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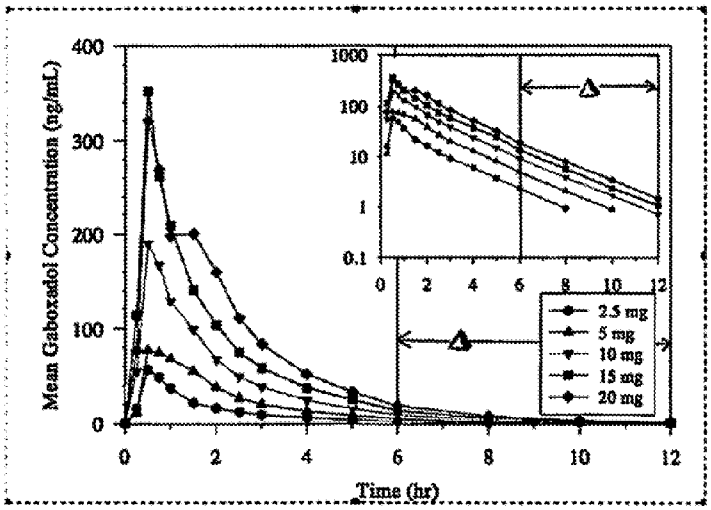

FIG. 1

(57) Abstract: Methods of treating developmental disorders such as Angelman syndrome, Fragile X syndrome, Fragile X-associated tremor/ataxia syndrome (FXTAS), Autistic Spectrum Disorder, Autism, Asperger's syndrome, pervasive developmental disorder, Childhood Disintegrative Disorder, Rett syndrome, Lanau-Kleffner Syndrome, Prader-Willi Syndrome, Tardive Dyskinesia, and/or Williams Syndrome with gaboxadol or a pharmaceutically acceptable salt thereof are provided. The methods provide therapeutic compositions that may be used to improve one or more symptoms of the developmental disorder.

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METHODS OF TREATING DEVELOPMENTAL DISORDERS WITH GABOXADOL

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit of and priority to U.S. Provisional Application Nos. 62/346,763, filed June 7, 2016, 62/332,567, filed May 6, 2016, 62/207,595 filed Aug 20, 2015, and 62/193,717, filed July 17, 2015, all of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

Methods of treating developmental disorders with gaboxadol, or a pharmaceutically acceptable salt thereof are provided.

BACKGROUND

Gaboxadol (4,5,6,7-tetrahydroisoxazolo [5,4-c]pyridine-3-ol) (THIP)) is described in EP Patent No. 0000338 and in EP Patent No. 0840601, U.S. Patent Nos. 4,278,676, 4,362,731, 4,353,910, and WO 2005/094820. Gaboxadol is a selective $GABA_A$ receptor agonist with a preference for δ-subunit containing $GABA_A$ receptors. In the early 1980s gaboxadol was the subject of a series of pilot studies that tested its efficacy as an analgesic and anxiolytic, as well as a treatment for tardive dyskinesia, Huntington's disease, Alzheimer's disease, and spasticity. In the 1990s gaboxadol moved into late stage development for the treatment of insomnia. The development was discontinued after the compound failed to show significant effects in sleep onset and sleep maintenance in a three-month efficacy study. Additionally, patients with a history of drug abuse who received gaboxadol experienced a steep increase in psychiatric adverse events.

Treatments for developmental disorders such as Autistic Spectrum Disorder, Rett syndrome, Angelman syndrome, and Fragile X syndrome treatments are limited. For example, Angelman syndrome is a neurodevelopmental disorder caused by loss of function of the *UBE3A* gene encoding a ubiquitin E3 ligase. Motor dysfunction is a characteristic feature of

Angelman syndrome, but neither the mechanisms of action nor effective therapeutic strategies have yet been elucidated. Administering low doses of gaboxadol has been shown to improve the abnormal firing properties of a population of Purkinje cells in cerebellar brain slices and reduces cerebellar ataxia in *Ube3a*-deficient mice in vivo. These results suggest that pharmacologically increasing tonic inhibition may be a useful strategy for alleviating motor dysfunction in Angelman syndrome. Egawa, *et al.*, *Science Translational Medicine*, 4:163ra157 (2012).

Fragile X syndrome may be the most common genetic cause of intellectual disability and the most common single-gene cause of autism. It is caused by mutations on the fragile X mental retardation gene (FMR1) and lack of fragile X mental retardation protein, which in turn, leads to decreased inhibition of translation of many synaptic proteins. The main efforts have focused on metabotropic glutamate receptor (mGluR) targeted treatments; however, investigation on the gamma-aminobutyric acid (GABA) system and its potential as a targeted treatment is less emphasized. The fragile X mouse models (Fmr1-knock out) show decreased GABA subunit receptors, decreased synthesis of GABA, increased catabolism of GABA, and overall decreased GABAergic input in many regions of the brain. These symptoms are also observed in individuals with autism and other neurodevelopmental disorders, therefore the targeted treatments for Fragile X syndrome are leading the way in the treatment of other neurodevelopmental syndromes and autism. Potential GABAergic treatments, such as riluzole, gaboxadol, tiagabine, and vigabatrin have been discussed. However, further studies are needed to determine the safety and efficacy of GABAergic treatments for Fragile X syndrome. Moreover, further studies in fragile X animal models are necessary to provide cumulative evidence in the efficacy and safety of gaboxadol. Lozano *et al.*, Neuropsychiatr Dis Treat.,10: 1769–1779 (2014).

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset disorder, usually occurring after age 50. Mutations in the *FMR1* gene increase the risk of developing FXTAS. The mutation relates to a DNA segment known as a CGG triplet repeat which is expanded within the *FMR1* gene. Normally,

this DNA segment is repeated from 5 to about 40 times. In people with FXTAS the CGG segment may be repeated 55 to 200 times. This mutation is known as an *FMR1* gene premutation. An expansion of more than 200 repeats, a full mutation, causes Fragile X syndrome discussed above. FXTAS is typically characterized by problems with movement and thinking ability (cognition). FXTAS signs and symptoms usually worsen with age. Affected individuals have areas of damage in the cerebellum, the area of the brain that controls movement. Characteristic features of FXTAS are intention tremor, which is trembling or shaking of a limb when trying to perform a voluntary movement such as reaching for an object, and problems with coordination and balance (ataxia). Many affected individuals develop other movement problems, such as parkinsonism, which includes tremors when not moving (resting tremor), rigidity, and unusually slow movement (bradykinesia). In addition, affected individuals may have reduced sensation, numbness or tingling, pain, or muscle weakness in the lower limbs, and inability to control the bladder or bowel. Other symptoms may include chronic pain syndromes, such as fibromyalgia and chronic migraine, hypothyroidism, hypertension, insomnia, sleep apnea, vertigo, olfactory dysfunction, and hearing loss. People with FXTAS commonly have cognitive disabilities such as short-term memory loss and loss of executive function, which is the ability to plan and implement actions and develop problem-solving strategies. Loss of this function impairs skills such as impulse control, self-monitoring, focusing attention appropriately, and cognitive flexibility. Many people with FXTAS experience psychiatric symptoms such as anxiety, depression, moodiness, or irritability.

There is currently no targeted therapeutic intervention that can arrest or reverse the pathogenesis of FXTAS. However a number of treatment approaches of potential symptomatic benefit have been suggested. Primidone, beta-blockers such as propanolol, topiramate, carbidopa/levodopa, and benzodiazepines have been suggested to control tremors associated with FXTAS; botulinum toxin for involuntary muscle activities, such as dystonia and spasticity; carbidopa/levodopa, amantadine and buspirone for ataxia; cholinesterase inhibitors such as donepezil, and memantine (an NMDA

antagonist) for cognitive deficits and dementia; and antidepressants and antipsychotics for psychiatric symptoms. See, e.g., Hagerman, *et al.*, Clin Interv Aging. 2008 Jun; 3(2): 251–262.

Accordingly, there remains a need for effective treatments of patients with for developmental disorders, such as Angelman syndrome, Fragile X syndrome, Fragile X–associated tremor/ataxia syndrome (FXTAS), Autistic Spectrum Disorder, Autism, Asperger's syndrome, pervasive developmental disorder, Childhood Disintegrative Disorder, Rett syndrome, Lanau-Kleffner Syndrome, Prader-Willi Syndrome, Tardive Dyskinesia, and/or Williams Syndrome.

SUMMARY

Methods of treating a developmental disorder described herein include administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides improvement in next day functioning. Methods of treating a developmental disorder described herein include administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides improvement in the patient for more than 6 hours after administration to the patient. Methods of treating a developmental disorder are described herein which include administering to a patient in need thereof gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides an *in vivo* plasma profile including a C_{max} less than about 400 ng/ml and wherein the method provides improvement in the patient for more than 6 hours after administration of the gaboxadol or a pharmaceutically acceptable salt thereof. Methods of treating a developmental disorder are described herein which include administering to a patient in need thereof gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides an *in vivo* plasma profile comprising a $AUC_{6\text{-}12}$ of less than about 900 ng•hr/ml and wherein the method provides improvement in the patient for more than 6 hours after administration of the gaboxadol or a pharmaceutically acceptable salt thereof. Methods of treating a

developmental disorder are described herein which include administering to a patient in need thereof a first pharmaceutical composition comprising gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition comprising gaboxadol or a pharmaceutically acceptable salt thereof wherein the second pharmaceutical composition provides an *in vivo* plasma profile comprising a mean $AUC_{0-\infty}$ of at least 20% less than the first pharmaceutical composition.

In embodiments, the developmental disorder may be an Autistic Spectrum Disorder, pervasive developmental disorder, Autism, Angelman syndrome, Fragile X syndrome, Fragile X–associated tremor/ataxia syndrome (FXTAS), Rett syndrome, Asperger's syndrome, Childhood Disintegrative Disorder, Lanau-Kleffner Syndrome, Prader-Willi Syndrome, Tardive Dyskinesia, and/or Williams Syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the arithmetic mean plasma concentration-time profiles of gaboxadol following single oral doses (2.5, 5, 10, 15, and 20 mg) as described in Example 1 with horizontal lines Δ indicating the change between 6 and 12 hours.

FIG. 2 shows the arithmetic mean plasma concentration-time profiles of gaboxadol following single oral doses (2.5, 5, 10, 15, and 20 mg) as described in Example 1.

FIG. 3 schematically illustrates treatment of three groups over a proposed 12 week course of treatment: 1) single evening dose 2) morning and evening dose and 3) placebo.

DETAILED DESCRIPTION

Described herein are methods of treating developmental disorders with gaboxadol or a pharmaceutically acceptable salt thereof. Many pharmaceutical products are administered as a fixed dose, at regular intervals, to achieve therapeutic efficacy. Its duration of action is reflected by its plasma half-life. Gaboxadol is a selective $GABA_A$ receptor agonist with a relatively

short half-life ($t_{1/2}$ = 1.5 h). Since efficacy is often dependent on sufficient exposure within the central nervous system administration of CNS drugs with a short half-life may require frequent maintenance dosing. Advantageously disclosed herein are methods of treating developmental disorders by administration of gaboxadol or a pharmaceutically acceptable salt thereof. For example, in embodiments, methods of treating a developmental disorder are provided which include administering to a patient in need thereof a pharmaceutical composition including about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides improvement for more than 6 hours after administration to the patient.

In embodiments, the developmental disorder is an Autistic Spectrum Disorder, pervasive developmental disorder, Autism, Angelman syndrome, Fragile X syndrome, Fragile X–associated tremor/ataxia syndrome (FXTAS), Rett syndrome, Asperger's syndrome, Childhood Disintegrative Disorder, Lanau-Kleffner Syndrome, Prader-Willi Syndrome, Tardive Dyskinesia, and/or Williams Syndrome. In embodiments, the developmental disorder Autism, Rett syndrome, Angelman syndrome, and/or Fragile X syndrome. In embodiments, the developmental disorder is a pervasive developmental disorder not otherwise characterized (PDD-NOS). Symptoms of PDD-NOS can vary widely from one child to the next. Overall, child with PDD-NOS can be characterized as having impaired social interaction, better language skills than children with autistic disorder but not as good as those with Asperger's syndrome, fewer repetitive behaviors than children with Asperger's syndrome or autistic disorder, and a later age of onset.

In embodiments, the developmental disorder is Autism. In other embodiments, the developmental disorder is Angelman syndrome. In embodiments the developmental disorder is Fragile X syndrome. In embodiments the developmental disorder is Fragile X–associated tremor/ataxia syndrome (FXTAS)

Embodiments described herein provide that a patient in need thereof is administered a pharmaceutical composition including gaboxadol or a

pharmaceutically acceptable salt thereof. Gaboxadol or pharmaceutically acceptable salt thereof may be provided as an acid addition salt, a zwitter ion hydrate, zwitter ion anhydrate, hydrochloride or hydrobromide salt, or in the form of the zwitter ion monohydrate. Acid addition salts, include but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic or theophylline acetic acid addition salts, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. In other suitable embodiments, inorganic acid addition salts, including but not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric or nitric acid addition salts may be used.

In embodiments, gaboxadol is provided as gaboxadol monohydrate. One skilled in the art will readily understand that the amounts of active ingredient in a pharmaceutical composition will depend on the form of gaboxadol provided. For example, pharmaceutical compositions of including 5.0, 10.0, or 15.0 mg gaboxadol correspond to 5.6, 11.3, or 16.9 mg gaboxadol monohydrate.

In embodiments, gaboxadol is crystalline, such as the crystalline hydrochloric acid salt, the crystalline hydrobromic acid salt, or the crystalline zwitter ion monohydrate. In embodiments, gaboxadol is provided as a crystalline monohydrate.

Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. Accordingly the use of deuterium enriched gaboxadol is contemplated and within the scope of the methods and compositions described herein. Deuterium can be incorporated in any position in replace of hydrogen synthetically, according to the synthetic procedures known in the art. For example, deuterium may be incorporated to various positions having an exchangeable proton, such as the amine N--H, via proton-deuterium equilibrium exchange. Thus, deuterium may be incorporated

selectively or non-selectively through methods known in the art to provide deuterium enriched gaboxadol. *See* Journal of Labeled Compounds and Radiopharmaceuticals 19(5) 689-702 (1982).

Deuterium enriched gaboxadol may be described by the percentage of incorporation of deuterium at a given position in the molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at that specified position. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy. In embodiments deuterium enriched gaboxadol means that the specified position is enriched with deuterium above the naturally occurring distribution (*i.e.*, above about.0156%). In embodiments deuterium enrichment is no less than about 1%, no less than about 5%, no less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98% of deuterium at a specified position.

In embodiments methods of treating a developmental disorder include administering to a patient in need thereof a pharmaceutical composition including about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical compositions include 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.5 mg to 25 mg, 0.5 mg to 20 mg, 0.5 to 15 mg, 1 mg to 25 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1.5 mg to 25 mg, 1.5 mg to 20 mg, 1.5 mg to 15 mg, 2 mg to 25 mg, 2 mg to 20 mg, 2 mg to 15 mg, 2.5 mg to 25 mg, 2.5 mg to 20 mg, 2.5 mg to 15 mg, 3 mg to 25 mg, 3 mg to 20 mg, 3 mg to 15 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical compositions include 5 mg to 20 mg, 5 mg to 10 mg, 4 mg to 6 mg, 6 mg to 8 mg, 8 mg to 10 mg, 10 mg to 12 mg, 12 mg to 14 mg, 14 mg to 16 mg, 16 mg to 18 mg, or 18 mg to 20 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical compositions include 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg gaboxadol or a pharmaceutically acceptable salt thereof or amounts that are multiples of such doses. In embodiments, the pharmaceutical compositions include 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg gaboxadol or a pharmaceutically acceptable salt thereof.

Pharmaceutical compositions herein may be provided with immediate release, delayed release, extended release, or modified release profiles. In embodiments, pharmaceutical compositions with different drug release profiles may be combined to create a two phase or three-phase release profile. For example, pharmaceutical compositions may be provided with an immediate release and an extended release profile. In embodiments, pharmaceutical compositions may be provided with an extended release and delayed release profile. Such composition may be provided as pulsatile formulations, multilayer tablets, or capsules containing tablets, beads, granules, etc. Compositions may be prepared using a pharmaceutically acceptable "carrier" composed of materials that are considered safe and effective. The "carrier" includes all components present in the pharmaceutical formulation other than the active ingredient or ingredients. The term "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrants, fillers, and coating compositions.

In embodiments, the pharmaceutical compositions described herein are administered once, twice, or three times daily, or every other day. In embodiments, a pharmaceutical composition described herein is provided to the patient in the evening. In embodiments, a pharmaceutical composition described herein is provided to the patient once in the evening and once in the morning. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 1 mg to 30 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 1 mg to 20 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour

period is 5 mg, 10 mg, or 15 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 20 mg.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides improvement in at least one symptom of the developmental disorder. Symptoms may include, but are not limited to, ataxia, gait, speech impairment, vocalization, cognition, motor activity, clinical seizure, hypotonia, hypertonia, feeding difficulty, drooling, mouthing behavior, sleep difficulties, hand flapping, easily provoked laughter and short attention span. In embodiments, provided in accordance with the present disclosure is improvement in cognition. Cognition refers to the mental processes involved in gaining knowledge and comprehension, such as thinking, knowing, remembering, judging, and problem solving. These higher-level functions of the brain encompass language, imagination, perception, and the planning and execution of complex behaviors.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides improvement of at least one symptom for more than 4 hours after administration of the pharmaceutical composition to the patient. In embodiments, the improvement of at least one symptom for more than 6 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure. In embodiments, improvement of at least one symptom for more than, *e.g.*, 8 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 24 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure. In embodiments, improvement in at least one symptom for at least *e.g.*, 8 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 24 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the

present disclosure. In embodiments, improvement in at least one symptom for 12 hours after administration of the pharmaceutical composition to the patient is provided in accordance with the present disclosure.

In embodiments, provided herein methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides improvement in next day functioning to the patient.

FIG. 1 shows the arithmetic mean plasma concentration-time profiles of gaboxadol following single oral doses (2.5, 5, 10, 15, and 20 mg)(see, Example 1, below) with horizontal lines Δ indicating the change between 6 and 12 hours. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 50% and the method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 55% and the method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 60% and the

method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 65% and the method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 70% and the method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 75% and the method provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration.

In embodiments, provided herein are methods of treating a developmental disorder wherein the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient about 4 hours after administration of the pharmaceutical composition is less than about 75% of the administered dose. In embodiments, provided herein are methods wherein the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient about,

e.g., 6 hours, 8 hours, 10 hours, 12 hours, 15 hours, or 20 hours after administration of the pharmaceutical composition is less than about 75%.

In embodiments, provided herein are methods of treating a developmental disorder wherein the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient about 4 hours after administration of the pharmaceutical composition is less than about 80% of the administered dose. In embodiments, provided herein are methods wherein the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient about, *e.g.*, 6 hours, 8 hours, 10 hours, 12 hours, 15 hours, or 20 hours after administration of the pharmaceutical composition is less than about 80% of the administered dose.

In embodiments, provided herein are methods of treating a developmental disorder wherein the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient about 4 hours after administration of the pharmaceutical composition is between about 65% to about 85% of the administered dose. In embodiments, the amount of gaboxadol or pharmaceutically acceptable salt thereof within the patient after about, *e.g.*, 6 hours, 8 hours, 10 hours, 12 hours, 15 hours, or 20 hours after administration of the pharmaceutical composition is between about 65% to about 85% of the administered dose.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 75% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 80% of the administered dose and provides

improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 85% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 90% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 95% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma concentration 6 hours after administration which is less than 100% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma

profile having a C_{max} less than about 500 ng/ml. In embodiments, the composition provides improvement for more than 6 hours after administration to the patient.

In embodiments, the composition provides an *in vivo* plasma profile having a C_{max} less than about, *e.g.*, 450 ng/ml, 400 ng/ml 350 ng/ml, or 300 ng/ml and wherein the composition provides improvement of next day functioning of the patient. In embodiments, the composition provides an *in vivo* plasma profile having a C_{max} less than about, *e.g.*, 250 ng/ml, 200 ng/ml 150 ng/ml, or 100 ng/ml and wherein the composition provides improvement of next day functioning of the patient.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about 900 ng•hr/ml. In embodiments, the composition provides improvement in next day functioning of the patient. In embodiments, the compositions provide an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 850 ng•hr/ml, 800 ng•hr/ml, 750 ng•hr/ml, or 700 ng•hr/ml and wherein the composition provides improvement of next day functioning of the patient. In embodiments, the composition provides improvement in one or more symptom for more than 6 hours after administration.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 650 ng•hr/ml, 600 ng•hr/ml, 550 ng•hr/ml, 500 ng•hr/ml, or 450 ng•hr/ml . In embodiments, wherein the composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 400 ng•hr/ml, 350 ng•hr/ml, 300 ng•hr/ml, 250 ng•hr/ml, or 200 ng•hr/ml. In embodiments, the composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 150 ng•hr/ml, 100 ng•hr/ml, 75

ng•hr/ml, or 50 ng•hr/ml. In embodiments, the composition provides improvement of next day functioning of the patient after administration for more than, *e.g.*, 4 hours, 6 hours, 8 hours, 10 hours, or 12 hours, after administration of the composition to the patient.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 75% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 80% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 85% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 90% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 95% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments,

provided herein are methods of treating a developmental disorder including administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof which provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 100% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 75% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 80% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 85% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 90% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a

patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 95% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 100% of the C_{max} and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 75% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 80% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 85% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical

composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 90% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 95% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides an *in vivo* plasma profile having a AUC_{6-12} which is less than 100% of the administered dose and provides improvement in the patient for more than 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after administration. In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a first pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the second pharmaceutical composition provides an *in vivo* plasma profile having a mean $AUC_{0-\infty}$ of at least about 20% less than the first pharmaceutical composition.

In embodiments the first and/or the second pharmaceutical compositions are administered once, twice, or three times daily, or every other day. In embodiments, the first or the second pharmaceutical composition is provided to the patient in the evening. In embodiments, the second pharmaceutical composition includes an amount of gaboxadol that is at least one third of the amount of gaboxadol provided in the first pharmaceutical composition. In embodiments, the second pharmaceutical composition

includes an amount of gaboxadol that is at least half of the amount of gaboxadol provided in the first pharmaceutical composition.

In embodiments, the first or the second pharmaceutical composition is provided to the patient once in the evening and once in the morning. In embodiments, the total amount of gaboxadol or pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 1 mg to 30 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 1 mg to 20 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 10 mg, 15 mg, or 20 mg. In embodiments, the total amount of gaboxadol or a pharmaceutically acceptable salt thereof administered to a subject in a 24-hour period is 20 mg.

In embodiments, the first and/or the second pharmaceutical compositions may be provided with immediate release, delayed release, extended release, or modified release profiles. The first and second pharmaceutical compositions may be provided at the same time or separated by an interval of time, *e.g.*, 6 hours, 12 hours etc. In embodiments, the first and the second pharmaceutical compositions may be provided with different drug release profiles to create a two-phase release profile. For example, the first pharmaceutical composition may be provided with an immediate release profile and the second pharmaceutical composition may provide an extended release profile. In embodiments, one or both of the first and second pharmaceutical compositions may be provided with an extended release or delayed release profile. Such compositions may be provided as pulsatile formulations, multilayer tablets or capsules containing tablets, beads, granules, etc. In some embodiments, the first pharmaceutical composition is an immediate release composition. In embodiments, the second pharmaceutical composition is an immediate release composition. In embodiments, the first and second pharmaceutical compositions are provided as separate immediate release compositions, *e.g.*, tablets or capsules. In embodiments the first and second pharmaceutical compositions are provided 12 hours apart.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a first pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the second pharmaceutical composition provides an *in vivo* plasma profile having a mean $AUC_{0-\infty}$ of at least about, *e.g.*, 25%, 30%, 35%, 40%, 45% or 50% less than the first pharmaceutical composition. In embodiments, the composition provides improvement of next day functioning of the patient. For example, the composition may provide improvement in one or more symptoms for more than about, *e.g.*, 6 hours, 8 hours, 10 hours, or 12 hours after administration of the first and/or second pharmaceutical composition.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a first pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the second pharmaceutical composition provides an *in vivo* plasma profile having a mean $AUC_{0-\infty}$ of less than about 900 ng•hr/ml. In embodiments, the second pharmaceutical composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 800 ng•hr/ml, 750 ng•hr/ml, 700 ng•hr/ml, 650 ng•hr/ml, or 600 ng•hr/ml. In embodiments, the second pharmaceutical composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 550 ng•hr/ml, 500 ng•hr/ml, 450 ng•hr/ml, 400 ng•hr/ml, or 350 ng•hr/ml. In embodiments, the second pharmaceutical composition provides an *in vivo* plasma profile having a $AUC_{0-\infty}$ of less than about, *e.g.*, 300 ng•hr/ml, 250 ng•hr/ml, 200 ng•hr/ml, 150 ng•hr/ml, or 100 ng•hr/ml. In embodiments, the first and second pharmaceutical composition are administered wherein the compositions provide improvement of next day functioning of the patient. In embodiments, the first pharmaceutical composition provides improvement in one or more symptom for more than,

e.g., 6 hours, 8 hours or 12 hours after administration of the first pharmaceutical composition.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a first pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition including gaboxadol or a pharmaceutically acceptable salt thereof wherein the first composition provides an *in vivo* plasma profile with a C_{max} that is more than about 50% greater than the C_{max} provided by the administration of the second pharmaceutical composition. As used herein the C_{max} provided by the administration of the second pharmaceutical composition may or may not include the plasma profile contribution of the first pharmaceutical composition. In embodiments, the administration of the second pharmaceutical composition does not include the plasma profile contribution of the first pharmaceutical composition. In embodiments, the first composition provides an *in vivo* plasma profile having a C_{max} that is more than about e.g., 60%, 70%, 80%, or 90% greater than the C_{max} provided by the administration of the second pharmaceutical composition.

In embodiments, the T_{max} of the first pharmaceutical composition is less than 3 hours. In embodiments, the T_{max} of the first pharmaceutical composition is less than 2.5 hours. In embodiments, the T_{max} of the first pharmaceutical composition is less than 2 hours. In embodiments, the T_{max} of the first pharmaceutical composition is less than 1.5 hours. In embodiments, the T_{max} of the first pharmaceutical composition is less than 1 hour.

In embodiments, the first pharmaceutical composition provides a dissolution of at least about 80% within the first 20 minutes of administration to a patient in need thereof. In embodiments, the first pharmaceutical composition provides a dissolution of at least about, e.g., 85%, 90% or 95% within the first 20 minutes of administration to a patient in need thereof. In embodiments, the first pharmaceutical composition provides a dissolution of at least 80% within the first 10 minutes of administration to a patient in need thereof.

In embodiments the first and/or the second pharmaceutical compositions are sub therapeutic dosages. A sub therapeutic dosage is an amount of gaboxadol pharmaceutically acceptable salt thereof that is less than the amount required for a therapeutic effect. In embodiments, a sub therapeutic dosage is an amount of gaboxadol pharmaceutically acceptable salt thereof that alone may not provide improvement in at least one symptom of the developmental disorder but is sufficient to maintain such improvement. In embodiments, the methods provide administering a first pharmaceutical composition that provides improvement in at least one symptom of a developmental disorder and a second composition that maintains the improvement. In embodiments, after administration of the first pharmaceutical composition the second pharmaceutical composition may provide a synergistic effect to improve at least one symptom of a developmental disorder. In embodiments the second pharmaceutical composition may provide a synergistic effect to improve at least one symptom of a developmental disorder.

In embodiments, provided herein are methods of treating a developmental disorder including administering to a patient in need thereof a pharmaceutical composition including a first pharmaceutical dosage including gaboxadol or a pharmaceutically acceptable salt thereof wherein the composition provides improvement for more than 6 hours after administration and a second pharmaceutical composition including a sub therapeutic dosage of gaboxadol or a pharmaceutically acceptable salt thereof.

Administration of the first and second pharmaceutical compositions may be separated by an interval of time to achieve long-term improvement in at least one symptom. In embodiments, the first and second pharmaceutical composition may be administered 6 hours apart. In embodiments the first and second pharmaceutical composition may be administered 12 hours apart. In embodiments, the first and second pharmaceutical compositions may administered within, *e.g.*, 6 hours, 12 hours, 18 hours, 24 hours etc. In embodiments, the first and second pharmaceutical compositions may administered separated by at least, *e.g.*, 6 hours, 12 hours, 18 hours, 24 hours

etc. In embodiments, improvement in at least one symptom of a developmental disorder for more than 8 hours after administration to the patient is provided. In embodiments, improvement for more than about, *e.g.*, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 24 hours after administration to the patient is provided.

In embodiments, the first pharmaceutical composition and/or the second pharmaceutical composition include about 0.1 mg to about 40 mg gaboxadol or a pharmaceutically acceptable salt thereof. The amount of gaboxadol or a pharmaceutically acceptable salt thereof in the first pharmaceutical composition and the second pharmaceutical composition may be the same or different. In embodiments, the administration of the first and second pharmaceutical composition may provide a synergistic effect to improve at least one symptom of a developmental disorder.

In embodiments, the first and/or the second pharmaceutical composition include 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.5 mg to 25 mg, 0.5 mg to 20 mg, 0.5 to 15 mg, 1 mg to 25 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1.5 mg to 25 mg, 1.5 mg to 20 mg, 1.5 mg to 15 mg, 2 mg to 25 mg, 2 mg to 20 mg, 2 mg to 15 mg, 2.5 mg to 25 mg, 2.5 mg to 20 mg, 2.5 mg to 15 mg, 3 mg to 25 mg, 3 mg to 20 mg, or 3 mg to 15 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In embodiments, the first and/or the second pharmaceutical composition include 5 mg to 15 mg, 5 mg to 10 mg, 4 mg to 6 mg, 6 mg to 8 mg, 8 mg to 10 mg, 10 mg to 12 mg, 12 mg to 14 mg, 14 mg to 16 mg, 16 mg to 18 mg, or 18 mg to 20 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In embodiments, the first and/or the second pharmaceutical composition include 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg gaboxadol or a pharmaceutically acceptable salt thereof or amounts that are multiples of such doses. In embodiments, the first pharmaceutical compositions include 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg gaboxadol or a pharmaceutically acceptable salt thereof. In embodiments, the second pharmaceutical

compositions include 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg gaboxadol or a pharmaceutically acceptable salt thereof.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosure herein belongs.

The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 10%, up to 5%, and/or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

“Improvement” refers to the treatment of a developmental disorder measured relative to at least one symptom.

“Improvement in next day functioning” or “wherein there is improvement in next day functioning” refers to improvement wherein the beneficial effect of at least one symptom lasts over a period of time, *e.g.*, 6 hours, 12 hours, 24 hours etc.

"PK" refers to the pharmacokinetic profile. C_{max} is defined as the highest plasma drug concentration estimated during an experiment (ng/ml). T_{max} is defined as the time when C_{max} is estimated (min). $AUC_{0-\infty}$ is the total area under the plasma drug concentration-time curve, from drug administration until the drug is eliminated (ng•hr/ml). The area under the curve is governed by clearance. Clearance is defined as the volume of blood or plasma that is totally cleared of its content of drug per unit time (ml/min).

"Treating" or "treatment" refers to alleviating or delaying the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or

condition. In certain embodiments, “treating” or “treatment” may refer to preventing the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. "Treating" or "treatment" also refers to inhibiting the disease or condition, *e.g.*, arresting or reducing its development or at least one clinical or subclinical symptom thereof. "Treating" or "treatment" further refers to relieving the disease or condition, *e.g.*, causing regression of the disease or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated may be statistically significant, mathematically significant, or at least perceptible to the subject and/or the physician. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatment are two separate embodiments of the disclosure herein.

"Pharmaceutically acceptable" refers to molecular entities and compositions that are "generally regarded as safe"-*e.g.*, that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In embodiments, this term refers to molecular entities and compositions approved by a regulatory agency of the federal or a state government, as the GRAS list under section 204(s) and 409 of the Federal Food, Drug and Cosmetic Act, that is subject to premarket review and approval by the FDA or similar lists, the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

“Effective amount” or “therapeutically effective amount” means a dosage sufficient to alleviate one or more symptoms of a disorder, disease, or condition being treated, or to otherwise provide a desired pharmacological and/or physiologic effect.

“Patient in need thereof” may include individuals that have been diagnosed with a developmental disorder including, for example, Autism, Angelman’s syndrome, Fragile X syndrome, Fragile X–associated tremor/ataxia syndrome (FXTAS), or Rett’s syndrome. The methods may be

provided to any individual including, *e.g.*, wherein the patient is a neonate, infant, a pediatric patient (6 months to 12 years), an adolescent patient (age 12-18 years) or an adult (over 18 years).

EXAMPLES

The Examples provided herein are included solely for augmenting the disclosure herein and should not be considered to be limiting in any respect.

Example 1

The following Example provides the plasma concentration profiles and dose proportionality of gaboxadol monohydrate following single oral doses ranging from 2.5 to 20 mg. The absolute bioavailability of gaboxadol monohydrate capsules ranging from 2.5 to 20 mg is also assessed.

This study was composed of separate groups of 10 healthy adult subjects (at least 4 of each gender) who participated in a 6-period, double-blind, randomized, crossover study designed to access the dose proportionality and absolute bioavailabilty of 5 single oral doses of gaboxadol across the dose range of 2.5 to 20 mg. The order in which the subjects received the 5 single oral doses of gaboxadol (2.5; 5; 10; 15; and 20 mg) was randomized within Treatment Periods 1 through 5. Each subject was expected to complete all 6 treatment periods and there was a washout of at least 4 days between each treatment period.

Each oral dosing within Treatment Periods consisted of 2 capsules of test drug taken simultaneously at each scheduled dosing. The treatment designations for the orally administered study drugs were as follows: Treatment A - one 2.5 mg gaboxadol capsule and 1 matching placebo capsule; Treatment B - one 5 mg gaboxadol capsule and 1 matching placebo capsule; Treatment C - one 10 mg gaboxadol capsule and 1 matching placebo capsule; Treatment D - one 15 mg gaboxadol capsule and 1 matching placebo capsule; and Treatment E - 20 mg gaboxadol (two 10 mg gaboxadol capsules). Subjects received their study drug after an overnight fast with 240 mL of water in the morning about 8:00 AM. Water was permitted *ad libitum* except within 1 hour

prior to and after study drug administration. No food was allowed for 4 hours post dose.

For each subject in each treatment, plasma and urine samples were collected over 16 hours post-dosing for the determination of pharmacokinetic parameters (*e.g.*, AUC, C_{max}, T_{max}, apparent $t_{1/2}$, cumulative urinary excretion, renal clearance, clearance, and steady-state volume of distribution, as appropriate). AUC and C_{max} for gaboxadol were potency adjusted to facilitate comparison of pharmacokinetic data across studies. Table 1 provides the individual potency-adjusted pharmacokinetic parameters of gaboxadol following single oral doses (2.5, 5, 10, 15, and 20 mg).

Table 1. Pharmacokinetic parameters for gaboxadol following oral and IV administration

Parameter	Geometric Mean (N=10)						Slope (90% CI) [10]
	2.5 mg	5 mg	10 mg Oral	10 mg I.V.	15 mg	20 mg	
$AUC_{0-\infty}$ (ng·hr/mL)	90	171	346	380	539	669	0.98 (0.95, 1.01)
C_{max} (ng/mL) [1]	61	110	232	212	382	393	0.95 (0.88, 1.02)
T_{max} (hr) [3]	0.5	0.6	0.5	--	0.5	0.6	
Apparent $t_{\frac{1}{2}}$ (hr) [4]	1.5	1.5	1.6	1.5	1.5	1.6	
CL/F (mL/min) [5]	461	488	476	438	469	499	
$t_{\frac{1}{2}}$ (%)	43	45	53	53	50	53	
CL_R (mL/min)	196	222	250	208	234	265	
F (%) (90% CI) [6]	92% (0.86, 0.97)						

[1] C_{max} (ng/mL) for 10 mg IV.
[3] Median.
[4] Harmonic Mean.
[5] CL (mL/min) for 10 mg IV.
[6] Bioavailability relative to 10 mg I.V. reference based on pooled dose-adjusted (to 10 mg) oral $AUC_{0-\infty}$ values.
[10] Dose proportionality assessment of oral treatments only.

Figure 2 shows the arithmetic mean plasma concentration-time profiles of gaboxadol following single oral doses (2.5, 5, 10, 15, and 20 mg). The bioavailability of gaboxadol is approximately 92%. Plasma $AUC_{0-\infty}$ and C_{max} of gaboxadol show dose proportional increases and appear to be linear over the entire dose range examined, from of 2.5 to 20 mg. The time to peak plasma concentrations (T_{max} 30-60 min) and the half-life ($t_{½}$ of 1.5 h) for gaboxadol appear to be independent of dose across the gaboxadol dose range of 2.5 to 20 mg. The excretion of gaboxadol is mainly via urine, where 96.5% of the dose is recovered; 75% is recovered within 4 hours after administration.

Example 2

Assessment of Residual Effects Resulting from Gaboxadol Administration

This study was a double blind, double-dummy, randomized, active- and placebo-controlled, single dose, 3-period crossover study, followed by an open-label, single-dose, single period study in healthy elderly male and female subjects. Subjects were randomized to each of 3 treatments (Treatments A, B, and C) to be administered in a crossover manner over the first 3 treatment periods. For Treatment A, subjects received a single dose of gaboxadol 10 mg; for Treatment B, subjects received a single dose of flurazepam 30 mg; and for Treatment C, subjects received a single dose of placebo. Doses were administered orally at bedtime on Day 1. Subjects were domiciled from early in the evening of dosing until ~36 hours post-dose (morning of Day 3) during each treatment period. The subjects who participated in treatment periods 1-3 participated in a fourth treatment period. In this period, a single dose of gaboxadol 10 mg (Treatment D) was administered orally in an open-label manner on the morning of Day 1 for PK of gaboxadol. There was at least a 14-day washout between the doses of consecutive treatment periods. Study participants included healthy, elderly male and female subjects between 65 and 80 years of age, with a Mini Mental Status 24, weighing at least 55 kg. All subjects received 10 mg gaboxadol monohydrate capsules and 30 mg flurazepam (provided as 2 x 15 mg capsules), matching placebo was provided for both gaboxadol and flurazepam.

The primary endpoints evaluated included pharmacodynamics (measurement of psychomotor performance, memory, attention and daytime sleepiness the following pm dosing), gaboxadol pharmacokinetics, and safety. Gaboxadol (single dose 10 mg) did not show residual effect 9 hours post-dose on the primary endpoints Choice Reaction Time and Critical Flicker Fusion, whereas the active reference Flurazepam (30 mg single dose) showed significant effect on the same tests. In addition, gaboxadol did not show any signs of residual effects on other measurements applied in the study (Multiple Sleep Latency Test (MSLT); Digit symbol substitution test (DSST), Tracking, Memory tests, Body Sway, and Leeds Sleep Evaluation Questionnaire).

Example 3

Study of Driving Performance after Gaboxadol Administration

This study was a double blind, randomized, placebo and active controlled 5 way cross over study to investigate the effect of evening and middle of the night dosing of gaboxadol on driving performance. The study participants included healthy, male and female subjects between 21 and 45 years of age, with a valid drivers license for at least 3 years.

The effects of gaboxadol on driving performance were investigated using real driving on the road setting. Subjects received 15 mg gaboxadol either in the evening prior to going to bed or at 4 am in the middle of the night following a wake-up call. Following a cognitive and psychomotor test battery, the driving test started at 9 am and lasted for one hour. Gaboxadol 15 mg had a clinically relevant impairing effect on driving following middle-of-the-night administration.

Following the evening dose, a statistically significant effect of gaboxadol 15 mg was observed on driving. However, this effect was less than the effect observed at a 0.05% blood alcohol concentration, the concentration limit at which driving is prohibited in most European countries. There was generally a numerically greater effect following zopiclone (7.5 mg) and zolpidem (10 mg) administered in the evening and in the middle of the night, respectively. Both the evening and the middle-of-the-night dose of gaboxadol were well tolerated with the most frequent adverse events being dizziness, nausea and somnolence for the middle-of-the-night treatment and headache and somnolence for the evening treatment.

Subjects on the active reference zopiclone had a numerically greater effect in the same test. There was no effect on memory test, body sway, DSST or critical tracking, whereas zopiclone had effect on several of these tests.

Example 4

Study of Daytime Performance after Sleep Restriction

This study was a 4-night, parallel-group, randomized, double-blind (with in- house blinding), placebo-controlled, fixed-dose study to assess the

effects of gaboxadol on daytime performance in healthy adults subjected to a 5-hour sleep restriction. The study included a 2- night single-blind placebo run-in period, a 4-night double-blind treatment period during which sleep was restricted to 5 hours and a 2-night single-blind placebo run-out period. The study included healthy male and female volunteers 18 to <55 years of age.

2-night run-in period: All patients received placebo

4-night double-blind treatment period: Patients were randomized to gaboxadol 15 mg or matching placebo

2-night run-out period: All patients received placebo

The primary endpoints included observations based on the Multiple Sleep Latency Test (MSLT) and Slow Wave Sleep (SWS) assessment. The primary objective was to evaluate the efficacy of gaboxadol (15 mg) compared to placebo in reducing daytime sleep propensity as measured by MSLT. The gaboxadol subjects had significantly less daytime sleepiness during the Sleep Restriction period than did placebo subjects ($p=0.047$, 1 sided). The MSLT was on average 2.01 minutes longer for subjects treated with gaboxadol (15 mg) than for those with placebo on the last two Sleep Restriction days.

In addition, a secondary objective was to evaluate the efficacy of gaboxadol compared to placebo in increasing the amount of slow wave sleep (SWS) during the last 2 nights of sleep restriction. Subjects receiving gaboxadol experienced significantly more SWS during the Sleep Restriction period than did placebo subjects ($p<0.001$, 1 sided). Moreover, subjects treated with gaboxadol on average had 20.53 minutes of SWS longer than those treated with placebo on the last two Sleep Restriction nights.

Finally, this study examined the efficacy of gaboxadol compared to placebo during the last 2 nights/days of sleep restriction in: (1) improving memory and attention as assessed by a neurobehavioral battery; (2) reducing subjective sleepiness as measured by the Karolinska Sleepiness Score (KSS); (3) altering sleep parameters (e.g., total sleep time, latency to onset of Slow Wave Sleep (SWS), slow wave activity (SWA); and (4) reducing biological stress typified by increased heart rate variability, and decreased cortisol levels and decreased catecholamine levels, as well as decreased body temperature.

There was a trend towards less subjective daytime sleepiness for the gaboxadol subjects during the Sleep Restriction period as compared with placebo subjects. The Karolinska Sleepiness Score (KSS) was on average 0.68 less for subjects treated with gaboxadol than for those treated with placebo on the last two Sleep Restriction days (p=0.058, 1 sided) as evaluated by a Longitudinal data analysis (LDA) model with adjustment for baseline KSS, gender, and age. A supportive analysis using covariance (ANCOVA) also supports this finding. The effect sizes computed for the neurocognitive battery showed that there was no strong evidence that gaboxadol improves daytime performance. There were no differences between gaboxadol and placebo with respect to biophysiological measures of stress (heart rate variability, cortisol levels, catecholamine levels, body temperature).

Compared with placebo, gaboxadol has a protective effect on reducing daytime sleepiness as measured by the MSLT on the last 2 days of 4-nights of sleep restriction. Compared with placebo, gaboxadol increases the amount of slow wave sleep (SWS) during the last 2 nights of 4-nights of sleep restriction.

Example 5

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Angelman syndrome

This study is designed to determine whether gaboxadol will lead to an improvement in one or more symptoms of Angelman syndrome. Participants are randomized into 6 separate treatment groups (A-F). Inclusion criteria for randomization will require that each participant has been previously diagnosed with Angelman syndrome by clinical evaluation or that the participant is diagnosed with one or more of the major and minor criteria for Angelman syndrome.

Major Criteria include:

- Functionally severe developmental delay
- Speech impairment; none or minimal words used
- Movement or balance disorder
- Behavioral uniqueness, frequent laughs/smiling, excitable personality,

hand flapping, short attention span

Minor Criteria include:

- Deceleration in head circumference growth (post-natal)
- Seizures (myoclonic, absence, drop, tonic-clonic)
- Abnormal EEG (with patterns suggestive of AS, or hypsarrhythmia)
- Sleep disturbance
- Attraction to or fascination with water
- Drooling

After randomization the participants are placed into 6 separate treatment groups (A-F) and a placebo group. Treatment group A receives 20 mg gaboxadol in the evening. Treatment group B receives 15 mg gaboxadol in the evening. Treatment group C receives 15 mg gaboxadol in the evening and 5 mg gaboxadol in the morning. Treatment group D receives 10 mg gaboxadol in the evening. Treatment group E receives 10 mg gaboxadol in the evening and 10 mg gaboxadol in the morning. Treatment group F receives 10 mg gaboxadol in the evening and 5 mg gaboxadol in the morning.

Participants are assessed throughout the treatment period to determine whether gaboxadol administration leads to an improvement in one or more symptoms of Angelman syndrome. Several behavioral domains; communication, attention, maladaptive behaviors, and hyper-excitability are assessed. To quantify the communication behavior, participants engage in an unstructured play session to elicit speech and non-verbal communication attempts. Speech attempts by the child are transcribed phonetically and categorized into five different types of vocalizations using the *Stark Assessment of Early Vocal Development-Revised* (SAEVD-R) (Nathani, Ertmer et al. 2006) which categorizes non-speech and pre-speech sounds (protophones), as well as vowels, consonants and syllables.

Gait abnormalities occur in most cases of Angelman syndrome. Thus, five primary spatiotemporal parameters are analyzed: cadence, gait velocity, stride width, step length and percent stance. For each parameter, a principal component analysis is used to establish a gait index for assessment of the subjects.

In addition, primary outcome measures that may be assessed include changes in raw or standard scores between baseline and after trial completion of:

I. Bayley Scales of Infant and Toddler Development, 3rd edition (or the Mullen Scales of Early Learning in the more developmentally advanced subjects);

II. Vineland Adaptive Behavior Scales, 2nd edition (standard scores only);

III. Preschool Language Scale, 4th edition;

IV. Aberrant Behavior Checklist - Community version; and

V. A change from baseline in the Clinical Global Impressions Severity Scale Score.

Secondary outcome measures may include normalization of the electroencephalogram (EEG) signature when comparing post gaboxadol administration results to baseline results.

Example 6

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Angelman syndrome

This study is designed to determine whether gaboxadol leads to an improvement in one or more symptoms of Angelman syndrome (AS). Angelman syndrome manifests as several distinct characteristics that range in severity and include developmental delay, movement and/or balance disorder, and tremulous movement of limbs. Perhaps the most unique behavioral characteristic is the combination of a happy demeanor, smiling and frequent of bouts of laughter. Moreover, these individuals possess an easily excitable personality exhibited by hand-flapping or waving movements. Finally, these individuals suffer from severe disruptions in sleep, impairments in speech, and frequent seizures with characteristic abnormal electroencephalogram (EEG) patterns. All main domains of symptoms of AS (sleep, gross and fine motor function, behavior and communication) will be investigated, using appropriate questionnaires, diaries or actimetric data. Main focus may include motor

ability and sleep. Well-established scales may be used, complemented by more innovative outcome measures for sleep and motor function. A potential confounding factor for behavior in AS is the co-existence of autism (Peters et al., Clin Genet, 2004;66[6]:530-6). At Screening, subjects may be assessed for this co-morbidity, using the Autism Diagnostic Observation Schedule (ADOS), and potentially excluded.

The primary objective of this study may be to evaluate the safety and tolerability from Baseline to Week 6 and Week 12 of gaboxadol in adult subjects with AS across different dose levels and in two dosing schedules. The following dosing schedules may be tested against placebo: (1) Once daily (o.d.): An evening dose, titrated to the target dose of 15 mg unless not tolerated; and (2) Twice daily (b.i.d.): Evening and morning doses titrated to the target doses of 15 mg evening dose and 10 mg morning dose unless not tolerated.

The Safety endpoints that relate to this study may include: (1) Frequency and severity of adverse events (AEs) and serious adverse events; (2) Vital signs (weight, blood pressure, temperature); (3) Laboratory parameters (electrolytes, lipids, glucose, liver and pancreas function tests, hematology, creatinine); (4) Suicidality assessed by ABC-Irritability Subscale; (5) EEG (change in background frequency, intensity of epileptiform discharges); and/or (6) Caregivers may maintain an electronic seizure diary (on same device as sleep log).

The secondary objective of this study may include the identification of a set of parameters that may best characterize the efficacy of gaboxadol in adult AS subjects for subsequent efficacy trials. These tests may be administered at four full day site visits (Screening, Baseline, Interim and End of Treatment) by an appropriately trained professional to provide the test to an adult AS patient. Assessments may be based on direct observation and input from caregivers. The efficacy assessments that may be explored include Gross Motor Ability/Function and Fine Motor Ability/Function. Evaluation of Gross Motor Ability/Function may include analysis of spatiotemporal and functional gait measurements (Zeno Walkway and PKMAS software analysis, provided

by ProtoKinetics) and Modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale assessed while subject is walking on Zeno Walkway. Evaluation of Fine Motor Ability/Function may include analysis of Pediatric Evaluation of Disability Inventory (PEDI-CAT); ADL (to document fine motor function) and mobility domains in the content-balanced (more extensive) version.

Evaluation of sleep may include analysis by actigraphy to measure: (1) Sleep Onset Latency (SOL); (2) Total Sleep Time (TST); (3) Wake After Sleep Onset (WASO) = total # of wake epochs after sleep onset; (4) Nocturnal Awakenings (NA); and/or (5) Sleep Efficiency = total sleep time (TST) of time in bed (TIB). Additional evaluation of sleep may include analysis of parent/caregiver logs of sleep patterns that may include: (1) bed time; (2) time of sleep onset; (3) number and duration of awakenings; (4) number of disruptive behavior; (5) time of last awakening; and (6) daytime sleepiness. This study may include three treatment groups. For example, a total of approximately 75 subjects may be enrolled and at the completion of the study, there may be approximately 25 subjects in each of the three treatment groups: 1) single evening dose 2) morning and evening dose and 3) placebo.

All subjects may receive a morning dose (either active or placebo) and an evening dose (either active or placebo) during the entire duration of treatment. For example, as illustrated in FIG. 3, two dosing schedules of gaboxadol may be tested: a single evening dose (o.d.; Schedule A) and a morning plus evening dose (b.i.d; Schedule B) designed to provide a more sustained exposure. Schedule C is morning and evening placebo. All subjects may be up-titrated to the target dose unless this target dose is not tolerated (titration conventions described below). All subjects may receive treatment for a maximum of 12 weeks at their optimal tolerated dose.

Doses may be progressively increased in 5 mg increments (active or placebo) to a target dose of 3 capsules evening dose in schedule A and B, and 2 capsules morning dose in schedule B. Each dose escalation may be performed after adequate tolerability has been assessed by caregiver and investigator. For example, treatment initiation at Day 1 with 1 capsule (active

(Act) or placebo (Plc)) in the evening. Then target up-titration may begin at Day 3 (window + 2 days): If no adverse event (AE) related to the study drug is observed by caregiver and/or the investigator, another capsule (active or placebo) is added in the evening. Again at Day 7 (window + 2 days), Day 10 (window + 2 days and Day 14 (window + 2 days) if no AE related to the study drug is observed by caregiver and/or the investigator, another capsule (active or placebo) may be added in the morning. Table II below provides a graphic illustration of the titration schedule.

Table II. Titration Schedule

Schedule/Time		**Days 1 to 2**	**Days 3 to 6**	**Days 7 to 9**	**Days 10 to 13**	**Day 14***
Schedule A	**Evening**	5 mg 1 Capsule	10 mg 2 Capsules	15 mg 3 Capsules	15 mg 3 Capsules	15 mg 3 Capsules
	Morning	None	None	None	Placebo 1 Capsule	Placebo 2 Capsules
Schedule B	**Evening**	5 mg 1 Capsule	10 mg 2 Capsules	15 mg 3 Capsules	15 mg 3 Capsules	15 mg 3 Capsules
	Morning	None	None	None	5 mg 1 Capsule	10 mg 2 Capsules
Schedule C	**Evening**	Placebo 1 Capsule	Placebo 2 Capsules	Placebo 3 Capsules	Placebo 3 Capsules	Placebo 3 Capsules
	Morning	None	None	None	Placebo 1 Capsule	Placebo 2 Capsules

* To end of study treatment period

Slowed up-titration or delayed up-titration will be acceptable if tolerability does not allow immediate further dose-escalation at any of the above detailed days (3, 7, 10, 14). Down-titration in the case tolerability is not acceptable (e.g., somnolence, dizziness, change in behavior) after a previous up-titration step or during the course of the 12 week treatment, dose can be reduced to the previous level or even further. However, once a tolerable dose has been reached, it shall remain constant for the duration of the treatment period. Once a target dose is achieved the treatment may continue. For

example, at Day 14: Earliest day the target dose can be reached (2 capsules in the morning and 3 in the evening) the subject may be kept stable until End of Treatment visit (week 12) unless intolerability requires down-titration.

All subjects will be screened for participation in the study up to 28 days prior to the first dose administration. Inclusion criteria may include one or more of the following: (1) Age ≥ 18 years, ≤ 40 years; (2) Must possess a clinical diagnosis of AS according to the 2005 consensus criteria with developmental delay, movement or balance disorder, and speech disorder; (3) Must possess a previous or current molecular confirmation of AS; (4) Subjects must be receiving a stable dose of concomitant medications, including anti-epileptic medication, supplements, and special diets, for at least 4 weeks prior to Baseline, and be able to maintain these throughout the duration of the study.

Exclusion Criteria may include one or more of the following: (1) Non-ambulatory subjects (e.g. requiring a wheelchair) not able to perform the tests for Assessment of Motor Ability/Function (as described above); (2) Poorly controlled seizures defined as > 3 absence-type seizure per week and/or > 1 major seizure episodes per month; (3) Concomitant cardiovascular, respiratory diseases; Concomitant liver disease with alanine aminotransferase or aspartate aminotransferase >2.5 x upper limit of normal (ULN); (4) Concomitant renal disease with creatinine above ULN (5) Concomitant hematologic disease with absolute neutrophil count >2 x 10^9/L or platelets <50 x10^9/L or hemoglobin <80 g/L; (6) Other genetic disorders; (7) Concomitant use of minocycline, levodopa, sleep medication and any other use of any investigational agent, device, and/or investigational procedure 4 weeks prior to Baseline and during the study; (8) At risk of suicide based on ABC- Irritability Subscale

Descriptive statistics may be used to summarize all primary and secondary endpoints as well as baseline variables, by treatment group. For continuous variables, n, number of missing values, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, frequency and percentage will be presented for each category. Confidence intervals (CI) will be provided where meaningful. All CIs will be two-sided 95% confidence intervals.

Example 7

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Angelman syndrome

This study is designed to determine whether lower doses of gaboxadol lead to an improvement in younger patients or patients with less severe clinically evaluated symptoms. For example, adolescent patients (age 12-18 years) may have the similar clinical presentation and baseline disease characteristics as the adult population but the reduction in ambulation may be less severe. In these patients it is anticipated that the target benefit of gaboxadol will also include the reduction in ataxia and the improvement in ambulatory function.

In pediatric patients (6 months to 12 years) the diagnosis of Angelman Syndrome is usually made around 1 year of age based on important delay in the development status and eventually persistent seizures. As the child grows older, additional neurologic deficit will contribute to the disease presentation leading to ataxia and walking disability. For these prospective participants, the inclusion criteria for randomization and assessment procedures is similar to that previously described.

After randomization the participants are placed into 6 separate treatment groups (A-F) and a placebo group. Treatment group A receives 7.5 mg gaboxadol in the evening. Treatment group B receives 5 mg gaboxadol in the evening. Treatment group C receives 5 mg gaboxadol in the evening and 2.5 mg gaboxadol in the morning. Treatment group D receives 2.5 mg gaboxadol in the evening. Treatment group E receives 2.5 mg gaboxadol in the evening and 1 mg gaboxadol in the morning. Treatment group F receives 1 mg gaboxadol in the evening.

Example 8

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Fragile X syndrome

This study is designed to determine whether gaboxadol leads to an improvement in one or more symptoms of Fragile X syndrome. Participants

are randomized into 6 separate treatment groups (A-F). Inclusion criteria for randomization require patients that have been diagnosed with Fragile X syndrome. For example, patients who are at least moderately ill based on a Clinical Global Impression Severity score of at least 4 and have qualifying scores on the ABC-C and IQ test

After randomization the participants are separated into 6 treatment groups (A-F) and a placebo group. Treatment group A receives 20 mg gaboxadol in the evening. Treatment group B receives 15 mg gaboxadol in the evening. Treatment group C receives 15 mg gaboxadol in the evening and 5 mg gaboxadol in the morning. Treatment group D receives 10 mg gaboxadol in the evening. Treatment group E receives 10 mg gaboxadol in the evening and 10 mg gaboxadol in the morning. Treatment group F receives 10 mg gaboxadol in the evening and 5 mg gaboxadol in the morning.

Participants are assessed throughout the treatment period to determine whether administration of gaboxadol leads to an improvement in one or more symptoms of Fragile X syndrome. In particular, patients are assessed using one or more primary and secondary outcome measures. Primary Outcome Measures may include:

Change From Baseline in Behavioral Symptoms of Fragile X Syndrome Using the Aberrant Behavior Checklist-Community Edition (ABC-CFX) Total Score;

Global Improvement of Symptoms in Fragile X Using the Clinical Global Impression- Improvement (CGI-I) Scale;

Change From Baseline in Irritability, Lethargy/Withdrawal, Stereotypic Behavior, Hyperactivity, Inappropriate Speech and Social Avoidance Assessed by the Individual Subscales of the ABC-CFX Scale;

Change From Baseline in Repetitive Behaviors Assessed Using the Repetitive Behavior Scale - Revised (RBS-R) Scores;

Visual Analogue Scale (Behavior); Expressive Vocabulary Test; Vineland Adaptive Behavior Scale-II (VABS-II) Adaptive Behavior Composite Score; and Aberrant Behavior Checklist-Community Edition (ABC-C) Composite Score.

Example 9

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Fragile X Syndrome.

This study is designed to determine whether lower doses of gaboxadol will lead to an improvement in younger patients or patients with less severe clinically evaluated symptoms. For these participants, the inclusion criteria for randomization and assessment procedures will be similar to that previously described.

After randomization the participants are randomized into 6 separate treatment groups (A-F) and a placebo group. Treatment group A receives 7.5 mg gaboxadol in the evening. Treatment group B receives 5 mg gaboxadol in the evening. Treatment group C receives 5 mg gaboxadol in the evening and 2.5 mg gaboxadol in the morning. Treatment group D receives 2.5 mg gaboxadol in the evening. Treatment group E will receive 2.5 mg gaboxadol in the evening and 1 mg gaboxadol in the morning. Treatment group F receives 1 mg gaboxadol in the evening.

Example 10

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Fragile X-Associated Tremor/Ataxia Syndrome

This protocol is directed to treating symptomatic permutation carriers who have pre-FXTAS or FXTAS symptoms including neuropathy, central pain symptoms, insomnia, and full FXTAS involving tremor and ataxia which is often associated with cognitive decline.

This will be a two-site study. Participants will be individuals with the premutation and FXTAS. *FMR1* CGG repeat lengths will be quantified in all subjects using conventional procedures. FXTAS will be diagnosed following published criteria (Bacalman et al., Clin Psychiatry 2006, 67:87–94; Jacquemont et al., Lancet Neurol 2003, 6:45–55). The study will involve a controlled trial of gaboxadol lasting three months followed by a three month open-label so that those individuals that were treated for the first three months on gaboxadol would continue for a second three months and those individuals

on placebo would go on gaboxadol for the second three months. Each site would enroll 20 patients per year for a total of 40 at each site over a two year period and between the sites there would be 80 patients participating.

Identical appearing tablets containing either gaboxadol or placebo will be administered. After randomization the participants are randomized into separate treatment groups and a placebo group. Treatment group A receives 7.5 mg gaboxadol in the evening. Treatment group B receives 5 mg gaboxadol in the evening. Treatment group C receives 5 mg gaboxadol in the evening and 2.5 mg gaboxadol in the morning. Treatment group D receives 2.5 mg gaboxadol in the evening. Treatment group E receives 2.5 mg gaboxadol in the evening and 1 mg gaboxadol in the morning. Treatment group F receives 1 mg gaboxadol in the evening.

At baseline, and then at three months, and then at six months, the following studies would be done: An assessment of the severity of pain using a pain index and documentation of the type of pain; and a sleep diary will be implemented. Quantitative measures will be implemented using an actometer to observe the severity of sleep disturbances over a one week period of time. Neuropsychological measures would include the Mini-Mental State Examination (MMSE), Behavioral Dyscontrol Scale (BDS-II), Wechsler Memory Scale IV, the California Verbal Learning Test 2 (CVLT-2), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the SCL-90 for a determination of emotional improvements. Any improvements in the MMSE, the BDS-II, and in event related potential (ERP) studies, particularly with the N4 Repetition Paradigm, and in volumetric changes in the hippocampus will be assessed. Motor assessments will be made which documents abnormalities in those with FXTAS compared to other movement disorders. An FXTAS rating scale will be utilized. MRI volumetric studies with the 3Tesla MRI along with DTIs will be conducted. Eye-tracking measures looking at an inhibitory paradigm will be evaluated. The P6 repetition effect over a six month will be evaluated. All of these measures will be at baseline, three months, and six months. Baseline cognitive testing using the Wechsler Scale and WAIS-IV will be carried out

also. This could be repeated after one year but typically not sooner. Improvement in neuropathy may be detected and followed through clinical examination using neurodiagnostic studies or electrophysiological studies.

EXAMPLE 11

Prospective Assessment of the Efficacy of Gaboxadol in Patients with Fragile X-Associated Tremor/Ataxia Syndrome

This study is designed to determine whether gaboxadol leads to an improvement in cognitive symptoms, i.e., attentional processes which are fundamental to executive function/dysfunction associated with Fragile X-associated tremor/ataxia syndrome (FXTAS) and involves a placebo-controlled, double-blind, randomized clinical trial and an auditory "oddball" task. Participants will be individuals with FXTAS. *FMR1* CGG repeat lengths will be quantified in all subjects using conventional procedures. FXTAS will be diagnosed following published criteria (Bacalman et al., Clin Psychiatry 2006, 67:87–94; Jacquemont et al., Lancet Neurol 2003, 6:45–55). For the main gaboxadol trial, 200 potential participants will be screened for eligibility. Randomization to either placebo or gaboxadol will be blinded to all study personnel, investigators, and participants until the end of the one year trial period. Participants will participate in an auditory "oddball"/event related potentials (ERPs) experiment.

Identical appearing tablets containing either gaboxadol or placebo will be administered. After randomization the participants are randomized into 6 separate treatment groups (A-F) and a placebo group. Treatment group A receives 7.5 mg gaboxadol in the evening. Treatment group B receives 5 mg gaboxadol in the evening. Treatment group C receives 5 mg gaboxadol in the evening and 2.5 mg gaboxadol in the morning. Treatment group D receives 2.5 mg gaboxadol in the evening. Treatment group E receives 2.5 mg gaboxadol in the evening and 1 mg gaboxadol in the morning. Treatment group F receives 1 mg gaboxadol in the evening.

In the auditory "oddball" experiment, patients will be instructed to detect an infrequent "oddball" tone embedded in a train of non-target standard

tones. Subjects will press a button to each target detected and also keep a mental count of the number of targets in that experimental block. Prior studies in premutation carriers using the same "oddball" paradigm have demonstrated an altered frontal P300 (P3) ERP component in FXTAS patients, which tracks their executive dysfunction. See, Yang et al., Ann Neurol 74, 275–283 (2013); Yang et al., Cereb Cortex 23, 2657–2666 (2013). In these studies and others, the earlier abnormalities of prolonged N100 latency and reduced P200 (P2) amplitude were also found in a predominately male FXTAS group but not in female premutation carriers asymptomatic of FXTAS9.

Neuropsychological testing will involve examining each patient's EEG. Accordingly, EEG during a two-stimulus auditory oddball experiment will be recorded in a sound-attenuated, dimly-lit chamber. Lower (113 Hz) and higher (200 Hz) frequency pure tones will be presented at 40 dB above individual hearing level in 4 blocks, each containing 100 tones, with a stimulus onset asynchrony jittered from 1.0–1.5 seconds. Prior to each block, subjects will be instructed to respond to the infrequent (probability equaling 25%) "oddball" tones (high or low target tones, counterbalanced across blocks). A dual task will be employed in which subjects are instructed to press a button to each target tone, and to also keep a mental count of the number of targets in each block. The mental count of target tones will be reported immediately following completion after each block. 32-channel EEG will be recorded with a Nicolet-SM-2000 amplifier (band-pass = 0.016–100 Hz, sampled at 250 Hz). Data Analysis will involve the |count-hit| discrepancy in each block (i.e., the absolute value of the difference between correct button-presses and mental count to target tones within a block) will be calculated for each participant, as an inverse measure (i.e., a lower value represents better performance) of attention/working memory performance during the oddball task. Event-locked EEG segments contaminated with blinks, eye movements, excessive muscle activity, or amplifier blocking will be rejected using a semi-automated computer algorithm. Artifact-free EEG segments of 1024 ms (with a 100 ms pre-stimulus baseline period, and 924 ms post-stimulus onset) will be averaged by experimental condition to obtain the ERPs. Mean amplitude and local peak latency of 4 ERP components will be quantified in the following time windows: N100 (N1, 70–150 ms), P2 (160–260 ms), N200 (N2,

170–300 ms), and P3 (300–650 ms). The waveforms to both target and standard tones will be used to measure N1. The P2 will be measured from ERPs to standard tones. The N2 component is defined from the difference wave (ERPs to targets minus standards). The P3 will be measured from both the difference wave and the ERP waveform to targets. ERP measures will be submitted to repeated-measures ANOVAs (SPSS 22, IBM) with the between-subjects factor of treatment, and the within-subjects factors of visit and electrode. Analyses of N1 and P2 will include 4 fronto-central electrodes (Fz, Cz, FC1/2). Five central channels (Cz, FC1/2, CP1/2) will be used for the N2 analyses. P3 analyses will be carried out with 26 scalp electrodes (all except FP1/2). The Greenhouse-Geiser correction will be used to adjust for violations of sphericity, where appropriate. To further characterize the modulatory effects of gaboxadol on the P2 component, a habituation analysis will be conducted for P2 amplitude. P2 mean amplitude in response to the first 30 standard tones will be compared to the amplitude of response to the last 30 standard tones within the first block of each study, with the between-subjects factor of treatment, and the within-subjects factors of visit, trial position, and electrode. Data from a group of 16 age-matched normal controls, each of whom will have only underwent one ERP recording, will be used to demonstrate the normal habituation effect. Linear regression will be used to examine the correlations between changes (1-year follow-up minus baseline) in the |count-hit| discrepancy and in ERP measures for which significant treatment effects are shown. Correlations between local peak amplitudes of P2 (measured after application of a 30 Hz low-pass filter) and CGG repeats will be tested.

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. Such equivalents are intended to be encompassed by the claims.

What is claimed is:

1. A method of treating a developmental disorder comprising administering to a patient in need thereof about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides improvement in the patient for more than 6 hours after administration.

2. The method of claim 1, wherein the developmental disorder is selected from the group consisting of an Autistic Spectrum Disorder, pervasive developmental disorder, Autism, Angelman syndrome, Fragile X syndrome, Fragile X–associated tremor/ataxia syndrome (FXTAS), Rett syndrome, Asperger's syndrome, Childhood Disintegrative Disorder, Lanau-Kleffner Syndrome, Prader-Willi Syndrome, Tardive Dyskinesia, and Williams Syndrome.

3. The method of claim 1, wherein the developmental disorder is Angelman syndrome.

4. The method of claim 1, wherein the developmental disorder is Fragile X syndrome.

5. The method of claim 1, wherein the developmental disorder is Fragile X–associated tremor/ataxia syndrome (FXTAS).

6. The method of claim 1, wherein the patient is administered a composition comprising about 1 mg to about 15 mg gaboxadol or a pharmaceutically acceptable salt thereof.

7. The method of claim 1, wherein the patient is administered a composition comprising about 1 mg to about 10 mg gaboxadol or a pharmaceutically acceptable salt thereof.

8. The method of claim 1, wherein the patient is administered a composition comprising about 1 mg to about 5 mg gaboxadol or a pharmaceutically acceptable salt thereof.

9. The method of claim 1, wherein the *in vivo* plasma profile of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is reduced by more than 50%.

10. The method of claim 1, wherein the AUC_{6-12} of the patient 6 hours after administration of the gaboxadol or pharmaceutically acceptable salt thereof is less than 75% of the administered dose.

11. The method of claim 1, wherein the method provides improvement in at least one symptom selected from the group consisting of ataxia, gait, speech impairment, vocalization, cognition, motor activity, clinical seizure, hypotonia, hypertonia, feeding difficulty, drooling, mouthing behavior, sleep difficulties, hand flapping, easily provoked laughter and short attention span.

12. The method of claim 1, wherein the method provides improvement in the patient for more than 6 hours.

13. The method of claim 1, wherein the method provides improvement in the patient for more than 8 hours.

14. The method of claim 1, wherein the composition provides improvement in the patient for at least 12 hours.

15. A method of treating a developmental disorder comprising administering to a patient in need thereof gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides an *in vivo* plasma profile comprising a C_{max} less than about 400 ng/ml and wherein the method provides improvement in the patient for more than 6 hours after

administration of the gaboxadol or a pharmaceutically acceptable salt thereof.

16. A method of treating a developmental disorder comprising administering to a patient in need thereof gaboxadol or a pharmaceutically acceptable salt thereof wherein the method provides an *in vivo* plasma profile comprising a AUC_{6-12} of less than about 900 ng•hr/ml and wherein the method provides improvement in the patient for more than 6 hours after administration of the gaboxadol or a pharmaceutically acceptable salt thereof.

17. A method of treating a developmental disorder comprising administering to a patient in need thereof a first pharmaceutical composition comprising gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition comprising gaboxadol or a pharmaceutically acceptable salt thereof wherein the second pharmaceutical composition provides an *in vivo* plasma profile comprising a mean $AUC_{0-\infty}$ of at least 20% less than the first pharmaceutical composition.

18. The method of claim 17, wherein the second pharmaceutical composition provides an *in vivo* plasma profile comprising a mean $AUC_{0-\infty}$ of less than about 900 ng•hr/ml.

19. The method of claim 17, wherein the C_{max} of the first pharmaceutical composition is more than 20% greater than the C_{max} of the second pharmaceutical composition.

20. The method of claim 17, wherein the T_{max} of the first pharmaceutical composition is less than 2 hours.

21. The method of claim 17, wherein the first pharmaceutical composition comprises a dissolution of at least 80% within the first 10 minutes.

22. The method of claim 17, wherein the first pharmaceutical composition and the second pharmaceutical composition are provided in a single dosage form.

23. The method of claim 17, wherein the patient is provided about 0.05 mg/kg/day to about 5 mg/kg/day gaboxadol or a pharmaceutically acceptable salt thereof in the first pharmaceutical composition.

24. The method of claim 17, wherein the first pharmaceutical composition comprises about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof.

25. The method of claim 17, wherein the second pharmaceutical composition comprises about 0.05 mg to about 30 mg gaboxadol or a pharmaceutically acceptable salt thereof.

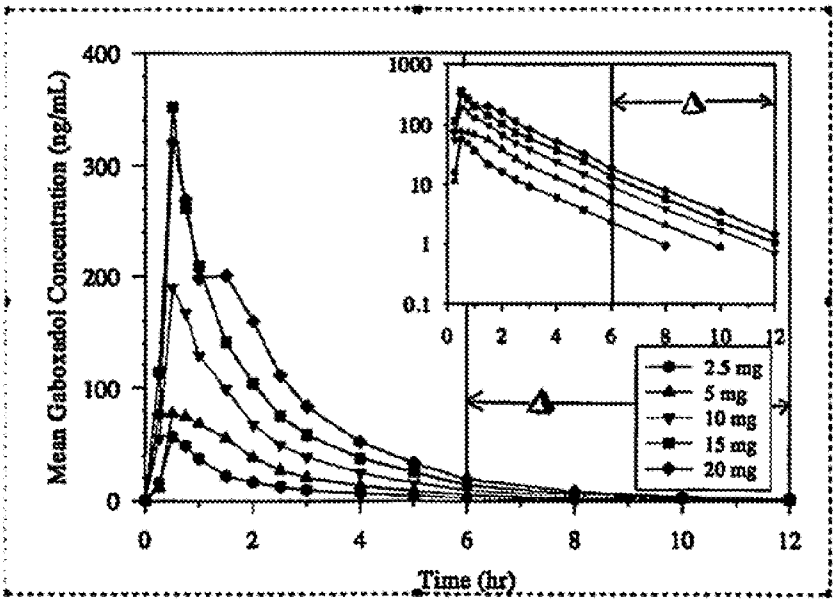
Mean Gaboxadol Concentration (ng/mL)
Time (hr)
2.5 mg
5 mg
10 mg
15 mg
20 mg
Δ
Δ

FIG. 1

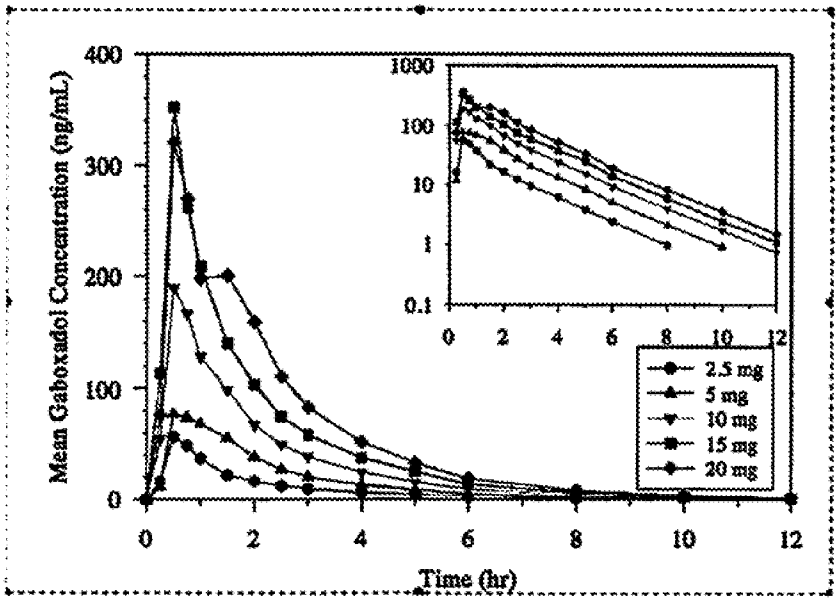
Mean Gaboxadol Concentration (ng/mL)
Time (hr)
2.5 mg
5 mg
10 mg
15 mg
20 mg

FIG. 2

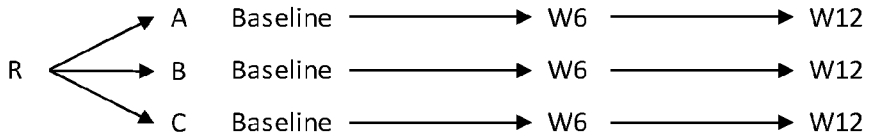

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/42238

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/424; A61K 31/4353; A61P 25/00 (2016.01)
CPC - A61K 31/424; A61K 31/4353
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/424; A61K 31/4353; A61P 25/00 (2016.01)
CPC: A61K 31/424; A61K 31/4353

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/300; 514/379; 514/380 (key word limited; see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar
Search terms used: gaboxadol, developmental disorder, treat, autistic/autism, pervasive developmental disorder, Fragile X/ataxia syndrome, Angelman syndrome

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OLMOS-SERRANO J. L. et al., "The GABA(A) Receptor Agonist THIP Ameliorates Specific Behavioral Deficits in the Mouse Model of Fragile X Syndrome", Developmental Neuroscience 2011, Vol 33, issue 5, pp. 395-403; see entire document, especially pg 396 and 401	1-25
Y	US 2008/0269278 A1 (LUNDAHL et al.) 30 October 2008 (30.10.2008); para [0015], [0020], [0031]	1-16
Y	US 2010/0029770 A1 (ROBERTS et al.) 04 February 2010 (04.02.2010); para [0058], [0064]-[0065]	3, 5
Y	US 2009/0143335 A1 (LARSEN et al.) 04 June 2009 (04.06.2009); para [0033], [0080]; Figs. 1-4	9-10, 15-25
Y	US 2003/0077297 A1 (CHEN et al.) 24 April 2003 (24.04.2003); para [0013], [0078], [0217], [0227], [0370]	17-25
Y	US 2007/0112017 A1 (BARLOW et al.) 17 May 2007 (17.05.2007); para [0150], [0193]	23

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 September 2016 (01.09.2016)	27 SEP 2016

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

(19)中华人民共和国国家知识产权局

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A61K 31/424(2006.01)
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A61P 25/00(2006.01)

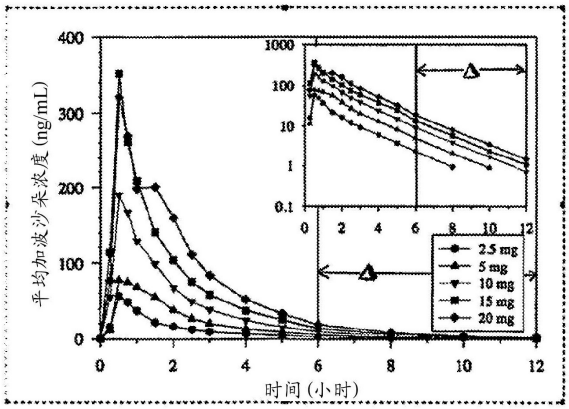
权利要求书2页 说明书23页 附图1页

(54)发明名称

用加波沙朵治疗发育障碍的方法

(57)摘要

提供了用加波沙朵或其药学上可接受的盐治疗发育障碍的方法，所述发育障碍诸如Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)、孤独症谱系障碍、孤独症、阿斯伯格综合征、广泛性发育障碍、儿童期崩解症、Rett综合征、Lanau-Kleffner综合征、Prader-Willi综合征、迟发性运动障碍、和/或威廉姆斯综合征。所述方法提供了可以用于改进发育障碍的一种或更多种症状的治疗性组合物。



CN 108024997 A

1.一种治疗发育障碍的方法,所述方法包括将约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中所述方法提供在施用之后持续多于6小时的所述患者中的改进。

2.根据权利要求1所述的方法,其中所述发育障碍选自由以下组成的组:孤独症谱系障碍、广泛性发育障碍、孤独症、Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)、Rett综合征、阿斯伯格综合征、儿童期崩解症、Lanau-Kleffner综合征、Prader-Willi综合征、迟发性运动障碍和威廉姆斯综合征。

3.根据权利要求1所述的方法,其中所述发育障碍是Angelman综合征。

4.根据权利要求1所述的方法,其中所述发育障碍是脆性X综合征。

5.根据权利要求1所述的方法,其中所述发育障碍是脆性X相关的震颤/共济失调综合征(FXTAS)。

6.根据权利要求1所述的方法,其中所述患者被施用一种组合物,所述组合物包含约1mg至约15mg加波沙朵或其药学上可接受的盐。

7.根据权利要求1所述的方法,其中所述患者被施用一种组合物,所述组合物包含约1mg至约10mg加波沙朵或其药学上可接受的盐。

8.根据权利要求1所述的方法,其中所述患者被施用一种组合物,所述组合物包含约1mg至约5mg加波沙朵或其药学上可接受的盐。

9.根据权利要求1所述的方法,其中在所述加波沙朵或其药学上可接受的盐施用6小时之后所述患者的体内血浆谱降低多于50%。

10.根据权利要求1所述的方法,其中在所述加波沙朵或其药学上可接受的盐施用6小时之后所述患者的AUC_{6-12}是所施用剂量的小于75%。

11.根据权利要求1所述的方法,其中所述方法提供选自由以下组成的组的至少一种症状的改进:共济失调、步态、言语障碍、发声、认知、运动活动、临床癫痫发作、张力减退、张力亢进、喂食困难、流口水、口部行为、睡眠困难、拍手、容易发笑和注意力短暂。

12.根据权利要求1所述的方法,其中所述方法提供持续多于6小时的所述患者中的改进。

13.根据权利要求1所述的方法,其中所述方法提供持续多于8小时的所述患者中的改进。

14.根据权利要求1所述的方法,其中所述组合物提供持续至少12小时的所述患者中的改进。

15.一种治疗发育障碍的方法,所述方法包括将加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中所述方法提供包括小于约400ng/ml的C_{max}的体内血浆谱,并且其中所述方法提供在所述加波沙朵或其药学上可接受的盐施用之后持续多于6小时的所述患者中的改进。

16.一种治疗发育障碍的方法,所述方法包括将加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中所述方法提供包括小于约900ng·hr/ml的AUC_{6-12}的体内血浆谱,并且其中所述方法提供在所述加波沙朵或其药学上可接受的盐施用之后持续多于6小时的所述患者中的改进。

17.一种治疗发育障碍的方法,所述方法包括将第一药物组合物和第二药物组合物施

用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中所述第二药物组合物提供包括比所述第一药物组合物小至少20％的平均$AUC_{0-\infty}$的体内血浆谱。

18.根据权利要求17所述的方法，其中所述第二药物组合物提供包括小于约900ng·hr/ml的平均$AUC_{0-\infty}$的体内血浆谱。

19.根据权利要求17所述的方法，其中所述第一药物组合物的C_{max}比所述第二药物组合物的C_{max}大多于20％。

20.根据权利要求17所述的方法，其中所述第一药物组合物的T_{max}为小于2小时。

21.根据权利要求17所述的方法，其中所述第一药物组合物包括在前10分钟内至少80％的溶出度。

22.根据权利要求17所述的方法，其中所述第一药物组合物和所述第二药物组合物以单一剂型提供。

23.根据权利要求17所述的方法，其中以所述第一药物组合物向所述患者提供约0.05mg/kg/天至约5mg/kg/天的加波沙朵或其药学上可接受的盐。

24.根据权利要求17所述的方法，其中所述第一药物组合物包含约0.05mg至约30mg加波沙朵或其药学上可接受的盐。

25.根据权利要求17所述的方法，其中所述第二药物组合物包含约0.05mg至约30mg加波沙朵或其药学上可接受的盐。

用加波沙朵治疗发育障碍的方法

[0001] 相关申请的交叉引用

[0002] 本申请要求2016年6月7日提交的美国临时申请第62/346,763号;2016年5月6日提交的美国临时申请第62/332,567号;2015年8月20日提交的美国临时申请第62/207,595号和2015年7月17日提交的美国临时申请第62/193,717号的权益和优先权,其的所有通过引用以其整体并入本文。

技术领域

[0003] 提供了用加波沙朵(gaboxadol)或其药学上可接受的盐治疗发育障碍(developmental disorders)的方法。

[0004] 背景

[0005] 加波沙朵(4,5,6,7-四氢异噁唑并[5,4-c]吡啶-3-醇)(THIP))在EP专利第0000338号中和在EP专利第0840601号、美国专利第4,278,676号、第4,362,731号、第4,353,910号和WO 2005/094820中描述。加波沙朵是一种选择性$GABA_A$受体激动剂,具有对包含δ-亚基的$GABA_A$受体的偏好。在20世纪80年代早期,加波沙朵是一系列试验性研究的主题,这些试验性研究测试了其作为镇痛药和抗焦虑药的效力,以及对迟发性运动障碍、亨廷顿氏舞蹈病(Huntington's disease)、阿尔茨海默病和痉挛状态的治疗的效力。在20世纪90年代,加波沙朵进入后期开发阶段,用于治疗失眠。在该化合物在三个月的效力研究中未能显示出对睡眠开始(sleep onset)和睡眠维持的显著作用之后,开发停止。另外,接受加波沙朵的具有药物滥用史的患者经历了精神不良事件的急剧增加。

[0006] 用于发育障碍的治疗,诸如孤独症谱系障碍、Rett综合征、Angelman综合征、和脆性X综合征的治疗是有限的。例如,Angelman综合征是由编码泛素E3连接酶的UBE3A基因的功能损失引起的神经发育障碍。运动功能异常是Angelman综合征的特征性特征(characteristic feature),但作用机制和有效的治疗策略均尚未被阐明。已经显示,施用低剂量的加波沙朵改进小脑脑切片中Purkinje细胞群体的异常放电特性,并且降低Ube3a缺陷小鼠体内的小脑共济失调。这些结果表明,药理学上增加的紧张性抑制(tonic inhibition)可以是用于减轻Angelman综合征中的运动功能异常的有用策略。Egawa,等,Science Translational Medicine,4:163ra157(2012)。

[0007] 脆性X综合征可能是智力残疾最常见的遗传病因,并且也是孤独症最常见的单基因病因。它是由脆性X智力低下基因(FMR1)上的突变以及脆性X智力低下蛋白的缺乏引起,这继而导致许多突触蛋白翻译的抑制减少。主要的努力已经集中在代谢型谷氨酸受体(mGluR)靶向的治疗;然而,关于γ-氨基丁酸(GABA)系统的研究及其作为靶向的治疗的潜力的研究不太受到重视。脆性X小鼠模型(Fmr1-敲除)显示GABA亚基受体减少、GABA合成减少、GABA分解代谢增加、以及在脑的许多区域中GABA能(GABAergic)输入总体减少。这些症状也在患有孤独症和其他神经发育障碍的个体中被观察到,因此针对脆性X综合征的靶向的治疗正引领其他神经发育综合征和孤独症的治疗。已经讨论了潜在的GABA能治疗,诸如利鲁唑(riluzole)、加波沙朵、噻加宾(tiagabine)和氨己烯酸(vigabatrin)。然而,需要进

一步研究以确定用于脆性X综合征的GABA能治疗的安全性和效力。此外，脆性X动物模型中的进一步研究对于提供加波沙朵的效力和安全性的累积证据是必要的。Lozano等，Neuropsychiatr Dis Treat.,10:1769-1779(2014)。

[0008] 脆性X相关的震颤/共济失调综合征(FXTAS)是一种迟发性障碍，通常发生在50岁之后。FMR1基因中的突变增加了发展FXTAS的风险。该突变涉及在FMR1基因内扩增的被称为CGG三联体重复的DNA区段。通常，该DNA区段被重复5次至约40次。在患有FXTAS的人中，CGG区段可以被重复55次至200次。这种突变被称为FMR1基因前突变。多于200次重复的扩增(全突变)引起以上讨论的脆性X综合征。FXTAS通常以关于运动和思维能力(认知)的问题为特征。FXTAS的征象和症状通常随着年龄而恶化。受影响的个体在小脑具有损伤区域，该脑区域控制运动。FXTAS的特征性特征是意向性震颤(其是当试图执行有意识运动(voluntary movement)诸如伸手去拿某个物体时的肢体颤抖或震动)、以及关于协调和平衡的问题(共济失调)。许多受影响的个体发展其他运动问题，诸如帕金森病，其包括当不动时的震颤(静止性震颤)、僵硬和异常缓慢运动(运动迟缓)。另外，受影响的个体可能具有降低的感觉、麻木或刺痛、疼痛或者下肢的肌肉无力，并且无法控制膀胱或肠。其他症状可以包括慢性疼痛综合征，诸如纤维肌痛和慢性偏头痛、甲状腺功能减退、高血压、失眠、睡眠呼吸暂停、眩晕、嗅觉功能异常和听力损失。患有FXTAS的人通常具有认知障碍，诸如短期记忆损失和执行功能损失，所述执行功能是计划和实施行动以及制定解决问题策略的能力。这种功能的损失削弱了技能诸如冲动控制、自我监控、适当集中注意力和认知灵活性。患有FXTAS的许多人经历精神病学症状，诸如焦虑、抑郁、情绪化或易怒。

[0009] 当前不存在可以阻止或逆转FXTAS发病机制的靶向的治疗性干预。然而，已经提出了具有潜在的症状性益处的许多治疗方法。已经提出扑米酮(primidone)，β-受体阻滞剂诸如心得安(propanolol)、托吡酯(topiramate)、卡比多巴(carbidopa)/左旋多巴(levodopa)、和苯二氮卓类(benzodiazepines)控制与FXTAS相关的震颤；肉毒杆菌(botulinum)毒素用于无意识的肌肉活动，诸如肌张力障碍和痉挛状态；卡比多巴/左旋多巴、金刚烷胺和丁螺环酮(buspirone)用于共济失调；胆碱酯酶抑制剂诸如多奈哌齐(donepezil)和美金刚(一种NMDA拮抗剂)用于认知缺陷和痴呆；以及抗抑郁药和抗精神病药用于精神病学症状。参见，例如，Hagerman,等,Clin Interv Aging.2008Jun;3(2):251-262。

[0010] 因此，对患有发育障碍的患者的有效治疗仍然存在需求，所述发育障碍诸如Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)、孤独症谱系障碍、孤独症、阿斯伯格综合征、广泛性发育障碍、儿童期崩解症、Rett综合征、Lanau-Kleffner综合征、Prader-Willi综合征、迟发性运动障碍和/或威廉姆斯综合征。

[0011] 概述

[0012] 本文描述的治疗发育障碍的方法包括将约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者，其中所述方法提供次日功能的改进。本文描述的治疗发育障碍的方法包括将约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者，其中所述方法提供在施用至患者之后持续多于6小时的患者中的改进。本文描述了治疗发育障碍的方法，所述方法包括将加波沙朵或其药学上可接受的盐施用至有相应需要的患者，其中所述方法提供包括小于约400ng/ml的C_{max}的体内血浆谱，并且其中所述

方法提供在加波沙朵或其药学上可接受的盐施用之后持续多于6小时的所述患者中的改进。本文描述了治疗发育障碍的方法，所述方法包括将加波沙朵或其药学上可接受的盐施用至有相应需要的患者，其中所述方法提供包括小于约900ng·hr/ml的AUC_{6-12}的体内血浆谱，并且其中所述方法提供在加波沙朵或其药学上可接受的盐施用之后持续多于6小时的所述患者中的改进。本文描述了治疗发育障碍的方法，所述方法包括将第一药物组合物和第二药物组合物施用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中所述第二药物组合物提供包括比所述第一药物组合物小至少20％的平均$AUC_{0-\infty}$的体内血浆谱。

[0013] 在实施方案中，发育障碍可以是孤独症谱系障碍、广泛性发育障碍、孤独症、Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)、Rett综合征、阿斯伯格综合征、儿童期崩解症、Lanau-Kleffner综合征、Prader-Willi综合征、迟发性运动障碍、和/或威廉姆斯综合征。

[0014] 附图简述

[0015] 图1示出了如实施例1中描述的在单次口服剂量(2.5mg、5mg、10mg、15mg和20mg)后加波沙朵的算术平均血浆浓度-时间谱，其中水平线Δ指示6小时与12小时之间的变化。

[0016] 图2示出了如实施例1中描述的在单次口服剂量(2.5mg、5mg、10mg、15mg和20mg)后加波沙朵的算术平均血浆浓度-时间谱。

[0017] 图3示意性地阐释了在提出的12周治疗过程中对三组的治疗：1)单次晚上剂量2)早晨和晚上的剂量以及3)安慰剂。

[0018] 详细说明

[0019] 本文描述了用加波沙朵或其药学上可接受的盐治疗发育障碍的方法。许多药物产品以固定剂量以规律间隔被施用，以达到治疗效力。其作用持续时间由其血浆半衰期反映。加波沙朵是一种选择性$GABA_A$受体激动剂，具有相对短的半衰期(t1/2＝1.5h)。由于效力通常取决于中枢神经系统内的足够暴露，具有短半衰期的CNS药物的施用可能需要频繁的维持给药。有利地，本文公开了通过加波沙朵或其药学上可接受的盐的施用治疗发育障碍的方法。例如，在实施方案中，提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含约0.05mg至约30mg加波沙朵或其药学上可接受的盐，其中所述组合物提供在施用至患者之后持续多于6小时的改进。

[0020] 在实施方案中，发育障碍是孤独症谱系障碍、广泛性发育障碍、孤独症、Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)、Rett综合征、阿斯伯格综合征、儿童期崩解症、Lanau-Kleffner综合征、Prader-Willi综合征、迟发性运动障碍、和/或威廉姆斯综合征。在实施方案中，发育障碍是孤独症、Rett综合征、Angelman综合征、和/或脆性X综合征。在实施方案中，发育障碍是未分类的广泛性发育障碍(PDD-NOS)。从一个儿童至另一个儿童，PDD-NOS的症状可能广泛不同。总体而言，患有PDD-NOS的儿童可以被表征为具有社交障碍(impaired social interaction)，比患有孤独性障碍的儿童好但不及患有阿斯伯格综合征的儿童的语言技能、比患有阿斯伯格综合征或孤独性障碍的儿童少的重复性行为，且发病较晚。

[0021] 在实施方案中，发育障碍是孤独症。在其他实施方案中，发育障碍是Angelman综合征。在实施方案中，发育障碍是脆性X综合征。在实施方案中，发育障碍是脆性X相关的震颤/

共济失调综合征(FXTAS)。

[0022] 本文描述的实施方案提供了,对有相应需要的患者施用一种药物组合物,所述药物组合物包含加波沙朵或其药学上可接受的盐。加波沙朵或其药学上可接受的盐可以以酸加成盐、两性离子水合物、两性离子无水物、盐酸盐或氢溴酸盐或者以两性离子一水合物的形式提供。酸加成盐包括但不限于,马来酸、富马酸、苯甲酸、抗坏血酸、琥珀酸、草酸、双亚甲基水杨酸(bis-methylenesalicylic)、甲磺酸、乙二磺酸、乙酸、丙酸、酒石酸、水杨酸、柠檬酸、葡糖酸、乳酸、苹果酸、扁桃酸、肉桂酸、柠康酸、天冬氨酸、硬脂酸、棕榈酸、衣康酸、乙醇酸、对氨基苯甲酸、谷氨酸、苯磺酸或茶碱乙酸的加成盐、以及8-卤代茶碱,例如8-溴-茶碱。在其他合适的实施方案中,可以使用无机酸加成盐,包括但不限于盐酸、氢溴酸、硫酸、氨基磺酸、磷酸或硝酸加成盐。

[0023] 在实施方案中,加波沙朵以加波沙朵一水合物的形式提供。本领域技术人员将容易地理解,药物组合物中活性成分的量将取决于所提供的加波沙朵的形式。例如,包含5.0mg、10.0mg、或15.0mg加波沙朵的药物组合物对应于5.6mg、11.3mg、或16.9mg加波沙朵一水合物。

[0024] 在实施方案中,加波沙朵是结晶,诸如结晶盐酸盐、结晶氢溴酸盐或结晶两性离子一水合物。在实施方案中,加波沙朵以结晶一水合物的形式提供。

[0025] 先前已经证明一些药物类别的药物的氘化改进了药代动力学(PK)、药效动力学(PD)和毒性谱。因此,预期了富含氘的加波沙朵的使用并且在本文描述的方法和组合物的范围内。根据本领域已知的合成程序,氘可以被掺入于任何位置以代替氢。例如,可以经由质子-氘平衡交换将氘掺入至具有可交换质子的多种位置,诸如胺N--H。因此,可以通过本领域已知的方法选择性地或非选择性地掺入氘以提供富含氘的加波沙朵。参见Journal of Labeled Compounds and Radiopharmaceuticals 19(5)689-702(1982)。

[0026] 富含氘的加波沙朵可以通过在分子中的给定位置处代替氢的氘的掺入百分比来描述。例如,给定位置处1%的氘富含意味着,给定样品中1%的分子在该指定位置处包含氘。氘富含可以使用常规的分析方法诸如质谱和核磁共振谱学来确定。在实施方案中,富含氘的加波沙朵意味着,高于天然存在的分布(即,高于约.0156%)的指定位置富含氘。在实施方案中,氘富含是指在指定位置处氘不少于约1%、不少于约5%、不少于约10%、不少于约20%、不少于约50%、不少于约70%、不少于约80%、不少于约90%、或不少于约98%。

[0027] 在实施方案中,治疗发育障碍的方法包括将一种药物组合物施用至有相应需要的患者,所述药物组合物包含约0.05mg至约30mg加波沙朵或其药学上可接受的盐。

[0028] 在实施方案中,药物组合物包含0.1mg至25mg、0.1mg至20mg、0.1mg至15mg、0.5mg至25mg、0.5mg至20mg、0.5mg至15mg、1mg至25mg、1mg至20mg、1mg至15mg、1.5mg至25mg、1.5mg至20mg、1.5mg至15mg、2mg至25mg、2mg至20mg、2mg至15mg、2.5mg至25mg、2.5mg至20mg、2.5mg至15mg、3mg至25mg、3mg至20mg、3mg至15mg加波沙朵或其药学上可接受的盐。

[0029] 在实施方案中,药物组合物包含5mg至20mg、5mg至10mg、4mg至6mg、6mg至8mg、8mg至10mg、10mg至12mg、12mg至14mg、14mg至16mg、16mg至18mg、或18mg至20mg加波沙朵或其药学上可接受的盐。

[0030] 在实施方案中,药物组合物包含0.1mg、0.25mg、0.5mg、1mg、2.5mg、3mg、4mg、5mg、7mg、7.5mg、10mg、12.5mg、15mg、17.5mg、20mg加波沙朵或其药学上可接受的盐或者是此类

剂量的倍数的量。在实施方案中，药物组合物包含2.5mg、5mg、7.5mg、10mg、15mg、或20mg加波沙朵或其药学上可接受的盐。

[0031] 本文中的药物组合物可以以立即释放、延迟释放、延长释放或修饰释放谱提供。在实施方案中，具有不同药物释放谱的药物组合物可以被组合以产生两相或三相释放谱。例如，药物组合物可以以立即释放和延长释放谱提供。在实施方案中，药物组合物可以以延长释放和延迟释放谱提供。此类组合物可以作为脉冲制剂、多层片剂或胶囊，包括片剂、珠、颗粒等提供。组合物可以使用由被认为是安全和有效的材料制成的药学上可接受的“载体”来制备。“载体”包括药物制剂中存在的除了一种或更多种活性成分(the active ingredient or ingredients)以外的所有组分。术语“载体”包括，但不限于，稀释剂、粘合剂、润滑剂、崩解剂、填料和包衣组合物。

[0032] 在实施方案中，本文描述的药物组合物每天一次、每天两次或每天三次或者每隔一天被施用。在实施方案中，本文描述的药物组合物在晚上被提供至患者。在实施方案中，本文描述的药物组合物在晚上一次且在早晨一次被提供至患者。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是1mg至30mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是1mg至20mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是5mg、10mg或15mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是20mg。

[0033] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供发育障碍的至少一种症状的改进。症状可以包括，但不限于，共济失调、步态、言语障碍、发声、认知、运动活动、临床癫痫发作、张力减退、张力亢进、喂食困难、流口水、口部行为(mouthing behavior)、睡眠困难、拍手、容易发笑和注意力短暂。在实施方案中，根据本公开内容提供认知改进。认知指牵涉获得知识及理解的心理过程，诸如思维、认识、记忆、判断、及解决问题。大脑的这些较高水平功能包括语言、想象、感知以及复杂行为的计划和执行。

[0034] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在药物组合物施用至患者之后持续多于4小时的至少一种症状的改进。在实施方案中，根据本公开内容提供了在药物组合物施用至患者之后持续多于6小时的至少一种症状的改进。在实施方案中，根据本公开内容提供了在药物组合物施用至患者之后持续多于，例如，8小时、10小时、12小时、15小时、18小时、20小时或24小时的至少一种症状的改进。在实施方案中，根据本公开内容提供了在药物组合物施用至患者之后持续至少，例如，8小时、10小时、12小时、15小时、18小时、20小时或24小时的至少一种症状的改进。在实施方案中，根据本公开内容提供了在药物组合物施用至患者之后持续12小时的至少一种症状的改进。

[0035] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物对患者提供次日功能的改进。

[0036] 图1示出了在单次口服剂量(2.5mg、5mg、10mg、15mg和20mg)(参见,下文实施例1)后加波沙朵的算术平均血浆浓度-时间谱,其中水平线Δ指示6小时与12小时之间的变化。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于50%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于55%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于60%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于65%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于70%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中,本文提供了治疗发育障碍的方法,所述方法包括将提供体内血浆谱的约0.05mg至约30mg加波沙朵或其药学上可接受的盐施用至有相应需要的患者,其中在加波沙朵或其药学上可接受的盐施用6小时之后患者的所述体内血浆谱被降低了多于75%并且所述方法提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。

[0037] 在实施方案中,本文提供了治疗发育障碍的方法,其中在药物组合物施用约4小时之后,患者中的加波沙朵或其药学上可接受的盐的量是所施用剂量的小于约75%。在实施方案中,本文提供了方法,其中在药物组合物施用约,例如,6小时、8小时、10小时、12小时、15小时或20小时之后,患者中的加波沙朵或其药学上可接受的盐的量是小于约75%。

[0038] 在实施方案中,本文提供了治疗发育障碍的方法,其中在药物组合物施用约4小时之后,患者中的加波沙朵或其药学上可接受的盐的量是所施用剂量的小于约80%。在实施方案中,本文提供了方法,其中在药物组合物施用约,例如,6小时、8小时、10小时、12小时、15小时或20小时之后,患者中的加波沙朵或其药学上可接受的盐的量是所施用剂量的小于约80%。

[0039] 在实施方案中,本文提供了治疗发育障碍的方法,其中在药物组合物施用约4小时

之后，患者中的加波沙朵或其药学上可接受的盐的量是所施用剂量的在约65％至约85％之间。在实施方案中，在药物组合物施用之后在约，例如，6小时、8小时、10小时、12小时、15小时或20小时之后，患者中的加波沙朵或其药学上可接受的盐的量是所施用剂量的在约65％至约85％之间。

[0040] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于75％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于80％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于85％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于90％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于95％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供在施用6小时之后为所施用剂量的小于100％的体内血浆浓度并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。

[0041] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有小于约500ng/ml的C_{max}的体内血浆谱。在实施方案中，组合物提供在施用至患者之后持续多于6小时的改进。

[0042] 在实施方案中，组合物提供具有小于约，例如，450ng/ml、400ng/ml、350ng/ml、或300ng/ml的C_{max}的体内血浆谱，并且其中组合物提供患者的次日功能的改进。在实施方案中，组合物提供具有小于约，例如，250ng/ml、200ng/ml、150ng/ml、或100ng/ml的C_{max}的体内血浆谱，并且其中组合物提供患者的次日功能的改进。

[0043] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中

组合物提供具有小于约900ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，组合物提供患者的次日功能的改进。在实施方案中，组合物提供具有小于约，例如，850ng·hr/ml、800ng·hr/ml、750ng·hr/ml、或700ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱，并且其中组合物提供患者的次日功能的改进。在实施方案中，组合物提供在施用之后持续多于6小时的一种或更多种症状的改进。

[0044] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有小于约，例如，650ng·hr/ml、600ng·hr/ml、550ng·hr/ml、500ng·hr/ml、或450ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，其中组合物提供具有小于约，例如，400ng·hr/ml、350ng·hr/ml、300ng·hr/ml、250ng·hr/ml或200ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，组合物提供具有小于约，例如，150ng·hr/ml、100ng·hr/ml、75ng·hr/ml或50ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，在组合物施用至患者之后，在施用持续多于，例如，4小时、6小时、8小时、10小时或12小时之后，组合物提供患者的次日功能的改进。

[0045] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于75％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于80％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于85％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于90％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于95％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一定量的加波沙朵或其药学上可接受的盐施用至有相应需要的患者，这提供具有为C_{max}的小于100％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。

[0046] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于75％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于

6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于80％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于85％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于90％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于95％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为C_{max}的小于100％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。

[0047] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为所施用剂量的小于75％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为所施用剂量的小于80％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为所施用剂量的小于85％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为所施用剂量的小于90％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药

学上可接受的盐，其中组合物提供具有为所施用剂量的小于95％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物施用至有相应需要的患者，所述药物组合物包含加波沙朵或其药学上可接受的盐，其中组合物提供具有为所施用剂量的小于100％的AUC_{6-12}的体内血浆谱并且提供了在施用之后持续多于6小时、8小时、10小时、12小时、14小时、16小时、18小时、20小时、22小时或24小时的患者中的改进。在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将第一药物组合物和第二药物组合物施用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中所述第二药物组合物提供具有比第一药物组合物小至少约20％的平均$AUC_{0-\infty}$的体内血浆谱。

[0048] 在实施方案中，第一药物组合物和/或第二药物组合物每天一次、每天两次或每天三次或者每隔一天被施用。在实施方案中，第一药物组合物或第二药物组合物在晚上被提供至患者。在实施方案中，第二药物组合物包含是第一药物组合物中提供的加波沙朵的量的至少三分之一的量的加波沙朵。在实施方案中，第二药物组合物包含是第一药物组合物中提供的加波沙朵的量的至少一半的量的加波沙朵。

[0049] 在实施方案中，第一药物组合物或第二药物组合物在晚上一次且在早晨一次被提供至患者。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是1mg至30mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是1mg至20mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是10mg、15mg或20mg。在实施方案中，在24小时时间段内被施用至受试者的加波沙朵或其药学上可接受的盐的总量是20mg。

[0050] 在实施方案中，第一药物组合物和/或第二药物组合物可以以立即释放、延迟释放、延长释放或修饰释放谱提供。第一药物组合物和第二药物组合物可以同时提供或相隔时间间隔，例如，6小时、12小时等。在实施方案中，第一药物组合物和第二药物组合物可以以不同的药物释放谱提供以产生两相释放谱。例如，第一药物组合物可以以立即释放谱提供，且第二药物组合物可以以延长释放谱提供。在实施方案中，第一药物组合物和第二药物组合物中的一个或两者可以以延长释放或延迟释放谱提供。此类组合物可以作为脉冲制剂、多层片剂或胶囊，包括片剂、珠、颗粒等提供。在一些实施方案中，第一药物组合物是立即释放组合物。在实施方案中，第二药物组合物是立即释放组合物。在实施方案中，第一药物组合物和第二药物组合物以单独的立即释放组合物，例如，片剂或胶囊提供。在实施方案中，第一药物组合物和第二药物组合物相隔12小时提供。

[0051] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将第一药物组合物和第二药物组合物施用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中所述第二药物组合物提供具有比第一药物组合物小至少约，例如，25％、30％、35％、40％、45％或50％的平均$AUC_{0-\infty}$的体内血浆谱。在实施方案中，组合物提供患者的次日功能的改进。例如，组合物可以提供在第一药物组合物和/或第二药物组合物施用之后持续多于约，例如，6小时、8小时、10小时或12小时的一种或更多种症状的改进。

[0052] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将第一药物组合物和第二药物组合物施用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中所述第二药物组合物提供具有小于约900ng·hr/ml的平均$AUC_{0-\infty}$的体内血浆谱。在实施方案中，第二药物组合物提供具有小于约，例如，800ng·hr/ml、750ng·hr/ml、700ng·hr/ml、650ng·hr/ml或600ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，第二药物组合物提供具有小于约，例如，550ng·hr/ml、500ng·hr/ml、450ng·hr/ml、400ng·hr/ml或350ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，第二药物组合物提供具有小于约，例如，300ng·hr/ml、250ng·hr/ml、200ng·hr/ml、150ng·hr/ml或100ng·hr/ml的$AUC_{0-\infty}$的体内血浆谱。在实施方案中，第一药物组合物和第二药物组合物被施用，其中组合物提供患者的次日功能的改进。在实施方案中，第一药物组合物提供在第一药物组合物施用之后持续多于，例如，6小时、8小时或12小时的一种或更多种症状的改进。

[0053] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将第一药物组合物和第二药物组合物施用至有相应需要的患者，所述第一药物组合物包含加波沙朵或其药学上可接受的盐，所述第二药物组合物包含加波沙朵或其药学上可接受的盐，其中第一组合物提供具有比通过施用第二药物组合物提供的C_{max}大多于约50％的C_{max}的体内血浆谱。如本文使用的，通过施用第二药物组合物提供的C_{max}可以包括或可以不包括第一药物组合物的血浆谱贡献。在实施方案中，第二药物组合物的施用不包括第一药物组合物的血浆谱贡献。在实施方案中，第一组合物提供具有比通过施用第二药物组合物提供的C_{max}大多于约，例如，60％、70％、80％、或90％的C_{max}的体内血浆谱。

[0054] 在实施方案中，第一药物组合物的T_{max}是小于3小时。在实施方案中，第一药物组合物的T_{max}是小于2.5小时。在实施方案中，第一药物组合物的T_{max}是小于2小时。在实施方案中，第一药物组合物的T_{max}是小于1.5小时。在实施方案中，第一药物组合物的T_{max}是小于1小时。

[0055] 在实施方案中，第一药物组合物提供在施用至有相应需要的患者的前20分钟内至少约80％的溶出度。在实施方案中，第一药物组合物提供在施用至有相应需要的患者的前20分钟内至少约，例如，85％、90％或95％的溶出度。在实施方案中，第一药物组合物提供在施用至有相应需要的患者的前10分钟内至少80％的溶出度。

[0056] 在实施方案中，第一药物组合物和/或第二药物组合物是亚治疗剂量。亚治疗剂量是小于治疗作用所需的量的加波沙朵或其药学上可接受的盐的量。在实施方案中，亚治疗剂量是单独不能提供发育障碍的至少一种症状的改进、但足以维持此类改进的加波沙朵或其药学上可接受的盐的量。在实施方案中，该方法提供了施用第一药物组合物和第二组合物，所述第一药物组合物提供发育障碍的至少一种症状的改进，且所述第二组合物维持该改进。在实施方案中，在第一药物组合物施用之后，第二药物组合物可以提供协同作用以改进发育障碍的至少一种症状。在实施方案中，第二药物组合物可以提供协同作用以改进发育障碍的至少一种症状。

[0057] 在实施方案中，本文提供了治疗发育障碍的方法，所述方法包括将一种药物组合物和第二药物组合物施用至有相应需要的患者，所述一种药物组合物包含第一药物剂量，所述第一药物剂量包括加波沙朵或其药学上可接受的盐，其中组合物提供在施用之后持续

多于6小时的改进，所述第二药物组合物包括亚治疗剂量的加波沙朵或其药学上可接受的盐。

[0058] 第一药物组合物和第二药物组合物的施用可以相隔一定的时间间隔以实现至少一种症状的长期改进。在实施方案中，第一药物组合物和第二药物组合物可以相隔6小时被施用。在实施方案中，第一药物组合物和第二药物组合物可以相隔12小时被施用。在实施方案中，第一药物组合物和第二药物组合物可以在，例如，6小时、12小时、18小时、24小时等内被施用。在实施方案中，第一药物组合物和第二药物组合物可以相隔至少，例如，6小时、12小时、18小时、24小时等被施用。在实施方案中，提供了在施用至患者之后持续多于8小时的发育障碍的至少一种症状的改进。在实施方案中，提供了在施用至患者之后持续多于约，例如，10小时、12小时、15小时、18小时、20小时或24小时的改进。

[0059] 在实施方案中，第一药物组合物和/或第二药物组合物包含约0.1mg至约40mg的加波沙朵或其药学上可接受的盐。第一药物组合物和第二药物组合物中的加波沙朵或其药学上可接受的盐的量可以相同或不同。在实施方案中，第一药物组合物和第二药物组合物的施用可以提供协同作用以改进发育障碍的至少一种症状。

[0060] 在实施方案中，第一药物组合物和/或第二药物组合物包含0.1mg至25mg、0.1mg至20mg、0.1mg至15mg、0.5mg至25mg、0.5mg至20mg、0.5mg至15mg、1mg至25mg、1mg至20mg、1mg至15mg、1.5mg至25mg、1.5mg至20mg、1.5mg至15mg、2mg至25mg、2mg至20mg、2mg至15mg、2.5mg至25mg、2.5mg至20mg、2.5mg至15mg、3mg至25mg、3mg至20mg、或3mg至15mg的加波沙朵或其药学上可接受的盐。

[0061] 在实施方案中，第一药物组合物和/或第二药物组合物包含5mg至15mg、5mg至10mg、4mg至6mg、6mg至8mg、8mg至10mg、10mg至12mg、12mg至14mg、14mg至16mg、16mg至18mg、或18mg至20mg的加波沙朵或其药学上可接受的盐。

[0062] 在实施方案中，第一药物组合物和/或第二药物组合物包含0.1mg、0.25mg、0.5mg、1mg、2.5mg、3mg、4mg、5mg、7mg、7.5mg、10mg、12.5mg、15mg、17.5mg、20mg加波沙朵或其药学上可接受的盐或者是此类剂量的倍数的量。在实施方案中，第一药物组合物包含2.5mg、5mg、7.5mg、10mg、15mg、或20mg加波沙朵或其药学上可接受的盐。在实施方案中，第二药物组合物包含2.5mg、5mg、7.5mg、10mg、15mg、或20mg加波沙朵或其药学上可接受的盐。

[0063] 除非另外定义，本文使用的所有技术术语和科学术语具有与本文中本公开内容所属领域的技术人员通常理解的相同的含义。

[0064] 如本文使用的术语“约”或“大约”意指在如由本领域普通技术人员确定的特定值的可接受误差范围之内，其将部分地取决于值如何被测量或确定，即，测量系统的局限性。例如，按照本领域的实践，“约”可以意指在3个或多于3个标准偏差内。可选地，“约”可以意指给定值的多达20％、多达10％、多达5％和/或多达1％的范围。可选地，特别地，关于生物系统或过程，该术语可以意指在值的数量级内，优选地在值的5倍内，且更优选地在值的2倍内。

[0065] “改进”指测量的发育障碍的至少一种症状的治疗。

[0066] “次日功能的改进”或“其中存在次日功能的改进”指其中至少一种症状的有益作用持续超过一定时间段，例如，6小时、12小时、24小时等的改进。

[0067] “PK”指药代动力学谱。C_{max}被定义为在实验期间估计的最高血浆药物浓度(ng/

ml)。T_{max}被定义为当C_{max}被估计的时间(min)。$AUC_{0-\infty}$是从药物施用直至药物被排出的血浆药物浓度时间曲线下的总面积(ng·hr/ml)。曲线下的面积由清除率决定。清除率被定义为每单位时间完全清除其药物含量的血液或血浆的体积(ml/min)。

[0068] “治疗(treating)”或“治疗(treatment)”指减轻或延缓可能罹患或易患疾病或状况但尚未经历或显示疾病或状况的临床或亚临床症状的受试者中疾病或状况的临床症状的出现。在某些实施方案中,“治疗(treating)”或“治疗(treatment)”可以指防止可能罹患或易患疾病或状况但尚未经历或显示疾病或状况的临床或亚临床症状的受试者中疾病或状况的临床症状的出现。“治疗(treating)”或“治疗(treatment)”还指抑制疾病或状况,例如,阻止或减少其发展或其至少一种临床或亚临床症状。“治疗(treating)”或“治疗(treatment)”还指缓解疾病或状况,例如,引起疾病或状况或其临床或亚临床症状的至少一种的消退。对待被治疗的受试者的益处可以是在统计学上显著的、数学上显著的或对受试者或对医师是至少可感知的。尽管如此,预防性(prophylactic)(预防性(preventive))和治疗性(therapeutic)(治愈性(curative))治疗是本文公开内容的两个独立的实施方案。

[0069] “药学上可接受的”指“通常被认为是安全的”——例如,是生理上可耐受的并且当被施用至人类时通常不产生过敏或相似的不良反应,诸如胃部不适等的分子实体和组合物。在实施方案中,该术语指由联邦或州政府的管理机构批准的、作为经历上市前审查并且被FDA批准的根据联邦食品、药物和化妆品法案的第204(s)和409节的GRAS清单或相似清单、美国药典或另一种公认的药典用于在动物并且更特别地用于人类中使用的分子实体和组合物。

[0070] “有效量”或“治疗有效量”意指足以减轻所治疗的障碍、疾病或状况的一种或更多种症状或者以其他方式提供期望的药理学和/或生理学作用的剂量。

[0071] “有相应需要的患者”可以包括已被诊断为患有发育障碍的个体,所述发育障碍包括,例如,孤独症、Angelman综合征、脆性X综合征、脆性X相关的震颤/共济失调综合征(FXTAS)或Rett综合征。该方法可以被提供至任何个体,包括,例如,其中患者是新生儿、婴儿、儿童患者(6个月至12岁)、青少年患者(12岁-18岁)或成人(18岁以上)。

实施例

[0072] 本文提供的实施例被包括仅用于增加本文的公开内容,并且不应该被认为是在任何方面的限制。

[0073] 实施例1

[0074] 以下实施例提供范围从2.5mg至20mg的单次口服剂量后的加波沙朵一水合物的血浆浓度谱和剂量均衡(dose proportionality)。还评价了范围从2.5mg至20mg的加波沙朵一水合物胶囊的绝对生物可利用度。

[0075] 该研究包括10个健康成人受试者的单独组(每种性别至少4名受试者),他们参加一项6周期、双盲、随机化、交叉研究,该研究被设计以评价跨2.5mg至20mg剂量范围的5个单次口服剂量的加波沙朵的剂量均衡和绝对生物可利用度。在治疗周期1至5内,受试者接受5个单次口服剂量的加波沙朵(2.5mg;5mg;10mg;15mg;和20mg)的顺序是随机的。预期每一名受试者完成所有6个治疗周期,并且在每一个治疗周期之间存在至少4天的洗出。

[0076] 在治疗周期内的每一次口服给药由在每一次预定的给药时同时服用2个测试药物胶囊组成。用于口服施用研究药物的治疗命名如下:治疗A-一个2.5mg加波沙朵胶囊和1个匹配的安慰剂胶囊;治疗B-一个5mg加波沙朵胶囊和1个匹配的安慰剂胶囊;治疗C-一个10mg加波沙朵胶囊和1个匹配的安慰剂胶囊;治疗D-一个15mg加波沙朵胶囊和1个匹配的安慰剂胶囊;和治疗E-20mg加波沙朵(两个10mg加波沙朵胶囊)。受试者在禁食过夜之后在早晨约8:00AM以240mL水接受其研究药物。除了在研究药物施用之前和之后的1小时内之外,允许随意饮水。给药后4小时不允许摄取食物。

[0077] 对于每一个治疗中的每一个受试者,在给药后16小时内收集血浆和尿液样品用于确定药代动力学参数(例如,视情况而定,AUC、C_{max}、T_{max}、表观t1/2、累积尿排泄、肾清除率、清除率和稳态分布体积)。对加波沙朵的AUC和C_{max}进行效力调整以便于跨研究比较药代动力学数据。表1提供了在单次口服剂量(2.5mg、5mg、10mg、15mg和20mg)后加波沙朵的单独的效力调整的药代动力学参数。

[0078] 表1.在口服和IV施用后加波沙朵的药代动力学参数

[0079]

参数	几何平均数(N=10)						斜率 (90% CI) ††
	2.5 mg	5 mg	10 mg 口服	10 mg I.V.	15 mg	20 mg	
$AUC_{0-\infty}$ (ng·hr/mL)	90	171	346	380	539	669	0.98 (0.95, 1.01)
C_{max} (ng/mL) †	61	110	232	212	382	393	0.95 (0.88, 1.02)
T_{max} (hr) ‡	0.5	0.6	0.5	--	0.5	0.6	
表观 $t_{½}$ (hr) §	1.5	1.5	1.6	1.5	1.5	1.6	
CL/F (mL/min) ¶	461	488	476	438	469	499	
f_e (%)	43	45	53	53	50	53	
CL_R (mL/min)	196	222	250	208	234	265	
F (%) (90% CI) #	92% (0.86, 0.97)						

† 对于10 mg IV为C_{coi}(ng/mL)。
‡ 中位数。
§ 调和平均数。
¶ 对于10 mg IV为CL (mL/min)。
# 基于合并的剂量-调整(至10 mg)的口服$AUC_{0-\infty}$值,相对于10 mg I.V.参考的生物可利用度。
†† 仅口服治疗的剂量均衡评价。

[0080] 图2示出了在单次口服剂量(2.5mg、5mg、10mg、15mg和20mg)后加波沙朵的算术平均血浆浓度-时间谱。加波沙朵的生物可利用度是大约92%。加波沙朵的血浆$AUC_{0-\infty}$和C_{max}显示出剂量均衡增加,并且在从2.5mg至20mg检查的整个剂量范围内表现为是线性的。加波沙朵的血浆浓度达峰时间(the time to peak plasma concentrations)(T_{max} 30-60min)和半衰期(1.5h的t1/2)表现为不依赖于跨2.5mg至20mg加波沙朵剂量范围的剂量。加波沙朵的排泄主要经由尿液,其中96.5%的剂量被回收;在施用之后4小时内回收75%。

[0081] 实施例2

[0082] 由加波沙朵施用产生的后遗效应(Residual Effect)的评价

[0083] 该研究是一项双盲、双模拟(double-dummy)、随机化、具有活性剂对照和安慰剂对照、单剂量、3周期交叉研究,随后是在健康老年男性和女性受试者中的开放标签(open-label)、单次剂量、单周期研究。将受试者随机分配至3个治疗(治疗A、B和C)中的每一个,所述治疗在前3个治疗周期内以交叉方式被施用。对于治疗A,受试者接受单次剂量的加波沙朵10mg;对于治疗B,受试者接受单次剂量的氟西泮(flurazepam)30mg;且对于治疗C,受试者接受单次剂量的安慰剂。剂量在第一天在睡觉时间被口服施用。受试者在每一个治疗周期期间从给药的晚上很早直至剂量后~36小时(第3天的早晨)在住处。参与治疗周期1-3的

受试者参与了第四治疗周期。在该周期中，对于加波沙朵的PK，在第1天的早晨以开放标签的方式口服施用单次剂量的加波沙朵10mg(治疗D)。在连续治疗周期的剂量之间存在至少14天的洗出。研究参与者包括年龄在65岁与80岁之间的健康、老年男性和女性受试者，其中简易精神状态(Mini Mental Status)为24，体重为至少55kg。所有受试者接受10mg加波沙朵一水合物胶囊和30mg氟西泮(作为2×15mg胶囊提供)，提供加波沙朵和氟西泮两者的匹配的安慰剂。

[0084] 评价的主要终点包括药效动力学(pm给药后的精神运动性表现(psychomotor performance)、记忆力、注意力和日间瞌睡的测量)、加波沙朵药代动力学和安全性。对于主要终点选择反应时间(Choice Reaction Time)和临界闪光融合值(Critical Flicker Fusion)，加波沙朵(单次剂量10mg)在剂量后9小时未显示后遗效应，而活性参考氟西泮(30mg单次剂量)在相同的测试中显示出显著效应。另外，加波沙朵在研究中应用的其他测量(多相睡眠潜伏期测试(MSLT)；数字符号替换测试(DSST)、追踪、记忆力测试、身体摇摆和利兹睡眠评价问卷)中未显示任何后遗效应征象。

[0085] 实施例3

[0086] 加波沙朵施用之后的驾驶行为表现的研究

[0087] 该研究是一项双盲、随机化、具有安慰剂对照和活性剂对照的5种方式的交叉研究，以调查晚上和半夜给药加波沙朵对驾驶行为表现的影响。研究参与者包括年龄在21岁与45岁之间的健康、男性和女性受试者，持有至少3年的有效驾驶执照。

[0088] 加波沙朵对驾驶行为表现的影响使用在道路环境的实际驾驶进行调查。受试者在晚上在上床睡觉之前或在半夜在4am在叫醒电话(wake-up call)后接受15mg加波沙朵。在认知和精神运动成套测试(cognitive and psychomotor test battery)之后，驾驶测试在9am开始，并且持续一个小时。15mg加波沙朵在半夜施用后对驾驶具有临床相关的损害作用。

[0089] 在晚上剂量后，观察到15mg加波沙朵对驾驶具有统计学显著影响。然而，该影响小于在0.05％的血液酒精浓度观察到的影响，这是大多数欧洲国家禁止驾驶的浓度限值。通常，分别在晚上和半夜施用佐匹克隆(zopiclone)(7.5mg)和唑吡坦(zolpidem)(10mg)后，存在数值上更大的影响。加波沙朵的晚上和半夜剂量两者被良好耐受，其中最常见的不良事件是对于半夜治疗的头晕、恶心和嗜睡以及对于晚上治疗的头痛和嗜睡。

[0090] 在相同的测试中，服用活性参考佐匹克隆的受试者具有数值上更大的影响。对于记忆力测试、身体摇摆、DSST或临界追踪不存在影响，而佐匹克隆对于这些测试中的一些具有影响。

[0091] 实施例4

[0092] 在睡眠受限之后的日间行为表现的研究

[0093] 该研究是一项4晚、平行组、随机化、双盲(内部盲法(with in-house blinding))、具有安慰剂对照、固定剂量的研究，以评价加波沙朵对经历5小时睡眠限制的健康成人的日间行为表现的影响。该研究包括2晚的单盲安慰剂导入周期(run-in period)，4晚的双盲治疗周期(在此期间，睡眠被限制在5小时)以及2晚的单盲安慰剂导出周期(run-out period)。该研究包括年龄18岁至<55岁的健康男性和女性志愿者。

[0094] 2晚导入周期:所有患者接受安慰剂

[0095] 4晚双盲治疗周期:患者被随机分配至15mg加波沙朵或匹配的安慰剂

[0096] 2晚导出周期:所有患者接受安慰剂

[0097] 主要终点包括基于多相睡眠潜伏期测试(MSLT)和慢波睡眠(SWS)评价的观察结果。主要目的是评价加波沙朵(15mg)与安慰剂相比在降低日间睡眠倾向方面的效力,如通过MSLT测量的。相比安慰剂受试者,加波沙朵受试者在睡眠受限周期具有显著较少的日间瞌睡(p=0.047,单侧(1sided))。在最后两个睡眠受限日,用加波沙朵(15mg)治疗的受试者的MSLT比用安慰剂治疗的那些受试者的MSLT长平均2.01分钟。

[0098] 另外,第二目的是评价在睡眠受限的最后2晚期间加波沙朵与安慰剂相比在增加慢波睡眠(SWS)的量方面的效力。相比安慰剂受试者,接受加波沙朵的受试者在睡眠受限周期期间经历显著更多的SWS(p<0.001,单侧)。此外,在最后两个睡眠受限夜晚,用加波沙朵治疗的受试者平均具有比用安慰剂治疗的那些受试者长20.53分钟的SWS。

[0099] 最后,该研究在睡眠受限的最后2晚/天检查了加波沙朵与安慰剂相比在以下方面的效力:(1)改进记忆力和注意力,如通过神经行为成套测试(neurobehavioral battery)评价的;(2)减少主观瞌睡,如通过卡罗林斯卡嗜睡评分(Karolinska Sleepiness Score)(KSS)测量的;(3)改变睡眠参数(例如,总睡眠时间、至慢波睡眠(SWS)开始的潜伏期、慢波活动(SWA));以及(4)减少以以下为典型特征的生物应激:增加的心率变化性、以及减少的皮质醇水平和减少的儿茶酚胺水平以及降低的体温。

[0100] 在睡眠受限周期期间,与安慰剂受试者相比,加波沙朵受试者存在较少主观日间瞌睡的趋势。在最后两个睡眠受限日,用加波沙朵治疗的受试者的卡罗林斯卡嗜睡评分(KSS)比用安慰剂治疗的那些受试者平均低0.68(p=0.058,单侧),如通过纵向数据分析(LDA)模型并针对基线KSS、性别和年龄进行调整所评价的。使用协方差(ANCOVA)的支持性分析也支持这一发现。针对神经认知成套测试(neurocognitive battery)计算的效应大小显示,不存在加波沙朵改进日间行为表现的强有力的证据。关于应激的生物生理学量度(心率变化性、皮质醇水平、儿茶酚胺水平、体温)方面,加波沙朵与安慰剂之间不存在差异。

[0101] 与安慰剂相比,加波沙朵对减少日间瞌睡具有保护作用,如在4晚睡眠受限的最后2天通过MSLT测量的。在4晚睡眠受限的最后2晚期间,与安慰剂相比,加波沙朵增加慢波睡眠(SWS)的量。

[0102] 实施例5

[0103] 加波沙朵在患有Angelman综合征的患者中的效力的前瞻性评价

[0104] 该研究被设计为确定加波沙朵是否会导致Angelman综合征的一种或更多种症状的改进。参与者被随机分配至6个独立的治疗组(A-F)。随机化的入选标准将要求,每一个参与者先前已经通过临床评价被诊断为患有Angelman综合征,或者参与者被诊断为具有Angelman综合征的一个或更多个主要和次要标准。

[0105] 主要标准包括:

[0106] ●功能严重的发育迟缓

[0107] ●言语障碍;不使用或很少使用词语

[0108] ●运动或平衡障碍

[0109] ●行为独特、频繁的笑/微笑、易兴奋的个性、拍手、注意力短暂

[0110] 次要标准包括:

[0111] ●头围生长减速(出生后)

[0112] ●癫痫发作(肌阵挛、失神(absence)、跌倒、强直-阵挛)

[0113] ●异常EEG(具有提示AS、或高度节律失常的模式)

[0114] ●睡眠障碍

[0115] ●被水吸引或迷恋水

[0116] ●流口水

[0117] 在随机化之后,将参与者置于6个独立的治疗组(A-F)和安慰剂组。治疗组A在晚上接受20mg加波沙朵。治疗组B在晚上接受15mg加波沙朵。治疗组C在晚上接受15mg加波沙朵,并且在早晨接受5mg加波沙朵。治疗组D在晚上接受10mg加波沙朵。治疗组E在晚上接受10mg加波沙朵,并且在早晨接受10mg加波沙朵。治疗组F在晚上接受10mg加波沙朵,并且在早晨接受5mg加波沙朵。

[0118] 在整个治疗周期评价参与者以确定加波沙朵施用是否导致Angelman综合征的一种或更多种症状的改进。对几个行为领域;交流、注意力、适应不良行为和超兴奋性进行评价。为了定量交流行为,参与者参加无拘无束的游戏会话(an unstructured play session)以引起言语和非语言交流的尝试。将儿童的言语尝试进行语音学上录音并且使用对早期声音发育的严厉评价-修订版(Stark Assessment of Early Vocal Development-Revised)(SAEVD-R)(Nathani Ertmer等2006)分类为5个不同类型的发声,其分类为非言语和预言语声音(protophones)、以及元音、辅音和音节。

[0119] 在Angelman综合征的大多数病例中会出现步态异常。因此,分析五个主要的时空参数:节奏、步态速度、跨步宽度、步长和姿态百分比。对于每一个参数,主成分分析用于建立步态指数,以用于评价受试者。

[0120] 另外,可以被评价的主要结果量度包括基线与试验完成之后之间的以下方面的原始或标准评分的变化:

[0121] I.贝利婴幼儿发育量表(Bayley Scales of Infant and Toddler Development),第3版(或者对发育更高级的受试者的Mullen早期学习量表(Mullen Scales of Early Learning));

[0122] II.文兰适应行为量表(Vineland Adaptive Behavior Scales),第2版(仅标准评分);

[0123] III.学前语言量表(Preschool Language Scale),第4版;

[0124] IV.异常行为量表(Aberrant Behavior Checklist)-社区版;以及

[0125] V.临床总体印象严重程度量表评分(the Clinical Global Impressions Severity Scale Score)中从基线的变化。

[0126] 次要结果量度可以包括当比较加波沙朵施用后结果与基线结果时脑电图(EEG)特征(signature)的归一化。

[0127] 实施例6

[0128] 加波沙朵在患有Angelman综合征的患者中的效力的前瞻性评价

[0129] 该研究被设计为确定加波沙朵是否导致Angelman综合征(AS)的一种或更多种症状的改进。Angelman综合征表现为严重程度变动的几个不同的特征,并且包括发育迟缓、运动和/或平衡障碍、以及肢体的震颤性运动。也许最独特的行为特征是快乐的举止、微笑和

频繁的阵阵笑声的组合。此外，这些个体具有容易兴奋的个性，通过拍手或挥舞运动展示。最后，这些个体罹患严重的睡眠中断、言语障碍和频繁癫痫发作，具有特征性的异常脑电图(EEG)模式。将使用适当的问卷、日记或actimetric数据调查AS症状(睡眠、大运动功能和精细运动功能、行为和交流)的所有主要方面。主要焦点可以包括运动能力和睡眠。可以使用良好建立的量表，辅之以对睡眠和运动功能的更具创新性的结果量度。AS行为的潜在混淆因素是孤独症的共存(Peters等，Clin Genet，2004;66[6]:530-6)。在筛查时，可以使用孤独症诊断观察时间表(ADOS)评价受试者的这种共发病(co-morbidity)，并且潜在地进行排除。

[0130] 该研究的主要目的可以是以不同的剂量水平和以两个给药时间表评价患有AS的成年受试者中的加波沙朵从基线至第6周和第12周的安全性和耐受性。可测试以下给药时间表(安慰剂作对照)：(1)每天一次(o.d.)：晚上剂量，调整至15mg的靶剂量，除非不被耐受；以及(2)每天两次(b.i.d.)：晚上和早晨剂量，调整至15mg晚上剂量和10mg早晨剂量的靶剂量，除非不被耐受。

[0131] 与该研究相关的安全性终点可以包括：(1)不良事件(AE)及严重不良事件的频率和严重程度；(2)生命体征(Vital signs)(体重、血压、体温)；(3)实验室参数(电解质、脂质、葡萄糖、肝和胰腺功能测试、血液学、肌酐)；(4)通过ABC-易怒分量表(ABC-Irritability Subscale)评价的自杀倾向；(5)EEG(背景频率的变化，癫痫样放电的强度)；和/或(6)护理者可以维持电子癫痫发作日记(在与睡眠日志相同的装置上)。

[0132] 该研究的次要目的可以包括鉴定一组参数，该组参数可以最好地表征随后效力试验的成人AS受试者中加波沙朵的效力。这些测试可以由受过适当培训的专业人员进行四次全天实地随访(筛查、基线、治疗期中(Interim)和治疗结束)，以向成人AS患者提供测试。评价可以是基于直接观察和来自护理者的输入。可以被探索的效力评价包括大运动能力/功能和精细运动能力/功能。大运动能力/功能的评价可以包括分析当受试者在Zeno Walkway上行走时评价的时空和功能步态测量(Zeno Walkway和PKMAS软件分析，由ProtoKintetics提供)和修改的行为导向活动性评价-步态(Modified Performance Oriented Mobility Assessment-Gait)(MPOMA-G)量表。精细运动能力/功能的评价可以包括分析儿童残疾评价调查表(Pediatric Evaluation of Disability Inventory)(PEDI-CAT)；ADL(以记录精细运动功能)和内容平衡(更广泛)版本的活动性方面。

[0133] 睡眠的评价可以包括通过活动变化记录仪(actigraphy)的分析来测量：(1)睡眠开始潜伏期(SOL)；(2)总睡眠时间(TST)；(3)睡眠开始之后的觉醒(WASO)＝睡眠开始之后的觉醒时期的总数#；(4)夜间觉醒(NA)；和/或(5)睡眠效率＝卧床时间(TIB)中的总睡眠时间(TST)。另外的睡眠评价可以包括分析睡眠模式的父母/护理者日志，其可以包括：(1)就寝时间；(2)睡眠开始的时间；(3)觉醒的次数和持续时间；(4)中断行为的次数；(5)最后一次觉醒的时间；和(6)日间瞌睡。该研究可以包括三个治疗组。例如，总计大约75名受试者可以被招募，并且在研究完成时，在三个治疗组的每一个中可以存在大约25名受试者：1)单次晚上剂量2)早晨和晚上的剂量以及3)安慰剂。

[0134] 所有受试者可以在整个治疗持续时间期间接受早晨剂量(活性剂或安慰剂)和晚上剂量(活性剂或安慰剂)。例如，如图3中阐释的，可以测试加波沙朵的两个给药时间表：单次晚上剂量(o.d.；时间表A)和被设计以提供更持续暴露的早晨加晚上剂量(b.i.d；时间表

B)。时间表C是早晨和晚上安慰剂。除非靶剂量不被耐受，所有受试者可以上调至该靶剂量(下文描述的调整协定)。所有受试者可以以其最佳耐受的剂量接受最多12周的治疗。

[0135] 剂量可以以5mg增量(活性剂或安慰剂)逐渐增加至时间表A和B中的3个胶囊晚上剂量以及时间表B中的2个胶囊早晨剂量的靶剂量。在由护理者和研究者已经评价充分的耐受性之后，可以执行每一个剂量递增。例如，在第1天在晚上用1个胶囊(活性剂(Act)或安慰剂(Plc))开始治疗。然后，可以在第3天(窗口+2天)开始靶上调：如果护理者和/或研究者未观察到与研究药物相关的不良事件(AE)，在晚上添加另一个胶囊(活性剂或安慰剂)。同样，在第7天(窗口+2天)、第10天(窗口+2天)和第14天(窗口+2天)，如果护理者和/或研究者未观察到与研究药物相关的AE，可以在早晨添加另一个胶囊(活性剂或安慰剂)。下文表II提供了调整时间表的图解说明。

[0136] 表II.调整时间表

[0137]

时间表/时间		第1天至第2天	第3天至第6天	第7天至第9天	第10天至第13天	第14天*
时间表A	晚上	5 mg 1个胶囊	10 mg 2个胶囊	15 mg 3个胶囊	15 mg 3个胶囊	15 mg 3个胶囊
	早晨	无	无	无	安慰剂 1个胶囊	安慰剂 2个胶囊
时间表B	晚上	5 mg 1个胶囊	10 mg 2个胶囊	15 mg 3个胶囊	15 mg 3个胶囊	15 mg 3个胶囊
	早晨	无	无	无	5 mg 1个胶囊	10 mg 2个胶囊
时间表C	晚上	安慰剂 1个胶囊	安慰剂 2个胶囊	安慰剂 3个胶囊	安慰剂 3个胶囊	安慰剂 3个胶囊
	早晨	无	无	无	安慰剂 1个胶囊	安慰剂 2个胶囊

[0138] *至研究治疗周期结束

[0139] 如果耐受性不允许在以上详述的日期(第3天、第7天、第10天、第14天)中的任何一天的即时进一步剂量递增，则减慢的上调或延迟上调将是可接受的。在先前上调步骤之后或者在12周的治疗过程期间，在耐受性是不可接受的情况下(例如，嗜睡、头晕、行为变化)，进行下调，剂量可以被降低至先前水平或甚至进一步降低。然而，在已经达到可耐受的剂量后，它在治疗周期的持续时间应保持不变。在达到靶剂量后，治疗可以继续。例如，在第14天：可以达到靶剂量(在早晨2个胶囊和在晚上3个胶囊)的最早日期，受试者可以保持稳定直至治疗随访结束(第12周)，除非不可耐受需要下调。

[0140] 在第一剂量施用之前多达28天，将筛查所有受试者以确定参与该研究。入选标准可以包括以下一个或更多个：(1)年龄≥18岁、≤40岁；(2)必须具有根据2005共识标准具有发育迟缓、运动或平衡障碍及言语障碍的AS的临床诊断；(3)必须具有AS的先前或当前的分子证实；(4)受试者必须在基线之前持续至少4周接受稳定剂量的伴随药物治疗，包括抗癫痫药物治疗、补充剂和特殊饮食，并且能够在整个研究的持续时间保持这些。

[0141] 排除标准可以包括以下一个或更多个：(1)不能执行用于评价运动能力/功能的测试(如以上描述)的不能走动(non-ambulatory)受试者(例如需要轮椅)；(2)被定义为>3次失神型癫痫发作/周和/或>1次癫痫大发作/月的控制不良的癫痫发作；(3)伴随心血管、呼吸系统疾病；伴随具有丙氨酸转氨酶或天冬氨酸转氨酶>2.5×正常上限(ULN)的肝脏疾病；(4)伴随具有高于ULN的肌酐的肾疾病；(5)伴随具有嗜中性粒细胞绝对计数>$2x10^9$/L或血小板<$50x10^9$/L或血红蛋白<80g/L的血液疾病；(6)其他遗传性疾病；(7)伴随米诺环素(minocycline)、左旋多巴(levodopa)、睡眠药物的使用以及基线之前4周和研究期间的任何研究剂、装置和/或研究程序的任何其他使用；(8)基于ABC-易怒分量表处于自杀风险。

[0142] 描述性统计可以用于根据治疗组总结所有主要和次要终点以及基线变量。对于连续变量n，将提供缺失值的数目、平均值、标准偏差、中位数、最小值和最大值。对于分类变量，将针对每一个类别呈现频率和百分比。置信区间(CI)将在有意义的情况下被提供。所有CI将是双侧95％置信区间。

[0143] 实施例7

[0144] 加波沙朵在患有Angelman综合征的患者中的效力的前瞻性评价

[0145] 该研究被设计为确定较低剂量的加波沙朵是否导致较年轻患者或具有不太严重临床评价症状的患者中的改进。例如，青少年患者(年龄12岁-18岁)可能与成人群体具有相似的临床表现和基线疾病特征，但走动方面的减少可能不太严重。在这些患者中，预期加波沙朵的靶益处还将包括共济失调的减轻和走动功能的改进。

[0146] 对于儿童患者(6个月至12岁)，Angelman综合征的诊断通常基于发育状态的严重迟缓在1岁左右作出，并且最终持续存在的癫痫发作。随着儿童年龄增长，另外的神经系统缺陷将促成导致共济失调和步行残疾的疾病表现。对于这些潜在参与者，随机化和评价程序的入选标准与先前描述的相似。

[0147] 在随机化之后，将参与者置于6个独立的治疗组(A-F)和安慰剂组。治疗组A在晚上接受7.5mg加波沙朵。治疗组B在晚上接受5mg加波沙朵。治疗组C在晚上接受5mg加波沙朵，并且在早晨接受2.5mg加波沙朵。治疗组D在晚上接受2.5mg加波沙朵。治疗组E在晚上接受2.5mg加波沙朵，并且在早晨接受1mg加波沙朵。治疗组F在晚上接受1mg加波沙朵。

[0148] 实施例8

[0149] 加波沙朵在患有脆性X综合征的患者中的效力的前瞻性评价

[0150] 该研究被设计为确定加波沙朵是否导致脆性X综合征的一种或更多种症状的改进。参与者被随机分配至6个独立的治疗组(A-F)。随机化的入选标准要求患者已经被诊断为患有脆性X综合征。例如，基于临床总体印象严重程度评分为至少4的至少中度患病并且具有ABC-C和IQ测试的合格评分的患者。

[0151] 在随机化之后，将参与者分为6个治疗组(A-F)和安慰剂组。治疗组A在晚上接受20mg加波沙朵。治疗组B在晚上接受15mg加波沙朵。治疗组C在晚上接受15mg加波沙朵，并且在早晨接受5mg加波沙朵。治疗组D在晚上接受10mg加波沙朵。治疗组E在晚上接受10mg加波沙朵，并且在早晨接受10mg加波沙朵。治疗组F在晚上接受10mg加波沙朵，并且在早晨接受5mg加波沙朵。

[0152] 在整个治疗周期评价参与者以确定加波沙朵的施用是否导致脆性X综合征的一种或更多种症状的改进。具体地，使用一种或更多种主要和次要结果量度对患者进行评价。主

要结果量度可以包括：

[0153] 使用异常行为量表-社区版(ABC-CFX)总评分评价的脆性X综合征的行为症状从基线的变化；

[0154] 使用临床总体印象改进(CGI-I)量表评价的脆性X中的症状的总体改进；

[0155] 通过ABC-CFX量表的单独分量表评价的易怒、昏睡/退缩(Withdrawal)、刻板行为、多动、不适当的言语和社会回避从基线的变化；

[0156] 使用重复性行为量表-修订版(Repetitive Behavior Scale-Revised)(RBS-R)评分评价的重复性行为从基线的变化；

[0157] 视觉模拟评分(行为)；表达性词汇测试；文兰适应行为量表-II(VABS-II)适应行为综合评分；和异常行为量表-社区版(ABC-C)综合评分。

[0158] 实施例9

[0159] 加波沙朵在患有脆性X综合征的患者中的效力的前瞻性评价。

[0160] 该研究被设计为确定较低剂量的加波沙朵是否会导致较年轻患者或具有不太严重临床评价症状的患者中的改进。对于这些参与者，随机化和评价程序的入选标准将与先前描述的相似。

[0161] 在随机化之后，参与者被随机分配至6个独立的治疗组(A-F)和安慰剂组。治疗组A在晚上接受7.5mg加波沙朵。治疗组B在晚上接受5mg加波沙朵。治疗组C在晚上接受5mg加波沙朵，并且在早晨接受2.5mg加波沙朵。治疗组D在晚上接受2.5mg加波沙朵。治疗组E将在晚上接受2.5mg加波沙朵，并且将在早晨接受1mg加波沙朵。治疗组F在晚上接受1mg加波沙朵。

[0162] 实施例10

[0163] 加波沙朵在患有脆性X相关的震颤/共济失调综合征的患者中的效力的前瞻性评价

[0164] 该方案涉及治疗患有前FXTAS(pre-FXTAS)或FXTAS症状(包括神经病、中枢性疼痛症状、失眠)和牵涉震颤和通常与认知衰退相关的共济失调的完全FXTAS的症状性前突变携带者。

[0165] 这将是一个双场所(two-site)的研究。参与者将是患有前突变(premutation)和FXTAS的个体。将使用常规程序在所有受试者中定量FMR1CGG重复长度。FXTAS将遵循被公布的标准(Bacalman等,Clin Psychiatry 2006,67:87-94;Jacquemont等,Lancet Neurol 2003,6:45-55)被诊断。该研究将牵涉持续3个月的加波沙朵受控制试验，随后是3个月的开放标签，以便前3个月以加波沙朵治疗的那些个体将继续持续第二个3个月，并且以安慰剂治疗的那些个体将继续以加波沙朵治疗持续第二个3个月。每一个场所每年将招募20名患者，在两年周期内在每一个场所总计40名，并且在场所之间将存在80名患者参与。

[0166] 包含加波沙朵或安慰剂的相同外观的片剂将被施用。在随机化之后，参与者被随机分配至独立的治疗组和安慰剂组。治疗组A在晚上接受7.5mg加波沙朵。治疗组B在晚上接受5mg加波沙朵。治疗组C在晚上接受5mg加波沙朵，并且在早晨接受2.5mg加波沙朵。治疗组D在晚上接受2.5mg加波沙朵。治疗组E在晚上接受2.5mg加波沙朵，并且在早晨接受1mg加波沙朵。治疗组F在晚上接受1mg加波沙朵。

[0167] 在基线，并且然后在三个月，并且然后在六个月，将进行以下研究：使用疼痛指数评价疼痛的严重程度并且记录疼痛类型；并且将实施睡眠日记。定量量度将使用活动度测

量计(actometer)来实施以观察在一周时间段内睡眠障碍的严重程度。神经心理学量度将包括简易精神状态检查(MMSE)、行为失控量表(Behavioral Dyscontrol Scale)(BDS-II)、韦氏记忆量表(Wechsler Memory Scale)IV、加利福尼亚词语学习测试2(California Verbal Learning Test 2)(CVLT-2)、重复性成套神经心理学状态评价测试(Repeatable Battery for the Assessment of Neuropsychological Status)(RBANS)和用于确定情绪改进的SCL-90。将评价MMSE、BDS-II和事件相关电位(ERP)研究(特别是N4重复范式)和海马体积变化方面的任何改进。将进行运动评价,其记录患有FXTAS的那些患者与其他运动障碍相比的异常情况。将利用FXTAS评定量表。将进行3Tesla MRI和DTI的MRI体积研究。将评价查看(look at)抑制范式的眼睛追踪量度(Eye-tracking measures)。将评价6个月内的P6重复作用。所有这些测量将在基线、三个月和六个月时进行。还将进行使用韦氏量表和WAIS-IV的基线认知测试。这可以在一年之后重复,但通常不会更早。神经病的改进可以使用神经诊断研究或电生理学研究来检测并且随后为临床检查。

[0168] 实施例11

[0169] 加波沙朵在患有脆性X相关的震颤/共济失调综合征的患者中的效力的前瞻性评价

[0170] 该研究被设计为确定加波沙朵是否导致对与脆性X相关的震颤/共济失调综合征(FXTAS)相关的执行功能/功能异常重要的认知症状,即注意过程的改进,并且牵涉具有安慰剂对照、双盲、随机化临床试验和听觉“畸变(oddball)”任务。参与者将是患有FXTAS的个体。将使用常规程序在所有受试者中定量FMR1CGG重复长度。FXTAS将遵循被公布的标准(Bacalman等,Clin Psychiatry 2006,67:87-94;Jacquemont等,Lancet Neurol 2003,6:45-55)被诊断。对于主要的加波沙朵试验,将筛查200名潜在参与者的资格。对于安慰剂或加波沙朵的随机化对所有研究人员、研究者及参与者将是盲的,直到一年的试验期结束。参与者将参与听觉“畸变”/事件相关电位(ERP)实验。

[0171] 包含加波沙朵或安慰剂的相同外观的片剂将被施用。在随机化之后,参与者被随机分配至6个独立的治疗组(A-F)和安慰剂组。治疗组A在晚上接受7.5mg加波沙朵。治疗组B在晚上接受5mg加波沙朵。治疗组C在晚上接受5mg加波沙朵,并且在早晨接受2.5mg加波沙朵。治疗组D在晚上接受2.5mg加波沙朵。治疗组E在晚上接受2.5mg加波沙朵,并且在早晨接受1mg加波沙朵。治疗组F在晚上接受1mg加波沙朵。

[0172] 在听觉“畸变”实验中,患者将被指示检测嵌入一连串非靶标准音调中的偶发“畸变”音调。受试者将针对所检测的每一个靶按下按钮,并且同时保持该实验模块中靶数目的心理计数。使用相同“畸变”范式的前突变携带者中的先前研究已经证明FXTAS患者中的改变的额叶P300(P3)ERP组分,这追踪它们的执行功能异常。参见,Yang等,Ann Neurol 74,275-283(2013);Yang等,Cereb Cortex 23,2657-2666(2013)。在这些研究和其他研究中,在男性为主的FXTAS组中也发现了延长的N100潜伏期和降低的P200(P2)幅度的较早异常,但在无FXTAS9症状的女性前突变携带者中则未发现。

[0173] 神经心理学测试将牵涉检查每一个患者的EEG。因此,将在声音衰减的暗室(sound-attenuated,dimly-lit chamber)中记录在双刺激听觉畸变实验期间的EEG。较低(113Hz)和较高(200Hz)频率纯音调将以4个模块(每一个包含100个音调)中的高于个体听力水平的40dB呈现,其中刺激发生异步性从1.0-1.5秒抖动。在每一个模块之前,受试者将

被指示响应于偶发(概率等于25%)“畸变”音调(高或低靶音调,跨模块平衡)。将采用双重任务,其中受试者被指示针对每一个靶音调按下按钮,并且同时保持每一个模块中靶的数目的心理计数。靶音调的心理计数将在每一个模块之后完成后立即报告。32-通道EEG将用Nicolet-SM-2000放大器记录(带通=0.016-100Hz,在250Hz采样)。数据分析将牵涉将计算每一个参与者的每一个模块中的|计数-点击|差异(即,模块中的针对靶音调的正确按钮按压与心理计数之间的差异的绝对值),作为在畸变任务期间注意力/工作记忆表现的相反量度(即,较低的值表示较好的表现)。眨眼、眼球运动、过度肌肉活动或放大器阻断所污染的事件锁定的EEG区段将使用半自动计算机算法舍弃。1024ms(其中预刺激基线周期100ms,并且刺激开始后924ms)的无伪像EEG区段将通过实验条件进行平均以获得ERP。4个ERP组分的平均幅度和局部峰潜伏期将在以下时间窗口中定量:N100(N1,70-150ms)、P2(160-260ms)、N200(N2,170-300ms)和P3(300-650ms)。靶和标准音调两者的波形将用于测量N1。将根据标准音调的EPR测量P2。根据差异波形(靶的ERP减去标准的ERP)定义N2组分。将根据差异波形和靶的ERP波形两者测量P3。ERP量度将被提交至重复测量ANOVA(SPSS 22,IBM),考虑治疗的受试者之间的因素以及随访的受试者中的因素和电极。N1和P2的分析将包括4个额叶中心(fronto-central)电极(Fz、Cz、FC1/2)。五个中心通道(Cz、FC1/2、CP1/2)将被用于N2分析。P3分析将用26个头皮电极(除了FP1/2以外)来进行。在适当的情况下,Greenhouse-Geiser校正(Greenhouse-Geiser correction)将被用于对违反球形的情况(violations of sphericity)进行调整。为了进一步表征加波沙朵对P2组分的调节作用,将对P2幅度进行习惯化分析。将每一个研究的第一个模块内响应于前30个标准音调的P2平均幅度与响应于最后30个标准音调的幅度进行比较,考虑治疗的受试者之间的因素,以及随访的受试者内的因素、试验位置和电极。来自一组16名年龄匹配的正常对照的数据将被用于证明正常的习惯化作用,其中每一名将仅经历一次ERP记录。线性回归将用于检查示出显著治疗作用的|计数-点击|差异变化(1年随访减去基线)与ERP量度变化之间的相关性。将测试P2的局部峰幅度(在应用30Hz低通滤波器后测量的)与CGG重复之间的相关性。

[0174] 本领域技术人员使用不超过常规实验将认识到,或能够确定本文描述的具体实施方案的许多等同物。此类等同物意图被权利要求包括。

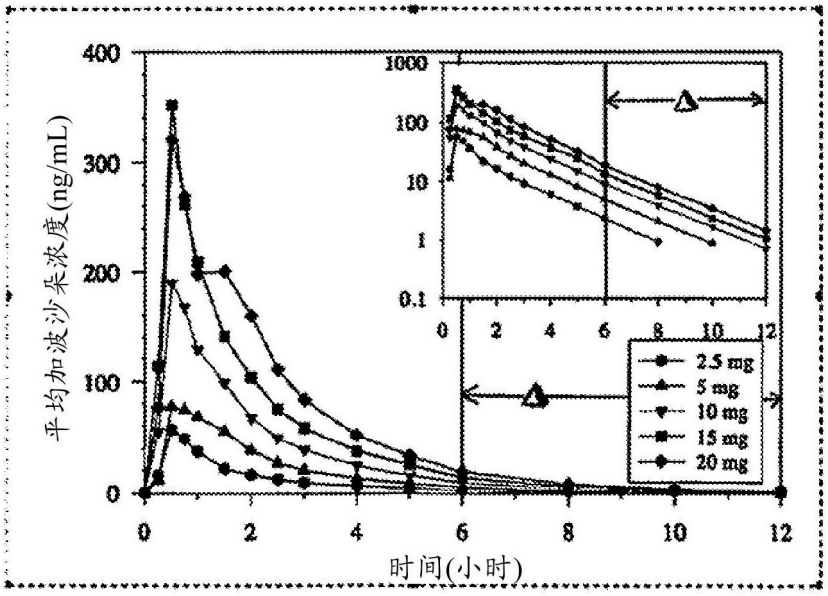

平均加波沙朵浓度(ng/mL)
时间(小时)
2.5 mg
5 mg
10 mg
15 mg
20 mg

图1

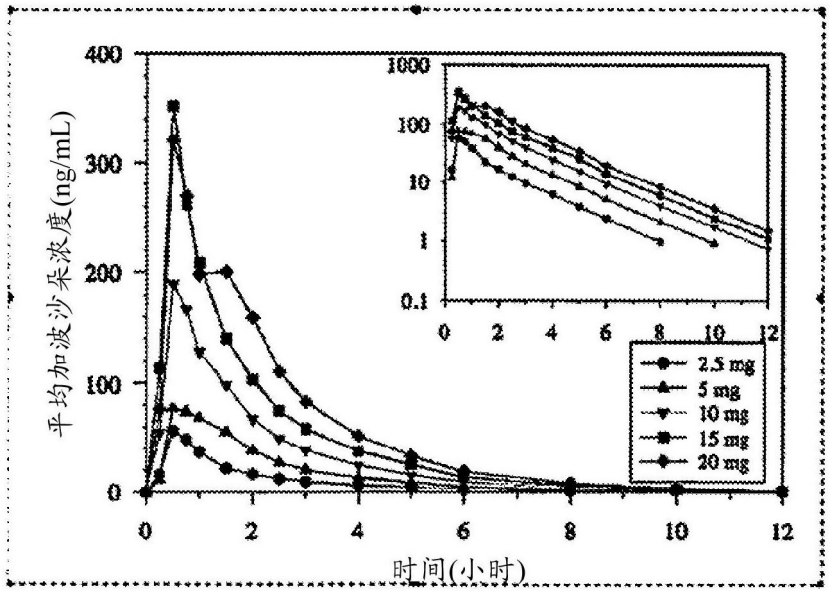

平均加波沙朵浓度(ng/mL)
时间(小时)
2.5 mg
5 mg
10 mg
15 mg
20 mg

图2

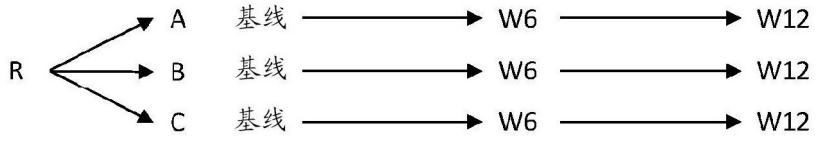

R
A 基线 W6 W12
B 基线 W6 W12
C 基线 W6 W12

图3