiments, the depressive disorder is bipolar depression (*i.e.*, the depressive disorder is depression associated with bipolar disorder). In some embodiments, the bipolar disorder is treatment-resistant bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, or bipolar disorder not otherwise specified. In some embodiments, the bipolar disorder is bipolar I disorder, bipolar II disorder, or cyclothymic disorder. In certain embodiments, the depressive disorder is depression associated with bipolar I disorder and/or bipolar II disorder. In certain embodiments, the depressive disorder is depression associated with bipolar I and/or II depression.

[0038] In another aspect, provided herein are methods of treating anhedonia in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject. In some embodiments, an effective amount of azetukalner is administered. In some embodiments, an effective amount of a pharmaceutically acceptable salt thereof of azetukalner is administered.

[0039] In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject. In some embodiments, azetukalner is orally administered to the pediatric subject. In certain embodiments, a pharmaceutically acceptable salt or azetukalner is orally administered to the pediatric subject.

[0040] The methods provided herein are for treating pediatric subjects. In certain embodiments the pediatric subject is at least 1 month of age. In certain embodiments the pediatric subject is at least 2 years of age. In certain embodiments the pediatric subject is at least 6 years of age. In certain embodiments the pediatric subject is at least 10 years of age. In certain embodiments the pediatric subject is at least 12 years of age. In certain embodiments the pediatric subject is at least 12 years of age through 18 years of age. In certain embodiments the pediatric subject is at least 12 years of age and less than 18 years of age. In some embodiments, the pediatric subject is less than 6 years of age. In some embodiments, the pediatric subject is less than 12 years of age. In certain embodiments, the pediatric subject is less than 18 years of age. In some embodiments, the pediatric subject is 6 years of age or younger. In some embodiments, the pediatric subject is 12 years of age or younger. In certain embodiments, the pediatric subject is 18 years of age or younger. In certain embodiments, the pediatric subject is at least 1 month of age through 18 years of age. In certain embodiments, the pediatric subject is at least 1 month of age and less than 18 years of age. In certain embodiments, the pediatric subject is at least 2 years of age through 18 years of age. In certain embodiments, the pediatric subject is at least 2 years of age and less than 18 years of age. In certain embodiments, the pediatric subject is at least 2 years of age through 6 years of age. In certain embodiments, the pediatric subject is at least 2 years of age and less than 6 years of age. In certain embodiments, the pediatric subject is at least 6 years of age through 12 years of age. In certain embodiments, the pediatric subject is at least 6 years of age and less than 12 years of age. In certain embodiments, the pediatric subject is at least 6 years of age through 18 years of age. In certain embodiments, the pediatric subject is at least 6 years of age and less than 18 years of age. In certain embodiments, the pediatric subject is at least 10 years of age through 18 years of age. In certain embodiments, the pediatric subject is at least 10 years of age and less than 18 years of age.

[0041] In some embodiments, the pediatric subject is at least 12 years of age and less than 18 years of age; less than 12 years of age; or at least 6 years of age and less than 12 years of age. In some embodiments, the pediatric subject is: at least 12 years of age and less than 18 years of age; less than 12 years of age; or at least 6 years of age and less than 12 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is: at least 12 years of age and less than 18 years of age; less than 12 years of age; or at least 6 years of age and less than 12 years of age.

[0042] In some embodiments, the pediatric subject is at least 12 years of age through 18 years of age; through 12 years of age; or at least 6 years of age through 12 years of age. In some embodiments, the pediatric subject is: at least 12 years of age through 18 years of age; through 12 years of age; or at

least 6 years of age through 12 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is: at least 12 years of age through 18 years of age; through 12 years of age; or at least 6 years of age through 12 years of age.

[0043] In some embodiments, the pediatric subject is at least 12 years of age and less than 18 years of age; at least 6 years of age and less than 12 years of age; or at least 2 years of age and less than 6 years of age. In some embodiments, the pediatric subject is at least 12 years of age and less than 18 years of age. In some embodiments, the pediatric subject is at least 6 years of age and less than 12 years of age. In some embodiments, the pediatric subject is at least 2 years of age and less than 6 years of age.

[0044] In some embodiments, the pediatric subject is at least 12 years of age through 18 years of age; at least 6 years of age through 12 years of age; or at least 2 years of age through 6 years of age. In some embodiments, the pediatric subject is at least 12 years of age through 18 years of age. In some embodiments, the pediatric subject is at least 6 years of age through 12 years of age. In some embodiments, the pediatric subject is at least 2 years of age through 6 years of age.

[0045] In some embodiments, the pediatric subject being treated for a seizure disorder is: at least 12 years of age and less than 18 years of age; at least 6 years of age and less than 12 years of age; or at least 2 years of age and less than 6 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 12 years of age and less than 18 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 6 years of age and less than 12 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 2 years of age and less than 6 years of age.

[0046] In some embodiments, the pediatric subject being treated for a seizure disorder is: at least 12 years of age through 18 years of age; at least 6 years of age through 12 years of age; or at least 2 years of age through 6 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 12 years of age through 18 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 6 years of age through 12 years of age. In some embodiments, the pediatric subject being treated for a seizure disorder is at least 2 years of age through 6 years of age.

[0047] In some embodiments, the pediatric subject being treated for focal onset seizures is: at least 12 years of age and less than 18 years of age; at least 6 years of age and less than 12 years of age; or at least 2 years of age and less than 6 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 12 years of age and less than 18 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 6 years of age and less than 12 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 2 years of age and less than 6 years of age.

[0048] In some embodiments, the pediatric subject being treated for focal onset seizures is: at least 12 years of age through 18 years of age; at least 6 years of age through 12 years of age; or at least 2 years of age through 6 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 12 years of age through 18 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 6 years of age through 12 years of age. In some embodiments, the pediatric subject being treated for focal onset seizures is at least 2 years of age through 6 years of age.

[0049] In some embodiments, the pediatric subject being treated for a depressive disorder is at least 10 years of age and less than 18 years of age. In some embodiments, the pediatric subject being treated for bipolar depression is at least 10 years of age and less than 18 years of age.

[0050] In some embodiments, the pediatric subject being treated for a depressive disorder is at least 10 years of age through 18 years of age. In some embodiments, the pediatric subject being treated for bipolar depression is at least 10 years of age through 18 years of age.

[0051] The methods disclosed herein may involve orally administering azetukalner under fed or fasted conditions. In certain embodiments, azetukalner is orally administered under fed conditions. In some embodiments, azetukalner is orally administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food. In certain embodiments, azetukalner is orally administered to the pediatric subject no more than 4 hours after the pediatric subject has consumed food. In some embodiments, azetukalner is orally administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food to no more than 4 hours after the pediatric subject has consumed food. In some embodiments, azetukalner is orally administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food. In certain embodiments, azetukalner is orally administered to the pediatric subject no more than 2 hours after the pediatric subject has consumed food. In some embodiments, azetukalner is orally administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food to no more than 2 hours after the pediatric subject has consumed food. In some embodiments, the oral administration of azetukalner to the subject is from 30 minutes prior to consuming food to no more than 2 hours after consuming food. In some aspects, the oral administration occurs from about 60, 45, 30, 25, 20, 15, 10, or 5 minutes prior to consuming food to about 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, or 240 minutes after consuming food. In some aspects, azetukalner is orally administered concurrently with the consumption of food, or up to 15 minutes after having consumed food.

[0052] The methods disclosed herein may involve orally administering azetukalner, or a pharmaceutically acceptable salt thereof, under fed or fasted conditions. In certain embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered under fed conditions. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally

administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food. In certain embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject no more than 4 hours after the pediatric subject has consumed food. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food to no more than 4 hours after the pediatric subject has consumed food. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food. In certain embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject no more than 2 hours after the pediatric subject has consumed food. In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food to no more than 2 hours after the pediatric subject has consumed food. In some embodiments, the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, to the subject is from 30 minutes prior to consuming food to no more than 2 hours after consuming food. In some aspects, the oral administration occurs from about 60, 45, 30, 25, 20, 15, 10, or 5 minutes prior to consuming food to about 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, or 240 minutes after consuming food. In some aspects, azetukalner, or a pharmaceutically acceptable salt thereof, is orally administered concurrently with the consumption of food, or up to 15 minutes after having consumed food.

[0053] In certain embodiments, the methods comprising oral administration are not dependent on the type of food consumed by the subject, *e.g.*, the food may include a high-fat or high-calorie meal or may not. In some embodiments of the present disclosure, the food product is a high-fat, high calorie meal. Representative high-fat meals have approximately 50% of total caloric content of the meal coming from fat and representative high-calorie meals have approximately 800 to 1000 calories. A representative meal may have approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

[0054] In certain embodiments, the methods provided herein comprise administering about 1 mg to about 400 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 2 mg to about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 2 mg to about 100 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 5 mg to about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 10 mg to about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein

comprise administering: about 2 mg to about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 2 mg to about 100 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 5 mg to about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or about 10 mg to about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering at least about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering at least about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering at least about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering at least about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering at least about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering at least about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering at least about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering: at least about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof; at least about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof; at least about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof; at least about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof; at least about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or at least about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 5 mg, about 10 mg, about 15 mg, about 20 mg, or about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering: about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof; about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

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about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0055] In certain embodiments, the effective amount is about 1 mg to about 400 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is about 2 mg to about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is about 2 mg to about 100 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 5 mg to about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is at least about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is at least about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is at least about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is at least about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is at least about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is at least about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is at least about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective amount is about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 2.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 5.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 7.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain

embodiments, the effective amount is about 10.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 12.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 15.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 17.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 20.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 22.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 25.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 27.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 30.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 32.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 35.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 37.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 40.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 42.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 45.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 47.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 50.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0056] In certain embodiments, the methods described herein comprise orally administering about 1 mg to about 400 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering about 2 mg to about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering about 2 mg to about 100 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 5 mg to about 50 mg of azetukalner, or a pharmaceutically

acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering at least about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering at least about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering at least about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering at least about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering at least about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering at least about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering at least about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some embodiments, the methods described herein comprise orally administering about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 2.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 5.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 7.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 10.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 12.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 15.0 mg of

azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 17.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 20.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 22.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 25.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 27.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 30.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 32.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 35.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 37.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 40.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 42.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 45.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 47.5 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 50.0 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In certain embodiments, the methods described herein comprise orally administering about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day.

[0057] In some embodiments, the methods described herein comprise orally administering about 5 to about 1000 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day, such as

about 5 to about 500 mg or about 5 to about 250 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. For example, the method can include orally administering about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, or about 1000 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day. In some aspects, the oral administration includes orally administering about 10-200 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day, such as about 5, about 10, about 15, about 20, about 25, about 30, about 35, or about 40 mg to about 75, about 100, about 125, about 150, about 175, or about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day, including about 20 to about 150 mg per day. In some aspects, the oral administration includes about 50, about 75, about 100, or about 125 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day, such as about 100 mg per day.

[0058] In some embodiments, the methods provided herein comprise administering about 0.05-2.0 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 0.1-1.0 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise administering about 0.2-0.6 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 0.3-0.5 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods provided herein comprise at most 0.6 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 0.10 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein comprise administering about 0.15 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods provided herein

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[0059] In some embodiments, the effective amount is about 0.05-2.0 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is about 0.1-

[illegible]

[0060] In one embodiment, azetukalner, or a pharmaceutically acceptable salt thereof, is provided in a dosage unit form suitable for oral administration. azetukalner, or a pharmaceutically acceptable salt thereof, is present in the dosage unit form at a level ranging from about 0.05 mg/kg to about 2.0 mg/kg. More specific representative levels include about 0.05 mg/kg, about 0.10 mg/kg, about 0.20 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.80 mg/kg, about 0.90 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg and about 2.0 mg/kg. In some aspects, the methods include orally administering about 0.1-1.0 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof. In some aspects, the methods include orally administering about 0.2-0.5 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0061] In certain embodiments, the effective amount is sufficient to reduce the severity of seizures, the frequency of seizures, or both. In certain embodiments, the effective amount is sufficient to reduce the severity of seizures. In certain embodiments, the effective amount is sufficient to reduce the frequency of seizures.

[0062] In some embodiments, the body mass of the pediatric subject is less than 30 kg (*e.g.*, between 10 kg and 30 kg, or between 15 kg and 30 kg, or between 20 kg and 30 kg). In some embodiments, the pediatric subject has a body mass less than 30 kg. In certain embodiments, the pediatric subject has a body mass less than 30 kg is orally administered about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass less than 30 kg and is orally administered about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass less than 30 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass less than 30 kg and is orally administered about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass less than 30 kg and is treated by oral administration of about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the body mass of the pediatric subject is at least about 30 kg. In some embodiments, the pediatric subject is less than about 45 kg. In some embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg. In certain embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable

salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is treated by oral administration of about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0064] In some embodiments, the body mass of the pediatric subject is at least about 35 kg. In some embodiments, the pediatric subject is less than about 45 kg. In some embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg. In certain embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is orally administered about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is orally administered about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is orally administered about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In certain embodiments, the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is treated by oral administration of about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0065] In certain embodiments, the pediatric subject has a body mass of at least about 45 kg. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is orally administered about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is orally administered about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is orally administered about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is orally administered about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject has a body mass of at least about 45 kg and is treated by oral administration of about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0066] In certain instances, the daily doses of azetukalner, or a pharmaceutically acceptable salt thereof, are orally administered as multiple doses per day, such as in two, three, four or five doses per day. For Example, a daily dose of 100 mg, maybe administered in four 25 mg doses throughout the day.

[0067] In some embodiments, azetukalner, or a pharmaceutically acceptable salt thereof, is administered once daily. In some embodiments, the above daily doses of azetukalner, or a pharmaceutically acceptable salt thereof, are orally administered as a single dose. For example, about 5, 10, 15, 20, 25, or 30 mg to about 50, 65, 75, 100, 125, or 150 mg of azetukalner, or a pharmaceutically acceptable salt thereof, per day can be orally administered as a single dose, including about 10-25 mg, about 10-30 mg, and about 10-40 mg per day as a single dose, such as about 10-25 mg per day as a single dose.

[0068] In certain embodiments, the methods described herein, when using the daily dosing disclosed herein, achieve a steady state for azetukalner, or a pharmaceutically acceptable salt thereof, within 6 to 9 days, such as in about 1 week.

[0069] In embodiments, the methods provided herein enhance opening of a Kv7 potassium channel, such as one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5. In certain instances, the method is selective for enhancing the opening of a Kv7 potassium channel selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5 over Kv7.1. In some embodiments, the method is selective for Kv7.2, optionally over Kv7.1. In other embodiments, the method is selective for Kv7.3, optionally over Kv7.1. In yet other embodiments, the method is selective for Kv7.4, optionally over Kv7.1. In yet further other embodiments, the method is selective for Kv7.5, optionally over Kv7.1. In certain embodiments, the method is selective for Kv7.2 and Kv7.3, optionally over Kv7.1.

[0070] In certain embodiments, the methods described herein comprise administering azetukalner, or a pharmaceutically acceptable salt thereof, in the form of a pharmaceutically acceptable composition that comprises azetukalner, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. The amount of azetukalner, or a pharmaceutically acceptable salt thereof, included in these compositions correspond to one or more of the amounts described herein. In some embodiments, the compositions are a unit dose.

[0071] Examples of pharmaceutically acceptable oral compositions that comprise azetukalner, or a pharmaceutically acceptable salt thereof, include solid formulations (such as tablets, capsules, lozenges, dragées, granules, powders, multi-particulates, and films) and liquid formulations (such as aqueous solutions, elixirs, tinctures, suspensions, and dispersions). In one embodiment, a pharmaceutically acceptable oral composition of azetukalner, or a pharmaceutically acceptable salt thereof, includes a pediatric suspension or granulate. All above-noted amounts of azetukalner, or a pharmaceutically acceptable salt thereof, may be included in such formulations, *e.g.*, a capsule comprising 5, 10, 15, 10, 25, 30, or 35 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

[0072] In another embodiment, kits are provided for oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, for treating pediatric seizure disorders. Such kits comprise a plurality of oral dosage unit forms of azetukalner, or a pharmaceutically acceptable salt thereof, in

combination with instructions for orally administering of azetukalner, or a pharmaceutically acceptable salt thereof, to a pediatric subject.

[0073] In certain embodiments herein, wherein a comparison is made involving a pediatric subject orally administered azetukalner, or a pharmaceutically acceptable salt thereof, under fasted conditions, an analogous comparison can be made involving a pediatric subject who has not consumed food during a time period between about 4 hours prior to the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, to about 4 hours after the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, such as between about 4, 3, 2, 1.5, 1, or 0.5 hours prior to the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof, to about 0.5, 1, 1.5, 2, 3, or 4 hours after the oral administration of azetukalner, or a pharmaceutically acceptable salt thereof.

[0074] Disclosed herein are the following numbered embodiments:

[0075] Embodiment 1. A method of treating a seizure disorder in a pediatric subject in need thereof, comprising administering an effective amount of Compound A, or a pharmaceutically acceptable salt thereof, to the pediatric subject; wherein Compound A is *N*-[4-(6-fluoro-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide.

[0076] Embodiment 2. The method of embodiment 1, wherein Compound A is administered to the pediatric subject.

[0077] Embodiment 3. The method of embodiment 1 or embodiment 2, wherein the seizure disorder is focal onset epilepsy, photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen's syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, Rett syndrome, multiple sclerosis, Alzheimer's disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof.

[0078] Embodiment 4. The method of embodiment 1 or embodiment 2, wherein the seizure disorder is primary generalized tonic-clonic seizures.

[0079] Embodiment 5. The method of embodiment 1 or embodiment 2, wherein the seizure disorder is generalized epilepsy.

[0080] Embodiment 6. A method of treating a depressive disorder in a pediatric subject in need thereof, comprising administering an effective amount of Compound A, or a pharmaceutically acceptable salt thereof, to the pediatric subject; wherein Compound A is *N*-[4-(6-fluoro-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide.

[0081] Embodiment 7. The method of embodiment 6, wherein Compound A is administered to the pediatric subject.

[0082] Embodiment 8. The method of embodiment 6 or 7, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, or prolonged depressive reaction, or a combination thereof.

[0083] Embodiment 9. The method of embodiment 6 or 7, wherein the depressive disorder is major depressive disorder (MDD).

[0084] Embodiment 10. The method of any one of embodiments 1-9, wherein the Compound A, or pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject.

[0085] Embodiment 11. The method of any one of embodiments 1-10, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered under fed conditions.

[0086] Embodiment 12. The method of any one of embodiments 1-11, wherein the pediatric subject is at least 12 years of age and less than 18 years of age.

[0087] Embodiment 13. The method of any one of embodiments 1-11, wherein the pediatric subject is less than 12 years of age.

[0088] Embodiment 14. The method of any one of embodiments 1-13, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food.

[0089] Embodiment 15. The method of any one of embodiments 1-14, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours after the pediatric subject has consumed food.

[0090] Embodiment 16. The method of any one of embodiments 1-15, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food to no more than 4 hours after the pediatric subject has consumed food.

[0091] Embodiment 17. The method of any one of embodiments 1-16, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food.

[0092] Embodiment 18. The method of any one of embodiments 1-17, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 2 hours after the pediatric subject has consumed food.

[0093] Embodiment 19. The method of any one of embodiments 1-18, wherein the Compound A, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food to no more than 2 hours after the pediatric subject has consumed food.

[0094] Embodiment 20. The method of any one of embodiments 1-19, comprising administering about 2 mg to about 200 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[0095] Embodiment 21. The method of any one of embodiments 1-20, comprising administering about 2 mg to about 100 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[0096] Embodiment 22. The method of any one of embodiments 1-21, comprising administering about 5 mg to about 50 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[0097] Embodiment 23. The method of any one of embodiments 1-22, comprising administering at least about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[0098] Embodiment 24. The method of any one of embodiments 1-23, comprising administering at least about 5 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[0099] Embodiment 25. The method of any one of embodiments 1-23, comprising administering at least about 10 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00100] Embodiment 26. The method of any one of embodiments 1-23, comprising administering at least about 15 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00101] Embodiment 27. The method of any one of embodiments 1-23, comprising administering at least about 20 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00102] Embodiment 28. The method of any one of embodiments 1-23, comprising administering at least about 25 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00103] Embodiment 29. The method of any one of embodiments 1-23, comprising administering at least about 30 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00104] Embodiment 30. The method of any one of embodiments 1-23, comprising administering about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00105] Embodiment 31. The method of any one of embodiments 1-23, comprising administering about 5 mg of Compound A, or a pharmaceutically acceptable salt thereof.

[00106] Embodiment 32. The method of any one of embodiments 1-23, comprising administering about 10 mg of Compound A, or a pharmaceutically acceptable salt thereof.

- [00107] Embodiment 33. The method of any one of embodiments 1-23, comprising administering about 15 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00108] Embodiment 34. The method of any one of embodiments 1-23, comprising administering about 20 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00109] Embodiment 35. The method of any one of embodiments 1-23, comprising administering about 25 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00110] Embodiment 36. The method of any one of embodiments 1-23, comprising administering about 30 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00111] Embodiment 37. The method of any one of embodiments 1-36, comprising administering about 0.05-2.0 mg/kg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00112] Embodiment 38. The method of any one of embodiments 1-37, comprising administering about 0.1-1.0 mg/kg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00113] Embodiment 39. The method of any one of embodiments 1-38, comprising administering about 0.2-0.6 mg/kg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00114] Embodiment 40. The method of any one of embodiments 1-39, comprising administering about 0.3-0.5 mg/kg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00115] Embodiment 41. The method of any one of embodiments 1-36, comprising administering at most 0.6 mg/kg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00116] Embodiment 42. The method of any one of embodiments 1-36, wherein the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg.
- [00117] Embodiment 43. The method of embodiment 42, wherein the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 15 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00118] Embodiment 44. The method of any one of embodiments 1-36, wherein the pediatric subject has a body mass of at least about 45 kg.
- [00119] Embodiment 45. The method of embodiment 44, wherein the pediatric subject has a body mass of at least about 45 kg and is orally administered about 25 mg of Compound A, or a pharmaceutically acceptable salt thereof.
- [00120] Embodiment 46. The method of any one of embodiments 1-45, wherein Compound A, or a pharmaceutically acceptable salt thereof, is administered once daily.
- [00121] Additional embodiments and examples of the present disclosure are described herein. These embodiments and examples are illustrative and should not be construed as limiting the scope of the claimed invention.

EXAMPLES

[00122] In order that the present disclosure may be more fully understood, the following examples are set forth. The examples described in this Application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1

[00123] A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to being conducted to evaluate the clinical efficacy, safety, and tolerability of azetukalner being administered as adjunctive treatment in pediatric subjects diagnosed with generalized epilepsy and experiencing probable or possible primary generalized tonic-clonic seizures (PGTCS) (with or without other subtypes of generalized seizures), and taking 1 to 3 anti-seizure medications (ASMs). Eligible subjects will be randomly assigned 1:1 to azetukalner or placebo: subjects aged ≥ 18 years will receive azetukalner 25 mg or placebo, and subjects aged ≥ 12 years and < 18 years will receive either azetukalner 15 mg, 25 mg, or placebo. Randomization will be stratified based on region, age group, and background use of CYP3A4-inducer ASMs. Eligible subjects will have up to 9.5 weeks durations to assess the baseline frequency of seizures, followed by a double-blind treatment period (DBP) where subjects will receive 12 weeks of blinded treatment. During the DBP, subjects will be instructed to orally take azetukalner or placebo once daily with an evening meal. Subjects who complete the 12-week DBP will have the opportunity to enroll in a separate open-label-extension (OLE) study for continued treatment with azetukalner. Subjects who do not enroll in the OLE will enter an 8 week post-treatment follow-up period. Primary endpoints being investigated include median percent change (MPC) in monthly (28 days) seizure (*e.g.*, PGTCS) frequency from baseline through the DBP for azetukalner versus placebo. Secondary endpoints being investigated include proportion of subjects experiencing $\geq 50\%$ reduction in monthly (28 days) seizure (*e.g.*, PGTCS) frequency from baseline through the DBP for azetukalner versus placebo, proportion of subjects experiencing seizure (*e.g.*, PGTCS) freedom from baseline through the DBP for azetukalner versus placebo, proportion of subjects experiencing “at least much improved” (including “much” and “very much improved”) in the Patient Global Impression of Change (PGI-C) (*e.g.*, at week 12), and severity and frequency of adverse events.

[00124] Other assessments may include, for example, evaluating the rating/score, such as change in the rating/score (*e.g.*, overtime from baseline), for Patient Global Impression of Severity (PGI-S), Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), and/or 48-Item Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48).

Example 2

[00125] To assess the clinical efficacy, safety, and tolerability of azetukalner in treating a depressive disorder in a pediatric patient, various clinical assessments could be used to compare patients treated with azetukalner versus placebo, such as, for example, evaluating the rating/score, such as change in the rating/score (*e.g.*, overtime from baseline), for Children's Depression Rating Scale – Revised (CDRS-R) and Clinical Global Impression of Severity (CGI-S), and severity and frequency of adverse events..

INCORPORATION BY REFERENCE

[00126] The present application refers to various issued patent, published patent applications, scientific journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

EQUIVALENTS AND SCOPE

[00127] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The present disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The present disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00128] Furthermore, the present disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the present disclosure, or aspects of the present disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the present disclosure or aspects of the present disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in *haec verba* herein. It is also noted that the terms “comprising” and

“containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the present disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00129] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the present disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00130] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

1. A method of treating a seizure disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject.
2. The method of claim 1, wherein azetukalner is administered to the pediatric subject.
3. The method of claim 1 or claim 2, wherein the seizure disorder is focal onset epilepsy, photosensitive epilepsy, intractable epilepsy, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, infantile spasms/West's syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy, generalized epilepsy with febrile seizures, paroxysmal dyskinesia, generalized onset seizures, focal onset seizures, or primary generalized tonic-clonic seizures, seizures associated with self-induced syncope, seizures associated with Angelman syndrome, seizures associated with hypothalamic hamartoma, seizures associated with Rasmussen's syndrome, seizures associated with neurocutaneous syndromes, seizures associated with tuberous sclerosis complex, seizures associated with Rett syndrome, seizures associated with multiple sclerosis, seizures associated with Alzheimer's disease, seizures associated with autism, seizures associated with ataxia, seizures associated with hypotonia, or a combination thereof.
4. The method of claim 1 or claim 2:
wherein the seizure disorder is primary generalized tonic-clonic seizures;
wherein the seizure disorder is generalized epilepsy; or
wherein the seizure disorder is focal onset epilepsy
5. A method of treating a depressive disorder in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject.

6. The method of claim 5, wherein azetukalner is administered to the pediatric subject.
7. The method of claim 5 or 6, wherein the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar depression, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, or prolonged depressive reaction, or a combination thereof.
8. The method of any one of claims 5-7:
wherein the depressive disorder is major depressive disorder (MDD); or
wherein the depressive disorder is bipolar depression.
9. A method of treating anhedonia in a pediatric subject in need thereof, comprising administering an effective amount of azetukalner, or a pharmaceutically acceptable salt thereof, to the pediatric subject.
10. The method of claim 9, wherein azetukalner is administered to the pediatric subject.
11. The method of any one of claims 1-10, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is orally administered to the pediatric subject.
12. The method of any one of claims 1-11, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered under fed conditions.
13. The method of any one of claims 1-12, wherein the pediatric subject is at least 1 month of age.
14. The method of any one of claims 1-13, wherein the pediatric subject is:
at least 12 years of age and less than 18 years of age;
at least 6 years of age and less than 12 years of age; or
at least 2 years of age and less than 6 years of age.
15. The method of any one of claims 1-13:
wherein the pediatric subject is at least 12 years of age and less than 18 years of age;
wherein the pediatric subject is less than 12 years of age; or

wherein the pediatric subject is at least 6 years of age and less than 12 years of age.

16. The method of any one of claims 1-13, wherein the pediatric subject is at least 10 years of age and less than 18 years of age.

17. The method of any one of claims 1-16, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food.

18. The method of any one of claims 1-16, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours after the pediatric subject has consumed food.

19. The method of any one of claims 1-18, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 4 hours prior to the pediatric subject consuming food to no more than 4 hours after the pediatric subject has consumed food.

20. The method of any one of claims 1-19, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food.

21. The method of any one of claims 1-20, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 2 hours after the pediatric subject has consumed food.

22. The method of any one of claims 1-21, wherein the azetukalner, or pharmaceutically acceptable salt thereof, is administered to the pediatric subject no more than 30 minutes prior to the pediatric subject consuming food to no more than 2 hours after the pediatric subject has consumed food.

23. The method of any one of claims 1-22:
comprising administering about 2 mg to about 200 mg of azetukalner, or a pharmaceutically acceptable salt thereof;
comprising administering about 2 mg to about 100 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering about 5 mg to about 50 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or

comprising administering about 10 mg to about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

24. The method of any one of claims 1-23, comprising administering at least about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

25. The method of any one of claims 1-24:

comprising administering at least about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering at least about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering at least about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering at least about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering at least about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or

comprising administering at least about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

26. The method of any one of claims 1-25, comprising administering about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

27. The method of any one of claims 1-26:

comprising administering about 5 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering about 10 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering about 20 mg of azetukalner, or a pharmaceutically acceptable salt thereof;

comprising administering about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof; or

comprising administering about 30 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

28. The method of any one of claims 1-27, comprising administering about 0.05-2.0 mg/kg of azetukalner, or a pharmaceutically acceptable salt thereof.

29. The method of any one of claims 1-28, wherein the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg.

30. The method of claim 29, wherein the pediatric subject has a body mass of at least about 30 kg and less than about 45 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

31. The method of any one of claims 1-28, wherein the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg.

32. The method of claim 31, wherein the pediatric subject has a body mass of at least about 35 kg and less than about 45 kg and is orally administered about 15 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

33. The method of any one of claims 1-28, wherein the pediatric subject has a body mass of at least about 45 kg.

34. The method of claim 33, wherein the pediatric subject has a body mass of at least about 45 kg and is orally administered about 25 mg of azetukalner, or a pharmaceutically acceptable salt thereof.

35. The method of any one of claims 1-28, wherein the pediatric subject has a body mass of less than 30 kg.

36. The method of claim 35, wherein the pediatric subject has a body mass of less than 30 kg and is orally administered about 15 mg of azetukalner, or pharmaceutically acceptable salt thereof.

37. The method of any one of claims 1-36, wherein azetukalner, or a pharmaceutically acceptable salt thereof, is administered once daily.