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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING BREXANOLONE, GANAXOLONE, OR ZURANOLONE, AND USE THEREOF

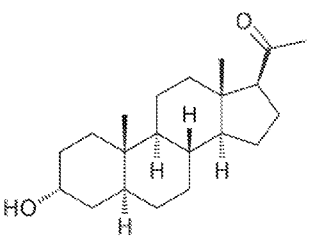

FIG. 2A

(57) Abstract: Disclosed herein is a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid that is a positive modulator of γ aminobutyric acid type A ($GABA_A$) receptors. Also disclosed are methods of treating diseases using the pharmaceutical composition and processes of producing the pharmaceutical composition.

PHARMACEUTICAL COMPOSITION CONTAINING BREXANOLONE, GANAXOLONE, OR ZURANOLONE, AND USE THEREOF

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 62/846,576, filed May 10, 2019, and U.S. Provisional Application No. 63/018,815, filed May 1, 2020, each of which is incorporated herein by reference in its entirety.

FIELD OF DISCLOSURE

[002] The present disclosure is related to a pharmaceutical composition comprising brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof for treating diseases such as epilepsy-related, depression and other central nervous system disorders.

BACKGROUND OF DISCLOSURE

[003] A number of endogenous and synthetic compounds, such as neuroactive steroids and derivatives, can impact central nervous system (CNS) function through multiple mechanism, include but not limited to, positive allosteric modulation of $GABA_A$ (γ aminobutyric acid type A) receptors that is related to many central nervous system disorders. Allopregnanolone is one of such neuroactive steroids that have short terminal half-lives and poor oral bioavailability, and have limited clinical use as oral therapies or parenteral therapy. Brexanolone is a synthetic compound that is chemically identical to endogenous allopregnanolone. Ganaxolone, another such neuroactive steroids and a synthetic pregnane steroid, has a relatively long half-life, approximately 20 hours in human plasma after oral administration and a short maximum concentration (T_{max}) (US Patent Application Publication No.: 20160228454). Both ganaxolone and brexanolone can modulate activities of $GABA_A$ receptors (PCT Patent Publications WO2017156103A1, WO2016127170A1, US Patent Nos.: 9,029,355, 9,452,176, 10,172,870.).

[004] Brexanolone intravenous injection product (brexanolone IV, ZULRESSO™, developed and under trademark of Sage Therapeutics, Cambridge, MA, USA) was recently approved by US Food and Drug Administration (FDA, March 2019) for the treatment of postpartum depression (PPD), a serious and potentially life-threatening

condition, for which no current pharmacotherapies are specifically indicated. However, ZULRESSO™ is inconvenient to use and is administered to a patient by continuous intravenous (IV) infusion that lasts for a total of about 60 hours (2.5 days).

[005] Ganaxolone is currently under clinical trials for treating severe postpartum depression (PPD) and pediatric epilepsy with efficacy successes (Marinus Pharmaceuticals). Both intravenous injection and oral formulations of ganaxolone are being developed and tested (US Patent Publication No.: 20160228454A1; Clinical Trial ID: NCT03228394, MAGNOLIA trial; Ligsay, et al., Journal of Neurodevelopmental Disorders, 9:26, 2017; Rasmusson, et al., Psychopharmacology, 234:2245–2257, 2017, DOI 10.1007/s00213-017-4649-y). However, effects of these formulations are still to be optimized.

[006] New and improved formulations are therefore needed for enhanced bioavailability, long lasting effect, and/or fast and convenient delivery.

SUMMARY OF THE INVENTION

[007] In one aspect, disclosed here is a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein plasma concentration of the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains the plasma concentration of more than about 5% of the C_{max} for at least about 5 days, after a single dose of the pharmaceutical composition is administered by intramuscular or subcutaneous injection.

[008] Also disclosed is a pharmaceutical composition comprising particles comprising at least one neuroactive steroid and one or more pharmaceutical acceptable excipients, the neuroactive steroid being a positive modulator of γ aminobutyric acid type A ($GABA_A$) receptors; wherein, the particles comprise large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm; and wherein, about 0.01% to about 50% of the particles are small particles and about 50% to 99.99% of the particles are large particles, percentage based on the total weight of the particles. The neuroactive steroid can be a positive modulator of $GABA_A$ receptors and can comprise tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane

pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof.

[009] In another aspect, disclosed here is a process for producing a pharmaceutical composition comprising particles, the process comprising: a) producing a particle mixture comprising neuroactive steroid selected from brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof and one or more pharmaceutical acceptable excipients; b) milling a first portion of the particle mixture to produce a large particle mixture, wherein at least 50% of the large particle mixture are large particles having a particle size in a range of from about 1.5 μm to about 15 μm, percentage based on the total weight of the particle mixture; and c) producing a pharmaceutical composition comprising the particles comprising about 50% to 99.99% of the large particles, percentage based on the total weight of the particles.

[010] In another aspect, disclosed here is a method for treating a disease in a subject in need thereof, the method comprising administering a subject a pharmaceutical composition disclosed here or a pharmaceutical composition produced by a process disclosed here. The pharmaceutical composition can be administered to the subject via intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) injection or a combination thereof.

[011] Also disclosed is a method of treating a disease in a subject in need thereof can comprise: administering a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid to the subject by intramuscular or subcutaneous injection with a single dose in a range of from 0.5 to 10 mg per kilogram of body weight of the subject, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein plasma concentration of the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains the plasma concentration of more than about 5% of the C_{max} for at least about 5 days in the subject, after he pharmaceutical composition is administered to the subject by intramuscular or subcutaneous injection.

INCORPORATION BY REFERENCE

[012] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each

individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF DRAWING

[013] Fig. 1A – Fig. 1D. Schematic illustrations of exemplary particle size distributions. Fig. 1A: a pharmaceutical composition comprises minimum amounts, such as less than 1% of small particles and mostly large particles. Fig. 1B: A pharmaceutical composition comprises some small particles and mostly large particles. Fig. 1C: A pharmaceutical composition comprises increasing amounts of small particles and large particles. Fig. 1D: A pharmaceutical composition comprises comparable amounts of small particles and large particles. D50=mass-median-diameter (MMD), wherein 50% of particles are below and 50% of particles are above a given diameter. Mean Large=mean particle size of the large particles. Mean Small= mean particle size of the small particles.

[014] Fig. 2A - Fig. 2E. Examples of pharmaceutical compositions comprising brexanolone. Fig. 2A: Brexanolone structure. Fig. 2B: Small brexanolone particle size distribution. Fig. 2C: Large brexanolone particle size distribution. Fig. 2D - Fig. 2E: Pharmacokinetics (PK) in rats showing rat plasma brexanolone concentrations over time after administration. Legend: Open diamond, brexanolone suspension of small particle, 25 mg/kg; Open square, brexanolone suspension of large particles, 25 mg/kg; Solid square, IV solution (Comparative) 1 mg/kg; and Solid triangle, IM solution (Comparative) 12.5 mg/kg.

[015] Fig. 3A - Fig. 3E. Examples of pharmaceutical compositions comprising ganaxolone. Fig. 3A: Ganaxolone structure. Fig. 3B: Distribution of 4.1 μm ganaxolone particles. Fig. 3C: Distribution of 3.6 μm ganaxolone particles. Fig. 3D-Fig. 3E: Pharmacokinetics (PK) in rats showing rat plasma concentrations over time after administration. Legend: Open diamond, ganaxolone suspension of 1 μm particles, 25 mg/kg; Open square, ganaxolone suspension of 4 μm particles, 25 mg/kg; Solid square, IV solution (Comparative); and Solid diamond, IM solution (Comparative).

[016] Fig. 4. Summary of crystal-form screen results under three conditions: 1) Temperature-cycled ripening of brexanolone slurries between 40-5 °C for two days (TC) (n=48); 2) Heating slurries to 40 °C followed by hot filtration, then storing of

brexanolone solutions at 4 °C for up to two days (RC) (n=48); 3) Evaporation of brexanolone solutions at ambient conditions for up to 7 days (EV) (n=48).

[017] **Fig. 5**. PXRD pattern overlay of Form A from the input brexanolone and a representative Form A pattern from the screen.

DETAILED DESCRIPTION

[018] The features and advantages of the disclosed compositions and methods will be more readily understood, by those of ordinary skill in the art, from reading the following detailed description. It is to be appreciated that certain features of the disclosed compositions and methods, which are, for clarity, described above and below in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. In addition, references in the singular may also include the plural (for example, "a" and "an" may refer to one, or one or more) unless the context specifically states otherwise.

[019] The use of numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both proceeded by the word "about." In this manner, slight variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. Also, the disclosure of these ranges is intended as a continuous range including every value between the minimum and maximum values.

[020] The term "about" and its grammatical equivalents in relation to a reference numerical value and its grammatical equivalents as used herein can include a range of values plus or minus 10% from that value, such as a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value. For example, the amount "about 10" includes amounts from 9 to 11.

[021] As used herein, the term "γ aminobutyric acid type A receptors", "gamma-aminobutyric acid type A receptors", "gamma-aminobutyric acid A receptors", "$GABA_A$ receptors", "$GABA_A$Rs", "$GABA_A$R" or a grammatic variation thereof, either in singular or in plural form, refers to gamma-aminobutyric acid type A receptors ($GABA_A$Rs) that are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA). GABA is the principal inhibitory

neurotransmitter in the cerebral cortex that is important for maintaining the inhibitory state that counterbalances neuronal excitation. Disorder in $GABA_A$ receptors or imbalance of GABA and neuroexcitation can lead to seizures and other central nervous system disfunctions. A number of natural and synthetic neuroactive steroids can bind to $GABA_A$Rs and modulate their activities.

[022] The term "neuroactive steroid", "neuroactive steroids" or a grammatic variation thereof refers to one or more neurosteroids that exert inhibitory actions on neurotransmission, specifically, on the $GABA_A$ receptors. Examples of neurosteroids can include, but not limited, tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone and zuranolone (SAGE-217).

[023] The term "particles" or grammatical variations thereof can refer to particles disclosed herein and, in examples, can also refer to stabilized particles that are stable under physiological conditions without changing its physical or chemical form for an extended period of time, such as for a time period in a range of from 0.1 to 20 hours, 1 to 50 hours, 2 to 75 hours, 5 to 100 hours, 1 to 5 days, 2 to 7 days, 3 to 10 days, 4 to 20 days, or longer.

[024] The terms D10, D50 and D90 are commonly used to represent the midpoint and range of the particle sizes of a given sample. The term "D10" refers to 10% of particles are below and 90% of particles are above a defined measurement, for example a particle diameter. The term "D50" refers to a mass-median-diameter (MMD), wherein 50% of particles are below and 50% of particles are above a defined measurement, for example a particle diameter. The term "D90" refers to 90% of particles are below and 10% of particles are above a defined measurement, for example a particle diameter. In examples, D50=1.5 μm means 50% of particles are below 1.5 μm and 50% of particle are above 1.5 μm. In further examples, D90=4.0 μm means 90% particles are below 4.0 μm in diameter and 10% of particles are above 4.0 μm in diameter. The percentage can be based on total volume of particles, total weight of particles, total number of particles or a total area of the particles measured. In examples, a sample of particles are measured by light scattering with about $1x10^6$ particles measured. A measurement data of D50=0.9 μm means about 50% of particles measured are below 0.9 μm and 50% are above 0.9 μm, percentage based on the total number of particles measured. In further examples, particle sizes are

measured using microscopy and imaging technology or optical granulometry techniques, wherein particles in certain fields are measured. With this, a percentage can be the total number of particles measured or a given area measured.

[025] The term "particle size" refers to a primary particle size or crystallite size that is the smallest particle size. When particles of primary size aggregate together, the aggregate can have an aggregate particle size that is typically a multiple of the primary particle size. The particle size used herein refers to the largest dimension of a primary particle, for example, a diameter of a spherical particle, a longest length of a rod or bar shaped particle, or a largest size measured across an irregular shaped particle.

[026] The term "mean particle size" refers to an average of particle sizes of the particles measured or selected.

[027] The term "C_{max}", "Cmax" or "maximum plasma concentration" refers to the maximum (or peak) plasma concentration that a drug reaches in a specified compartment or part of the body after the drug has been administered and before the administration of a second dose.

Pharmaceutical composition

[028] The disclosed pharmaceutical composition can comprise a pharmaceutically effective amount of a neuroactive steroid, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 10 minutes to 6 hours and maintains a plasma concentration of more than about 5% of the C_{max} for at least about 1 day, after a single dose of the pharmaceutical composition by intramuscular or subcutaneous injection.

[029] The pharmaceutical composition can comprise a pharmaceutically effective amount of a neuroactive steroid, wherein the amount of neuroactive steroid which can be combined with a carrier material to produce a single dosage form can vary depending upon the subject being treated and the particular mode of administration and can generally be that amount of the pharmaceutical composition which produces a therapeutic effect. Generally, the amount of neuroactive steroid can range from about 0.01% to about 99% (w/w) of the composition, for example, can be about 0.1%-1%, about 0.1%-5%, about 0.1-10%, about 0.1%-20%, about 0.5%-1%, about 0.5%-5%, about 0.5%-10%, about 0.5%-20%, about 1%-5%, about 1%-10%, about 1%-20%,

about 5%-10%, about 5%-20%, about 10%-20%, about 10%-30%, about 20%-30%, about 20%-40%, about 30%-40%, about 30%-50%, about 40%-50%, about 40%-60%, about 50%-60%, about 50%-70%, about 60%-70%, about 60%-80%, about 70%-80%, about 70%-90%, about 80%-90%, about 80%-95%, or 95%-99% of the pharmaceutical composition. Preferably, the amount of neuroactive steroid can be from about 0.1% to about 70%, and most preferably from about 1% to about 30% of the pharmaceutical composition.

[030] The pharmaceutical composition can comprise a pharmaceutically effective amount of a neuroactive steroid, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; wherein the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in a subject in about 10 minutes to 6 hours and maintains a plasma concentration of the neuroactive steroid in the subject more than about 5% of the C_{max} for at least about 1 day, after a single dose of the pharmaceutical composition is administered to the subject by intravenous (IV) injection, intramuscular (IM) injection, subcutaneous (SC) injection or a combination thereof; and wherein the maximum plasma concentration (C_{max}) is measured from one or more specimens from the subject.

[031] In some cases, the Cmax can be reached in about 10 minutes to about 360 minutes. In some cases, the Cmax can be reached in about 10 minutes to about 20 minutes, about 10 minutes to about 30 minutes, about 10 minutes to about 40 minutes, about 10 minutes to about 50 minutes, about 10 minutes to about 60 minutes, about 10 minutes to about 120 minutes, about 10 minutes to about 180 minutes, about 10 minutes to about 240 minutes, about 10 minutes to about 300 minutes, about 10 minutes to about 360 minutes, about 20 minutes to about 30 minutes, about 20 minutes to about 40 minutes, about 20 minutes to about 50 minutes, about 20 minutes to about 60 minutes, about 20 minutes to about 120 minutes, about 20 minutes to about 180 minutes, about 20 minutes to about 240 minutes, about 20 minutes to about 300 minutes, about 20 minutes to about 360 minutes, about 30 minutes to about 40 minutes, about 30 minutes to about 50 minutes, about 30 minutes to about 60 minutes, about 30 minutes to about 120 minutes, about 30 minutes to about 180 minutes, about 30 minutes to about 240 minutes, about 30 minutes to about 300 minutes, about 30 minutes to about 360 minutes, about 40 minutes to about 50 minutes, about 40 minutes to about 60 minutes, about 40 minutes to about 120 minutes, about 40 minutes to about 180 minutes, about 40 minutes to about 240 minutes, about 40

minutes to about 300 minutes, about 40 minutes to about 360 minutes, about 50 minutes to about 60 minutes, about 50 minutes to about 120 minutes, about 50 minutes to about 180 minutes, about 50 minutes to about 240 minutes, about 50 minutes to about 300 minutes, about 50 minutes to about 360 minutes, about 60 minutes to about 120 minutes, about 60 minutes to about 180 minutes, about 60 minutes to about 240 minutes, about 60 minutes to about 300 minutes, about 60 minutes to about 360 minutes, about 120 minutes to about 180 minutes, about 120 minutes to about 240 minutes, about 120 minutes to about 300 minutes, about 120 minutes to about 360 minutes, about 180 minutes to about 240 minutes, about 180 minutes to about 300 minutes, about 180 minutes to about 360 minutes, about 240 minutes to about 300 minutes, about 240 minutes to about 360 minutes, or about 300 minutes to about 360 minutes. In some cases, the Cmax can be reached in about 10 minutes, about 20 minutes, about 30 minutes, about 40 minutes, about 50 minutes, about 60 minutes, about 120 minutes, about 180 minutes, about 240 minutes, about 300 minutes, or about 360 minutes.

[032] In some cases, the neuroactive steroid can maintain a plasma concentration in the subject at a level more than about 5% of the Cmax for about 1 day to about 100 days. In some cases, the neuroactive steroid can maintain a plasma concentration in the subject at a level more than about 5% of the Cmax for at least about 1 day. In some cases, the neuroactive steroid can maintain a plasma concentration in the subject at a level more than about 5% of the Cmax for at most about 100 days. In some cases, the neuroactive steroid can maintain a plasma concentration in the subject at a level more than about 5% of the Cmax for about 1 day to about 5 days, about 1 day to about 10 days, about 1 day to about 20 days, about 1 day to about 30 days, about 1 day to about 50 days, about 1 day to about 100 days, about 5 days to about 10 days, about 5 days to about 20 days, about 5 days to about 30 days, about 5 days to about 50 days, about 5 days to about 100 days, about 10 days to about 20 days, about 10 days to about 30 days, about 10 days to about 50 days, about 10 days to about 100 days, about 20 days to about 30 days, about 20 days to about 50 days, about 20 days to about 100 days, about 30 days to about 50 days, about 30 days to about 100 days, or about 50 days to about 100 days. In some cases, the neuroactive steroid can maintain a plasma concentration in the subject at a level more than about 5% of the Cmax for about 1 day, about 5 days, about 10 days, about 20 days, about 30 days, about 50 days, or about 100 days.

[033] In some cases, a single dose of the disclosed pharmaceutical composition can be about 0.5 mg to about 50 mg per kilogram (kg) of body weight. In some cases, a single dose can be at least about 0.5 mg per kg of body weight. In some cases, a single dose can be at most about 50 mg per kg of body weight. In some cases, a single dose can be about 0.5 mg to about 2 mg per kg of body weight, about 0.5 mg to about 4 mg per kg of body weight, about 0.5 mg to about 6 mg per kg of body weight, about 0.5 mg to about 8 mg per kg of body weight, about 0.5 mg to about 10 mg per kg of body weight, about 0.5 mg to about 20 mg per kg of body weight, about 0.5 mg to about 50 mg per kg of body weight, about 2 mg to about 4 mg per kg of body weight, about 2 mg to about 6 mg per kg of body weight, about 2 mg to about 8 mg per kg of body weight, about 2 mg to about 10 mg per kg of body weight, about 2 mg to about 20 mg per kg of body weight, about 2 mg to about 50 mg per kg of body weight, about 4 mg to about 6 mg per kg of body weight, about 4 mg to about 8 mg per kg of body weight, about 4 mg to about 10 mg per kg of body weight, about 4 mg to about 20 mg per kg of body weight, about 4 mg to about 50 mg per kg of body weight, about 6 mg to about 8 mg per kg of body weight, about 6 mg to about 10 mg per kg of body weight, about 6 mg to about 20 mg per kg of body weight, about 6 mg to about 50 mg per kg of body weight, about 8 mg to about 10 mg per kg of body weight, about 8 mg to about 20 mg per kg of body weight, about 8 mg to about 50 mg per kg of body weight, about 10 mg to about 20 mg per kg of body weight, about 10 mg to about 50 mg per kg of body weight, or about 20 mg to about 50 mg per kg of body weight. In some cases, a single dose can be about 0.5 mg per kg of body weight, about 2 mg per kg of body weight, about 4 mg per kg of body weight, about 6 mg per kg of body weight, about 8 mg per kg of body weight, about 10 mg per kg of body weight, about 20 mg per kg of body weight, or about 50 mg per kg of body weight. In a particular example, the single dose can be about 3.5 mg to 5 mg per kg of body weight. The body weight refers to the body weight of a subject, such as a human patient or an animal subject.

[034] In some cases, a unit dose of the disclosed pharmaceutical composition can be about 50 mg to about 800 mg. In some cases, a single unit dose can be at least about 50 mg. In some cases, a single unit dose can be at most about 800 mg. In some cases, a single unit dose can be about 50 mg to about 100 mg, about 50 mg to about 200 mg, about 50 mg to about 300 mg, about 50 mg to about 400 mg, about 50 mg to about 600 mg, about 50 mg to about 800 mg, about 100 mg to about 200 mg, about 100 mg

to about 300 mg, about 100 mg to about 400 mg, about 100 mg to about 600 mg, about 100 mg to about 800 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 600 mg, about 200 mg to about 800 mg, about 300 mg to about 400 mg, about 300 mg to about 600 mg, about 300 mg to about 800 mg, about 400 mg to about 600 mg, about 400 mg to about 800 mg, or about 600 mg to about 800 mg. In some cases, a single unit dose can be about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, or about 800 mg. A unit dose is form of package of the pharmaceutical composition that can be administered to a subject in a single dose. For example, a 300 mg unit dose of a pharmaceutical composition can be packaged in a certain volume, such as one milliliter volume, in an injectable form that can be injected into a subject in a single injection. In other examples, a 300 mg of a pharmaceutical composition can be packaged in a certain number of tablets, such as one tablet, that can be administered to a subject in one oral dose. In yet other examples, a 300 mg unit dose of a pharmaceutical composition can be packaged in a certain volume, such as 0.5 milliliter volume, in an injectable form that can be injected into a subject in a single subcutaneous injection.

[035] In some cases, a single dose of the disclosed pharmaceutical composition can be about 50 mg to about 800 mg. In some cases, a single dose can be at least about 50 mg. In some cases, a single dose can be at most about 800 mg. In some cases, a single dose can be about 50 mg to about 100 mg, about 50 mg to about 200 mg, about 50 mg to about 300 mg, about 50 mg to about 400 mg, about 50 mg to about 600 mg, about 50 mg to about 800 mg, about 100 mg to about 200 mg, about 100 mg to about 300 mg, about 100 mg to about 400 mg, about 100 mg to about 600 mg, about 100 mg to about 800 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 600 mg, about 200 mg to about 800 mg, about 300 mg to about 400 mg, about 300 mg to about 600 mg, about 300 mg to about 800 mg, about 400 mg to about 600 mg, about 400 mg to about 800 mg, or about 600 mg to about 800 mg. In some cases, a single dose can be about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, or about 800 mg.

[036] A single dose can be adjusted when using a unit dose to administer the pharmaceutical composition to a subject based on the body weight of the subject. In one example, a unit dose of 300 mg in 1 mL injectable solution is designed for a single dose injection to a subject of body weight in a range of from 60 kg to 70 kg. For a subject having body weight less than 60 kg, an adjusted dose, such as 0.5 mL of

the 300 mg unit dose, can be injected to the subject in one injection. For a subject having body weight more than 70 kg, an adjusted dose, such as 1.5 mL of the 300 mg unit dose, can be injected to the subject in one injection. The single dose can be adjusted to have the required mg of the pharmaceutical composition per kilogram (kg) of body weight as disclosed herein.

[037] The single dose of the disclosed pharmaceutical composition can be in a range of from about 0.5 to 50 mg per kilogram (kg) of body weight and/or can be produced by combining one or more unit doses, or a part thereof, wherein each of the unit doses can be in a range of from 50 mg to 800 mg per unit dose. The ranges of single dose, unit dose or a combination thereof disclosed above and hereafter are suitable and are incorporated as examples.

[038] In some cases, the disclosed pharmaceutical composition can have a neuroactive steroid concentration of about 5 mg/mL to about 800 mg/mL. In some cases, the neuroactive steroid concentration can be at least about 5 mg/mL. In some cases, the neuroactive steroid concentration can be at most about 800 mg/mL. In some cases, the neuroactive steroid concentration can be about 5 mg/mL to about 10 mg/mL, about 5 mg/mL to about 50 mg/mL, about 5 mg/mL to about 100 mg/mL, about 5 mg/mL to about 200 mg/mL, about 5 mg/mL to about 400 mg/mL, about 5 mg/mL to about 800 mg/mL, about 10 mg/mL to about 50 mg/mL, about 10 mg/mL to about 100 mg/mL, about 10 mg/mL to about 200 mg/mL, about 10 mg/mL to about 400 mg/mL, about 10 mg/mL to about 800 mg/mL, about 50 mg/mL to about 100 mg/mL, about 50 mg/mL to about 200 mg/mL, about 50 mg/mL to about 400 mg/mL, about 50 mg/mL to about 800 mg/mL, about 100 mg/mL to about 200 mg/mL, about 100 mg/mL to about 400 mg/mL, about 100 mg/mL to about 800 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 800 mg/mL, or about 400 mg/mL to about 800 mg/mL. In some cases, the neuroactive steroid concentration can be about 5 mg/mL, about 10 mg/mL, about 50 mg/mL, about 100 mg/mL, about 200 mg/mL, about 400 mg/mL, or about 800 mg/mL.

[039] In some cases, the neuroactive steroid can maintain a plasma concentration of more than about 10%, 15%, 20%, 25%, or 30% of the C_{max} for at least about 10, 20, 30, 40, 50, or 60 days. The neuroactive steroid can maintain a plasma concentration of more than about 10% the C_{max} for at least about 10 days in one example, 15% the C_{max} for at least about 10 days in another example, 20% the C_{max} for at least about 10 days in yet another example, 25% the C_{max} for at least about 10 days in yet another

example, 35% the C_{max} for at least about 10 days in yet another example, 10% the C_{max} for at least about 20 days in another example, 15% the C_{max} for at least about 20 days in another example, 25% the C_{max} for at least about 20 days in yet another example, 35% the C_{max} for at least about 20 days in yet another example, 10% the C_{max} for at least about 30 days in another example, 15% the C_{max} for at least about 30 days in another example, 25% the C_{max} for at least about 30 days in yet another example, 35% the C_{max} for at least about 30 days in yet another example, 10% the C_{max} for at least about 40 days in another example, 15% the C_{max} for at least about 40 days in another example, 25% the C_{max} for at least about 40 days in yet another example, 35% the C_{max} for at least about 40 days in yet another example, 10% the C_{max} for at least about 50 days in another example, 15% the C_{max} for at least about 50 days in another example, 25% the C_{max} for at least about 50 days in yet another example, 35% the C_{max} for at least about 50 days in yet another example, 10% the C_{max} for at least about 60 days in another example, 15% the C_{max} for at least about 60 days in another example, 25% the C_{max} for at least about 60 days in yet another example, 35% the C_{max} for at least about 60 days in yet another example, 10% the C_{max} for at least about 60 or more days in another example, 15% the C_{max} for at least about 60 or more days in another example, 25% the C_{max} for at least about 60 or more days in yet another example or 35% the C_{max} for at least about 60 or more days in yet another example. In one particular example, the neuroactive steroid can maintain a plasma concentration of more than about 15% of the C_{max} for at least about 30 days.

[040] In some cases, the C_{max} can be about 1 ng/mL to about 100 ng/mL. In some cases, the C_{max} can be at least about 1 ng/mL. In some cases, the C_{max} can be at most about 100 ng/mL. In some cases, the C_{max} can be about 1 ng/mL to about 10 ng/mL, about 1 ng/mL to about 20 ng/mL, about 1 ng/mL to about 40 ng/mL, about 1 ng/mL to about 60 ng/mL, about 1 ng/mL to about 80 ng/mL, about 1 ng/mL to about 100 ng/mL, about 10 ng/mL to about 20 ng/mL, about 10 ng/mL to about 40 ng/mL, about 10 ng/mL to about 60 ng/mL, about 10 ng/mL to about 80 ng/mL, about 10 ng/mL to about 100 ng/mL, about 20 ng/mL to about 40 ng/mL, about 20 ng/mL to about 60 ng/mL, about 20 ng/mL to about 80 ng/mL, about 20 ng/mL to about 100 ng/mL, about 40 ng/mL to about 60 ng/mL, about 40 ng/mL to about 80 ng/mL, about 40 ng/mL to about 100 ng/mL, about 60 ng/mL to about 80 ng/mL, about 60 ng/mL to about 100 ng/mL, or about 80 ng/mL to about 100 ng/mL. In some cases, the C_{max} can be about 1 ng/mL, about 10 ng/mL, about 20 ng/mL, about 40 ng/mL, about 60

ng/mL, about 80 ng/mL, or about 100 ng/mL. In particular examples, the C_{max} is in a range of from 20 to 90 ng/mL.

[041] In some cases, the single dose can be in a range of from 3 to about 5 mg per kilogram of body weight, and/or the neuroactive steroid can maintain a plasma concentration of more than about 10 ng/mL for at least about 5 days. In particular examples, the neuroactive steroid can maintain a plasma concentration of more than 10, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 ng/mL for at least about 10, 20, 30, 40, 50, or 60 days. In some cases, the neuroactive steroid can maintain a plasma concentration of more than 10 ng/mL for at least about 10 days in one example, more than 20 ng/mL for at least about 10 days in another example, more than 30 ng/mL for at least about 10 days in yet another example, more than 40 ng/mL for at least about 10 days in yet another example, more than 50 ng/mL for at least about 10 days in yet another example, more than 60 ng/mL for at least about 10 days in yet another example, more than 70 ng/mL for at least about 10 days in yet another example, more than 80 ng/mL for at least about 10 days in yet another example, more than 90 ng/mL for at least about 10 days in yet another example, more than 100 ng/mL for at least about 10 days in yet another example, more than 10 ng/mL for at least about 20 days in one example, more than 20 ng/mL for at least about 20 days in another example, more than 30 ng/mL for at least about 20 days in yet another example, more than 40 ng/mL for at least about 20 days in yet another example, more than 50 ng/mL for at least about 20 days in yet another example, more than 60 ng/mL for at least about 20 days in yet another example, more than 70 ng/mL for at least about 20 days in yet another example, more than 80 ng/mL for at least about 20 days in yet another example, more than 90 ng/mL for at least about 20 days in yet another example, more than 100 ng/mL for at least about 20 days in yet another example, more than 10 ng/mL for at least about 30 days in one example, more than 20 ng/mL for at least about 30 days in another example, more than 30 ng/mL for at least about 30 days in yet another example, more than 40 ng/mL for at least about 30 days in yet another example, more than 50 ng/mL for at least about 30 days in yet another example, more than 60 ng/mL for at least about 30 days in yet another example, more than 70 ng/mL for at least about 30 days in yet another example, more than 80 ng/mL for at least about 30 days in yet another example, more than 90 ng/mL for at least about 30 days in yet another example, more than 100 ng/mL for at least about 30 days in yet another example, more than 10 ng/mL for at least about 40 days in one example, more than 20

ng/mL for at least about 40 days in another example, more than 30 ng/mL for at least about 40 days in yet another example, more than 40 ng/mL for at least about 40 days in yet another example, more than 50 ng/mL for at least about 40 days in yet another example, more than 60 ng/mL for at least about 40 days in yet another example, more than 70 ng/mL for at least about 40 days in yet another example, more than 80 ng/mL for at least about 40 days in yet another example, more than 90 ng/mL for at least about 40 days in yet another example, more than 100 ng/mL for at least about 40 days in yet another example, more than 10 ng/mL for at least about 50 days in one example, more than 20 ng/mL for at least about 50 days in another example, more than 30 ng/mL for at least about 50 days in yet another example, more than 40 ng/mL for at least about 50 days in yet another example, more than 50 ng/mL for at least about 50 days in yet another example, more than 60 ng/mL for at least about 50 days in yet another example, more than 70 ng/mL for at least about 50 days in yet another example, more than 80 ng/mL for at least about 50 days in yet another example, more than 90 ng/mL for at least about 50 days in yet another example, more than 100 ng/mL for at least about 50 days in yet another example, more than 10 ng/mL for at least about 60 days in one example, more than 20 ng/mL for at least about 60 days in another example, more than 30 ng/mL for at least about 60 days in yet another example, more than 40 ng/mL for at least about 60 days in yet another example, more than 50 ng/mL for at least about 60 days in yet another example, more than 60 ng/mL for at least about 60 days in yet another example, more than 70 ng/mL for at least about 60 days in yet another example, more than 80 ng/mL for at least about 60 days in yet another example, more than 90 ng/mL for at least about 60 days in yet another example, more than 100 ng/mL for at least about 60 days in yet another example, more than 10 ng/mL for at least about 60 or more days in one example, more than 20 ng/mL for at least about 60 or more days in another example, more than 30 ng/mL for at least about 60 or more days in yet another example, more than 40 ng/mL for at least about 60 or more days in yet another example, more than 50 ng/mL for at least about 60 or more days in yet another example, more than 60 ng/mL for at least about 60 or more days in yet another example, more than 70 ng/mL for at least about 60 or more days in yet another example, more than 80 ng/mL for at least about 60 or more days in yet another example, more than 90 ng/mL for at least about 60 or more days in yet another example and more than 100 ng/mL for at least about 60 or more days in yet

another example. In one further example, the neuroactive steroid can maintain a plasma concentration of more than 20 ng/mL for at least about 30 days.

[042] In some cases, the pharmaceutical composition releases less than about 5%-50% of the neuroactive steroid within about 1 hour of the single dose of the pharmaceutical composition by intramuscular or subcutaneous injection. Particularly, the pharmaceutical composition can release less than about 5%-50% in one example, 10%-50% in another example, 15%-50% in yet another example, 20%-50% in yet another example, 25%-50% in yet another example, 30%-50% in yet another example, 40%-50% in yet another example and 45%-50% in yet another example, of the neuroactive steroid into plasma of a subject within about 1 hour of the single dose of the pharmaceutical composition administered to the subject by intramuscular or subcutaneous injection. The percentage of release is based on measured plasma concentration of the neuroactive steroid and the total amount of the neuroactive steroid in the single dose of the pharmaceutical composition administered to the subject.

[043] In some cases, the pharmaceutical composition can have a relative bioavailability ($Bioavailability_{IM/SC}/Bioavailability_{IV}$) of about 2%-50% at 24 hours after the single dose by intramuscular or subcutaneous injection, in comparison to the same dose by intravenous administration. In some cases, the relative bioavailability can be about 2% to about 50%. In some cases, the relative bioavailability can be at least about 2%. In some cases, the relative bioavailability can be at most about 50%. In some cases, the relative bioavailability can be about 2% to about 5%, about 2% to about 10%, about 2% to about 20%, about 2% to about 30%, about 2% to about 40%, about 2% to about 50%, about 5% to about 10%, about 5% to about 20%, about 5% to about 30%, about 5% to about 40%, about 5% to about 50%, about 10% to about 20%, about 10% to about 30%, about 10% to about 40%, about 10% to about 50%, about 20% to about 30%, about 20% to about 40%, about 20% to about 50%, about 30% to about 40%, about 30% to about 50%, or about 40% to about 50%. In some cases, the relative bioavailability can be about 2%, about 5%, about 10%, about 20%, about 30%, about 40%, or about 50%.

[044] In some cases, the disclosed pharmaceutical composition can comprise particles comprising at least one neuroactive steroid and one or more pharmaceutical acceptable excipients, wherein the neuroactive steroid is a positive modulator of γ

aminobutyric acid type A ($GABA_A$) receptors; wherein, particles comprise large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm; and wherein, about 0.01% to about 50% of the particles are small particles and about 50% to 99.99% of the particles are large particles, percentage based on the total weight of the particles. In any of embodiments or examples of the pharmaceutical composition, the particles can be stabilized particles disclosed herein.

[045] In some cases, the disclosed pharmaceutical composition can comprise a pharmaceutically effective amount of a neuroactive steroid, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; wherein the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in a subject in about 30 minutes to 6 hours and maintains a plasma concentration of the neuroactive steroid more than about 5% of the C_{max} for at least about 5 days, after a single dose of the pharmaceutical composition is administered to the subject by intravenous (IV) injection, intramuscular (IM) injection, subcutaneous (SC) injection or a combination thereof; wherein, the pharmaceutical composition comprising particles of the neuroactive steroid; wherein, the particles comprise large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm; and wherein, about 0.01% to about 50% of the particles are small particles and about 50% to 99.99% of the particles are large particles, percentage based on the total weight of the particles.

[046] In some cases, the maximum plasma concentration (C_{max}) is measured from specimens from the subject.

[047] In some cases, the particles can have a D50 in a range of from 1.2 μm to about 6.0 μm. The D50 can be 1.2 μm in one example, 1.3 μm in another example, 1.4 μm in yet another example, 1.5 μm in yet another example, 1.6 μm in yet another example, 1.7 μm in yet another example, 1.8 μm in yet another example, 1.9 μm in yet another example, 2.0 μm in yet another example, 2.2 μm in yet another example, 2.4 μm in yet another example, 2.6 μm in yet another example, 2.8 μm in yet another example, 3.0 μm in yet another example, 3.5 μm in yet another example, 4.0 μm in yet another example, 4.5 μm in yet another example, 5.0 μm in yet another example, 5.5 μm in yet another example, 6.0 μm in yet another example, or any one value in the range of from 1.2 μm through 6.0 μm in a further example.

[048] The neuroactive steroid of the disclosed pharmaceutical composition can comprise tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof. For example, the neuroactive steroid can be brexanolone.

[049] In some cases, the large particles can have a mean particle size in a range of from 2.0 to 6.0 μm in one example, a mean particle size in a range of from 3.0 to 5.0 μm in another example, a mean particle size in a range of from 0.4 to 1.3 μm in yet another example and a mean particle size in a range of from 0.5 to 0.9 μm in a further example.

[050] The pharmaceutical composition can further comprise one or more pharmaceutical acceptable excipients. The pharmaceutical acceptable excipients can comprise surfactant, emulsifier, filler, carrier, isotonicfier, dispersing agent, viscosity modifier, resuspending agent, buffer or a combination thereof. Pharmaceutical excipients typically do not have properties of a medicinal or drug active ingredient, also known as active pharmaceutical ingredient (API) and are typically used to streamline the manufacture process or packaging of the active ingredients, or to deliver an API to a patient or other subject. Pharmaceutical acceptable excipients or inactive ingredients from the Inactive Ingredients Database available from US FDA (https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download) can be suitable. Some of Generally Recognized As Safe (GRAS) food substances available form US FDA's GRAS Substances (SCOGS) Database (https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database) can also be suitable.

[051] In some cases, the pharmaceutical acceptable excipients can comprise acacia, animal oils, benzyl alcohol, benzyl benzoate, calcium stearate, carbomers, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate,, glyceryl monooleate, glyceryl monostearate, hydrous, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin, medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer

(poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oils, water, xanthan gum, or a combinations thereof.

[052] In some cases, the pharmaceutical acceptable excipients can comprise dextrose, glycerin, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (Poloxamer 188, Poloxamer 407), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, or a combination thereof.

[053] The pharmaceutical composition can be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active ingredient can be coated in a material to protect it from the action of acids and other natural conditions that may inactivate it. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, the pharmaceutical composition can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, *e.g.*, intranasally, orally, vaginally, rectally, sublingually or topically. The pharmaceutical composition can be in the form of sterile aqueous solutions or dispersions. The pharmaceutical composition can also be formulated in a microemulsion, liposome, or other ordered structure suitable to high drug concentration.

[054] The pharmaceutical composition can comprise a population of particles comprising the neuroactive steroid, wherein the particles have a mean particle size of about 0.1-50 μm. In some cases, the particles can have a mean particle size of about 0.1 μm to about 50 μm. In some cases, the particles can have a mean particle size of at least about 0.1 μm. In some cases, the particles can have a mean particle size of at most about 50 μm. In some cases, the particles can have a mean particle size of about 0.1 μm to about 0.2 μm, about 0.1 μm to about 0.5 μm, about 0.1 μm to about 1 μm, about 0.1 μm to about 2 μm, about 0.1 μm to about 5 μm, about 0.1 μm to about 10 μm, about 0.1 μm to about 20 μm, about 0.1 μm to about 30 μm, about 0.1 μm to about 40 μm, about 0.1 μm to about 50 μm, about 0.2 μm to about 0.5 μm, about 0.2 μm to about 1 μm, about 0.2 μm to about 2 μm, about 0.2 μm to about 5 μm, about 0.2 μm to about 10 μm, about 0.2 μm to about 20 μm, about 0.2 μm to about 30 μm, about 0.2 μm to about 40 μm, about 0.2 μm to about 50 μm, about 0.5 μm to about 1 μm, about 0.5 μm to about 2 μm, about 0.5 μm to about 5 μm, about 0.5 μm to about 10 μm, about 0.5 μm to about 20 μm, about 0.5 μm to about 30 μm, about 0.5 μm to about 40 μm, about 0.5 μm to about 50 μm, about 1 μm to about 2 μm, about 1 μm to about 5 μm, about 1 μm to about 10 μm, about 1 μm to about 20 μm, about 1 μm to about 30 μm, about 1 μm to about 40 μm, about 1 μm to about 50 μm, about 2 μm to about 5 μm, about 2 μm to about 10 μm, about 2 μm to about 20 μm, about 2 μm to about 30 μm, about 2 μm to about 40 μm, about 2 μm to about 50 μm, about 5 μm to about 10 μm, about 5 μm to about 20 μm, about 5 μm to about 30 μm, about 5 μm to about 40 μm, about 5 μm to about 50 μm, about 10 μm to about 20 μm, about 10 μm to about 30 μm, about 10 μm to about 40 μm, about 10 μm to about 50 μm, about 20 μm to about 30 μm, about 20 μm to about 40 μm, about 20 μm to about 50 μm, about 30 μm to about 40 μm, about 30 μm to about 50 μm, or about 40 μm to about 50 μm. In some cases, the particles can have a mean particle size of about 0.1 μm, about 0.2 μm, about 0.5 μm, about 1 μm, about 2 μm, about 5 μm, about 10 μm, about 20 μm, about 30 μm, about 40 μm, or about 50 μm. The particles can have a mean particle size of about 1.5-15 μm in one example, about 3-5 μm in another example, about 0.2-1.5 μm in yet another example and about 0.5-0.9 μm in yet another example.

[055] The pharmaceutical composition can comprise at least 50%, 60%, 70%, 80%, or 90% by weight of the particles having a particle size of about 0.2-15 μm. The pharmaceutical composition can comprise about 0.01%-50% by weight of the

particles having an average particle size of about 1.5-15 μm and about 50% to 99.99% by weight of the particles having an average particle size of about 0.2-1.5 μm.

[056] The neuroactive steroid of the pharmaceutical composition can comprise brexanolone, ganaxolone. zuranolone (SAGE-217) or a combination thereof.

[057] In some cases, the neuroactive steroid can comprise brexanolone. The pharmaceutical composition can comprise in a range of from 5 mg/mL to 800 mg/mL brexanolone or any specific ranges of the neuroactive steroid disclosed hereabove or hereafter. The pharmaceutical composition can be a parenteral injection suspension comprising brexanolone. In some cases, the pharmaceutical composition can have large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm. A pharmaceutical composition comprising brexanolone can comprise particles having about 0.01% to about 50% of the small particles and about 50% to about 99.99% of the large particles, percentage based on the total weight of the particles. Such pharmaceutical composition comprising brexanolone can comprise in a range of from 0.01% to 50% in one example, 10% to 50% in another example, 15% to 50% in yet another example, 20% to 50% in yet another example, 25% to 50% in yet another example, 30% to 50% in yet another example, 40% to 50% in yet another example and 45% to 50% in yet another example of small particles; and in arrange of from 50% to 90% in one example, 55% to 90% in another example, 60% to 90% in yet another example, 65% to 90% in yet another example, 70% to 90% in yet another example, 75% to 90% in yet another example, 80% to 90% in yet another example and 85% to 90% in yet another example of large particles. In a particular example, the pharmaceutical composition can comprise about 10% to about 50% of the small particles and about 50% to about 90% of the large particles, percentage based on the total weight of the particles. In even further examples, the pharmaceutical composition can comprise about 0.1% to about 1% of the small particles and about 90% to about 99.9% of the large particles, percentage based on the total weight of the particles.

[058] The neuroactive steroid can comprise ganaxolone and the pharmaceutical composition comprises in a range of from 100 mg/mL to 800 mg/mL ganaxolone or any specific ranges the neuroactive steroid disclosed herein. The pharmaceutical composition can be a parenteral injection suspension comprising ganaxolone. A pharmaceutical composition comprising ganaxolone can comprise about 0.01% to

about 50% of small particles and about 50% to about 99.99% of large particles, percentage based on the total weight of the particles. Such pharmaceutical composition comprising ganaxolone can comprise particles in a range of from 0.01% to 50% in one example, 0.1% to 50% in another example, 1.0% to 50% in yet another example, 2.0% to 50% in yet another example, 4.0% to 50% in yet another example, 6.0% to 50% in yet another example, 8.0% to 50% in yet another example, 10% to 50% in one example, 15% to 50% in another example, 20% to 50% in yet another example, 25% to 50% in yet another example, 30% to 50% in yet another example, 40% to 50% in yet another example and 45% to 50% in yet another example of small particles; and in arrange of from 50% to 99.99% in one example, 55% to 99.99% in another example, 60% to 99.99% in yet another example, 65% to 99.99% in yet another example, 70% to 99.99% in yet another example, 75% to 99.99% in yet another example, 80% to 99.99% in yet another example and 85% to 99.99% in yet another example of large particles. In particular examples, the pharmaceutical composition can comprise about 0.01% to about 10% of the small particles and about 90% to about 99.99% of the large particles, percentage based on the total weight of the particles.

[059] Schematic illustrations of particle size distributions are shown in **Fig. 1A – Fig. 1D**. In one example, a pharmaceutical composition can comprise minimum amounts, such as in a range of from 0.01% to 1% of small particles and mostly large particles (**Fig. 1A**). In this example, D50 can be very close to the mean particle size of the large particles. In another example, a pharmaceutical composition can comprise some amounts of small particles, such as in arrange of from 1% to 5% and 95% to 99% of large particles (**Fig. 1B**). In yet another example, a pharmaceutical composition comprises increasing amounts, such as 5% to 10% of small particles and 90% to 95% of large particles (**Fig. 1C**). In yet another example, a pharmaceutical composition comprises comparable amounts, such as 10% to 40% of small particles and 60% to 90% of large particles (**Fig. 1D**).

[060] The pharmaceutical composition can be substantially free of cyclodextrins. In examples, the pharmaceutical composition is substantially free of cyclodextrins meaning that the pharmaceutical composition comprises 0 to 0.1 %, 0 to 0.01%, 0 to 0.001%, 0 to 0.0001% or less cyclodextrins, all percentages based on the total weight of the pharmaceutical composition.

[061] The pharmaceutical composition can be substantially free of sulfobutyl ether β-cyclodextrin. In examples, the pharmaceutical composition is substantially free of sulfobutyl ether β-cyclodextrin meaning that the pharmaceutical composition comprises 0 to 0.1 %, 0 to 0.01%, 0 to 0.001%, 0 to 0.0001% or less sulfobutyl ether β-cyclodextrin, all percentages based on the total weight of the pharmaceutical composition.

[062] In further examples, the pharmaceutical composition can be a liquid suspension for intramuscular (IM) or subcutaneous (SC) injection.

[063] Also disclosed is a process for producing the pharmaceutical composition disclosed herein. In some cases, the process can comprise: a) mixing a composition comprising the neuroactive steroid with one or more pharmaceutically acceptable excipients; and b) milling the composition to produce a population of particles to produce the pharmaceutical composition. In some cases, the process can comprise: a) milling a composition comprising the neuroactive steroid to produce a population of particles; and b) mixing the composition with one or more pharmaceutically acceptable excipients to produce the pharmaceutical composition. In some cases, the process comprises crystalizing the brexanolone polymorph Form A from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), acetonitrile (MeCN), and water. In some cases, the one or more solvents do not comprise acetonitrile. In some cases, the process further comprises: a) mixing the brexanolone polymorph Form A with one or more pharmaceutically acceptable excipients to form a composition; and b) milling said composition to produce a population of particles of said pharmaceutical composition. In some cases, the process further comprises: a) milling a composition comprising the brexanolone polymorph Form A to produce a population of particles; and b) mixing said composition with one or more pharmaceutically acceptable excipients to produce said pharmaceutical composition. In some cases, the pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.

[064] In some cases, disclosed herein is a method for producing a pharmaceutical composition comprising particles, comprising: producing a particle mixture comprising at least one neuroactive steroid and one or more pharmaceutical acceptable excipients; milling a first portion of the particle mixture to produce a large

particle mixture, wherein at least 50% of the large particle mixture are large particles having a particle size in a range of from about 1.5 μm to about 15 μm, percentage based on the total weight of the particle mixture; and producing the pharmaceutical composition comprising the particles comprising about 50% to 99.99% of the large particles, percentage based on the total weight of the particles.

[065] The neuroactive steroid can be selected from tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof. In one example, the neuroactive steroid is brexanolone. In another example, the neuroactive steroid is ganaxolone. In another example, the neuroactive steroid is zuranolone.

[066] Commercially available or proprietary neuroactive steroids API can be suitable as a starting material for producing the particle mixture. Typically, the commercially available neuroactive steroids API can have a large particle size. For example, a commercial brexanolone can have a particle size of about 7 to 10 μm in diameter. In another example, a commercial ganaxolone can have a particle size of about 40 to 50 μm. The milling process can reduce particles to a range of suitable sizes.

[067] Typical milling media, such milling beads can be used for milling the particles. The milling bead can have a diameter of 0.1 mm to about 1 mm. In examples, a rotary milling process with a rotation speed of 300 to 600 rpm can be suitable. The particles can be milled for 10 to 40 minutes, 10 to 40 cycles or a time and cycles sufficient to produce particles of desired size range. The milling can be conducted in the presence of one or more excipients disclosed herein.

[068] The large particles can have a mean particle size in a range of from 1.5 μm to about 15 μm in one example, 1.5 μm to 10 μm in another example, 1.5 μm to 8,000 μm in yet another example, 1.5 μm to 6.0 μm in yet another example and 1.5 μm to 4.5 μm in yet another example. In additional examples, the large particles can have a mean particle size in a range of from 2.0 to 6.0 μm. In further embodiments, the large particles can have a mean particle size in a range of from 2.0 to 5.0 μm. In one further example, the large particles can have a particle size of about 2.0 μm to about 4.5 μm.

[069] The process or method can further comprise: milling a second portion of the particle mixture to produce a small particle mixture, wherein the small particle mixture comprises small particles having a particle size in a range of from about 0.2

μm to about 1.5 μm. In some cases, the pharmaceutical composition is produced by mixing the large particle mixture and the small particle mixture to form the particles comprising about 50% to 99.99% of the large particles and 0.01% to 50% of the small particles, percentage based on the total weight of the particles.

[070] The first portion and the second portion can be the same or different. In some examples, the first portion and the second portion are the same and the particle mixture is configured to be milled to comprise the large particles and the small particles. In some further examples, the second portion can a part of the first portion and further milled to produce the small particles. In yet some examples, the first portion and the second portion are divided from the original particle mixture and milled separately to produce the large particle and the small particles, respectively.

[071] The small particles can have a mean particle size in a range of from 0.2 μm to about 1.5 μm in one example, 0.2 μm to 1.2 μm in another example, 0.2 μm to 1.0 μm in yet another example, 0.2 μm to 0.8 μm in yet another example and 0.2 μm to 0.7 μm in yet another example. In further examples, the small particles can have a mean particle size in a range of from 0.4 to 1.3 μm. In additional examples, the small particles can have a mean particle size in a range of from 0.5 to 0.9 μm. In an even further example, the small particles can have a mean particle size of about 0.7 μm.

[072] The suitable pharmaceutical acceptable excipients can be selected from acacia, animal oils, benzyl alcohol, benzyl benzoate, calcium stearate, carbomers, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate, glyceryl monooleate, glyceryl monostearate, histidine, hydrochloric acid, hydrous, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin, medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium

lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oils, water, xanthan gum, and a combinations thereof.

[073] In some cases, the pharmaceutical acceptable excipients can comprise dextrose, glycerin, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (Poloxamer 188, Poloxamer 407), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, or a combinations thereof.

[074] In some cases, the pharmaceutical composition can be formulated as a parenteral injection suspension and/or suitable for oral administration, intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) injection or a combination thereof.

[075] In some cases, the neuroactive steroid can comprise brexanolone and the pharmaceutical composition can comprise in a range of from 5 mg/mL to 800 mg/mL brexanolone or any specific ranges the neuroactive steroid disclosed herein, for example from 100 mg/mL to 800 mg/mL. The pharmaceutical composition can be formulated as a parenteral injection suspension comprising brexanolone. A pharmaceutical composition comprising brexanolone can comprise particles having about 0.01% to about 50% of the small particles and about 50% to about 99.99% of the large particles, percentage based on the total weight of the particles. Such pharmaceutical composition comprising brexanolone can be configured to comprise particles in a range of from 0.01% to 50% in one example, 10% to 50% in another example, 15% to 50% in yet another example, 20% to 50% in yet another example, 25% to 50% in yet another example, 30% to 50% in yet another example, 40% to 50% in yet another example and 45% to 50% in yet another example of small particles; and in arrange of from 50% to 90% in one example, 55% to 90% in another example, 60% to 90% in yet another example, 65% to 90% in yet another example, 70% to 90% in yet another example, 75% to 90% in yet another example, 80% to 90% in yet another example and 85% to 90% in yet another example of large particles. In a particular example, the pharmaceutical composition can comprise about 10% to about 50% of

the small particles and about 50% to about 90% of the large particles, percentage based on the total weight of the particles. In even further examples, the pharmaceutical composition can be configured to comprise about 0.1% to about 1% of the small particles and about 90% to about 99.9% of the large particles, percentage based on the total weight of the particles.

[076] The neuroactive steroid can comprise ganaxolone and the pharmaceutical composition can comprise in a range of from 100 mg/mL to 800 mg/mL ganaxolone or any specific ranges the neuroactive steroid disclosed herein. The pharmaceutical composition can be formulated as a parental injection suspension comprising ganaxolone. A pharmaceutical composition comprising ganaxolone can be configured to comprise about 0.01% to about 50% of small particles and about 50% to about 99.99% of large particles, percentage based on the total weight of the particles. Such pharmaceutical composition comprising ganaxolone can be configured to comprise in a range of from 0.01% to 50% in one example, 0.1% to 50% in another example, 1.0% to 50% in yet another example, 2.0% to 50% in yet another example, 4.0% to 50% in yet another example, 6.0% to 50% in yet another example, 8.0% to 50% in yet another example, 10% to 50% in one example, 15% to 50% in another example, 20% to 50% in yet another example, 25% to 50% in yet another example, 30% to 50% in yet another example, 40% to 50% in yet another example and 45% to 50% in yet another example of small particles; and in arrange of from 50% to 99.99% in one example, 55% to 99.99% in another example, 60% to 99.99% in yet another example, 65% to 99.99% in yet another example, 70% to 99.99% in yet another example, 75% to 99.99% in yet another example, 80% to 99.99% in yet another example and 85% to 99.99% in yet another example of large particles. In particular examples, the pharmaceutical composition can comprise about 0.01% to about 10% of the small particles and about 90% to about 99.99% of the large particles, percentage based on the total weight of the particles. In any of embodiments or examples of the process or method, the particles can be stabilized particles disclosed herein.

[077] In some cases, one advantage of the pharmaceutical composition is that it can comprise small particles and large particles and can provide controlled releases of brexanolone, ganaxolone, zuranolone (SAGE-217), or combination thereof. Not wishing to be bound by a particular theory or a mechanism, applicants believe that the smaller particles can provide early or fast release, while larger particles provide extended or sustained release. By optimizing the ratio of small particles and large

particles, an optimized release profile can be achieved for best treatment of the disease.

[078] In some cases, another advantage of the disclosed pharmaceutical composition is that, due to the optimized release profile, it can be administered to a subject in a short administration time period avoiding long injection time that are associated with the drugs currently available, such as ZULRESSO™.

[079] Also disclosed herein is a method for treating a disease in a subject in need thereof, the method comprising administering the subject a pharmaceutical composition disclosed herein or a pharmaceutical composition produced by a process disclosed herein, via intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) injection or a combination thereof. In some examples, intramuscular (IM) injection or subcutaneous (SC) injection is preferred. In some cases, the method can comprise: administering the pharmaceutical composition disclosed herein to a subject by intramuscular or subcutaneous injection.

[080] In some cases, disclosed is a method of treating a disease in a subject in need thereof, comprising: administering a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid to the subject by intramuscular or subcutaneous injection with a single dose in a range of from 0.5 to 10 mg per kilogram of body weight, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein plasma concentration of the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in the subject in about 30 minutes to 6 hours and maintains the plasma concentration in the subject of more than about 5% of the C_{max} for at least about 5 days, after intramuscular or subcutaneous injection to the subject.

[081] As mentioned above, the body weight can refer to the body weight of a subject, such as a human patient. The range include single doses of 0.5, 10 mg per kg of body weight and a continuous range including every value between the 0.5 and 10 mg per kg of body weight. For an animal subject, the single dose can be different as mentioned above.

[082] In some cases, the pharmaceutical composition can be administered to the subject via intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) injection or a combination thereof. The pharmaceutical composition can be administered to a subject in a bolus injection, in a continuous injection, or a combination thereof. The pharmaceutical composition can be administered to a

subject within a time period in a range of from 1 second to about 180 minutes. The pharmaceutical composition can be administered to a subject within a time period in a range of from about 1 second to about 180 minutes in one example, 1 minute to about 180 minutes in another example, 5 minutes to about 180 minutes in yet another example, 10 minutes to about 180 minutes in yet another example, 20 minutes to about 180 minutes in yet another example, 40 minutes to about 180 minutes in yet another example, 50 minutes to about 180 minutes in yet another example, 60 minutes to about 180 minutes in yet another example, or any time one value within the range. In further examples, the pharmaceutical composition can be administered to a subject within a time period in a range of from 1 second to about 150 minutes, 1 second to about 100 minutes, 1 second to about 80 minutes, 1 second to about 60 minutes, 1 second to about 30 minutes, 1 second to about 10 minutes, 1 second to about 5 minutes and 1 seconds to about 1 minute in yet another example. In a particular example, the pharmaceutical composition can be administered to a subject with one shot single injection. In additional examples, the pharmaceutical composition can be administered to a subject with two or more injections.

[083] In some cases, the disease can be selected from anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome. In some cases, the disease can be postpartum depression. The subject can have prior history of depression. In some cases, the subject can have prior history of postpartum depression.

[084] Also disclosed herein is a use of a composition comprising a neuroactive steroid for manufacturing a medicament for treating a disease, wherein the composition is a pharmaceutical composition disclosed herein. The disease can be selected from anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome. The neuroactive steroid can be selected from tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone),

allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217), and a combination thereof.

[085] In some cases, the composition comprises a neuroactive steroid for use in a method for the treatment of a disease, wherein the neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein plasma concentration of the neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains the plasma concentration of more than about 5% of the C_{max} for at least about 5 days, after a single dose of the neuroactive steroid by intramuscular or subcutaneous injection. The disease can be selected from anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome. The neuroactive steroid can be selected from tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217), and a combination thereof. In some cases, the composition is a pharmaceutical composition disclosed herein. In some cases, the method is a method disclosed above.

[086] In some cases, disclosed herein is a use of particles comprising at least one neuroactive steroid and one or more pharmaceutical acceptable excipients for manufacturing a medicament for treating a disease, wherein, the particles comprise large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm; and wherein, about 0.01% to about 50% of the particles are small particles and about 50% to 99.99% of the particles are large particles, percentage based on the total weight of the particles. The neuroactive steroid can be selected from tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, pregnane pregnanolone (eltanolone), allopregnanolone, brexanolone, ganaxolone, zuranolone (SAGE-217), and a combination thereof. In some cases, the large particles can have a mean particle size in a range of from 2.0 to 6.0 μm in one example, 3.0 to 5.0 μm in another example,

0.4 to 1.3 μm in yet another example, and 0.5 to 0.9 μm in yet another example. The particles can be stabilized particles disclosed herein.

[087] In some cases, the pharmaceutical acceptable excipients can comprise surfactant, emulsifier, filler, carrier, isotonicfier, dispersing agent, viscosity modifier, resuspending agent, buffer, and a combination thereof. In some cases, the pharmaceutical acceptable excipients comprise acacia, animal oils, benzyl alcohol, benzyl benzoate, calcium stearate, carbomers, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate,, glyceryl monooleate, glyceryl monostearate, hydrous, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin, medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oils, water, xanthan gum, or a combinations thereof.

[088] In some cases, the pharmaceutical acceptable excipients can comprise dextrose, glycerin, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (Poloxamer 188, Poloxamer 407), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, or a combinations thereof. In some cases, the pharmaceutical composition is a parenteral injection suspension.

[089] In some cases, the neuroactive steroid can comprise brexanolone and the pharmaceutical composition comprises in a range of from 80 mg/mL to 400 mg/mL brexanolone. In some cases, the neuroactive steroid can comprise ganaxolone and the pharmaceutical composition comprises in a range of from 80 mg/mL to 400 mg/mL ganaxolone.

[090] In some cases, the pharmaceutical composition can comprise about 10% to about 50% of the small particles and about 50% to about 90% of the large particles, percentage based on the total weight of the particles. In some cases, the pharmaceutical composition can comprise about 0.01% to about 50% of the small particles and about 50% to about 99.99% of the large particles, percentage based on the total weight of the particles.

[091] In some cases, the disease can be selected from anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome.

[092] Also disclosed is a method for producing a pharmaceutical composition for controlled release of at least one neuroactive steroid comprising brexanolone, ganaxolone, zuranolone (SAGE-217) or a combination thereof. The method comprises: producing large particles having a particle size in a range of from about 1.5 μm to about 15 μm and small particles having a particle size in a range of from about 0.2 μm to about 1.5 μm; mixing the small particles and the large particles to produce particles, wherein, about 0.01% to about 50% of the particles are the small particles and about 50% to 99.99% of the particles are the large particles, percentage based on the total weight of the particles; and producing the pharmaceutical composition comprising the particles by adjusting a ratio of the small particles and the large particles so that the pharmaceutical composition is configured to release the neuroactive steroid within 0.1 to 1 hour in a subject after administered to the subject in need thereof and continue to release the neuroactive steroid in the subject for a time period in a range of from 10 hours to about 200 hours after administered to the subject.

Crystal form of brexanolone

[093] Also disclosed is a pharmaceutical composition, comprising a brexanolone polymorph Form A, characterized by having at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 of the following peaks in an X-ray Powder Diffraction (XRPD) diffractogram, at 7.25, 8.88, 11.46, 14.50, 14.78, 17.77, 18.15, 18.32, 18.61, and 19.99 ± 0.1 °2θ.

[094] In some cases, the pharmaceutical composition is a liquid suspension. In some cases, the pharmaceutical composition is for intramuscular or subcutaneous injection. In some cases, the liquid suspension comprises the brexanolone polymorph Form A. In some cases, the brexanolone polymorph Form A has a chemical purity of greater than 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% (w/w). In some cases, the chemical purity is quantified by HPLC. In some cases, the brexanolone polymorph Form A has a melting point of about 170-180 °C. In some cases, the brexanolone polymorph Form A has a melting point of about 174 °C.

[095] In some cases, the brexanolone polymorph Form A is crystalized from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), acetonitrile (MeCN), and water. In some cases, the one or more solvents do not comprise acetonitrile.

EXAMPLES

[096] The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

Example 1: Brexanolone Suspensions

[097] Brexanolone was purchased from commercial vender as an active pharmaceutical ingredient (API) (**Fig. 2A**). The article size of the commercial brexanolone is about 7 to 8 μm.

[098] The commercial brexanolone was milled in the presence of water, saline, dextrose, HPMC, TWEEN 80, poloxamer 407 and glycerin with a rotation speed of

about 300 to 500 rpm for about 20 to 30 minutes. The milling was performed for 1-5 cycles depending on the desired particle size. The milling media used was beads having a diameter of 0.1 to 1.0 mm.

[099] By controlling the milling parameters, two sets of particles sizes were selected. One was small particle having a mean particle size of about 0.7 μm (**Fig. 2B**) and the other was large particle having a mean particle size of about 4.0 μm (**Fig. 2C**).

Example 2: Pharmacokinetics (PKs) of Brexanolone Compositions in Rats

[100] Suspensions of the 0.7 μm particles and the 4.0 μm particles were separately injected into rats via intramuscular (IM) injection at a dosage of 25 mg/kg of brexanolone. For comparison, comparative brexanolone solutions were injected via intramuscular (IM) injection at a dosage of 12.5 mg/kg, or intravenous (IV) injection at 1 mg/kg. Plasma brexanolone concentration were measured at indicated time points. Data are shown in **Fig. 2D – Fig. 2E**. PKs for the solutions were adjusted to have proportional doses.

Example 3: Injectable Brexanolone Pharmaceutical Compositions

[101] A first brexanolone composition is produced using the suspension of the 0.7 μm particles prepared above to have a desired pharmacokinetics profile.

[102] A second brexanolone composition is produced by mixing the suspensions of the 0.7 μm particles and 4.0 μm particles prepared above. The composition is adjusted to have about 10% of the 0.7 μm particles and about 90% of the 4.0 μm particles to have a desired pharmacokinetics profile.

[103] A third brexanolone composition is produced by mixing the suspensions of the 0.7 μm particles and 4.0 μm particles prepared above. The composition is adjusted to have about 30% of the 0.7 μm particles and about 70% of the 4.0 μm particles to have a desired pharmacokinetics profile.

[104] A fourth brexanolone composition is produced by mixing the suspensions of the 0.7 μm particles and 4.0 μm particles prepared above. The composition is adjusted to have about 40% of the 0.7 μm particles and about 60% of the 4.0 μm particles to have a desired pharmacokinetics profile.

[105] A fifth brexanolone composition is produced by mixing the suspensions of the 0.7 μm particles and 4.0 μm particles prepared above. The composition is adjusted to

have about 50% of the 0.7 μm particles and about 50% of the 4.0 μm particles to have a desired pharmacokinetics profile.

[106] A sixth brexanolone composition is produced using the suspension of the 4 μm particles prepared above to have a desired pharmacokinetics profile.

Example 4: Ganaxolone Suspensions

[107] Ganaxolone was purchased from commercial vender as an active pharmaceutical ingredient (API) (**Fig. 3A**). The article size of the commercial brexanolone is about 47 μm.

[108] The commercial ganaxolone was milled in the presence of water, saline, 1 mg/mL TWEEN 80 and 5 mg/mL HPMC with a rotation speed of about 200 rpm for about 20 minutes. The milling was performed for 3 cycles. The milling media used was beads having a diameter of 1.0 mm.

[109] The milled particles had less than 1% of particles having sizes less than 1.5 μm with mean sizes of about 4.1 μm (**Fig. 3B**) about 3.6 μm (**Fig. 3C**) in two batches. Particles of having a mean particle size of about 1.0 μm were also produced.

Example 5: Pharmacokinetics (PKs) of Ganaxolone Compositions in Rats

[110] Suspensions of the particles having 1 μm and 4.1 μm were separately injected into rats via intramuscular (IM) injection at a dosage of 25 mg/kg of ganaxolone. For comparison, comparative ganaxolone solutions were injected via intramuscular (IM) injection at a dosage of 12.5 mg/kg, or intravenous (IV) injection at 1 mg/kg. Plasma brexanolone concentration were measured at indicated time points. Data are shown in **Fig. 3D** and **Fig. 3E**. PKs for the solutions were adjusted to have proportional doses.

Example 6: Injectable Ganaxolone Pharmaceutical Compositions

[111] A first ganaxolone composition is produced using the suspension of the 1 μm particles prepared above to have a desired pharmacokinetics profile.

[112] A second ganaxolone composition is produced by mixing the suspensions of the 1 μm particles and 4.1 μm particles prepared above. The composition is adjusted to have about 10% of the 1 μm particles and about 90% of the 4.1 μm particles to have a desired pharmacokinetics profile.

[113] A third ganaxolone composition is produced by mixing the suspensions of the 1 μm particles and 4.1 μm particles prepared above. The composition is adjusted to

have about 30% of the 1 μm particles and about 70% of the 4.1 μm particles to have a desired pharmacokinetics profile.

[114] A fourth ganaxolone composition is produced by mixing the suspensions of the 1 μm particles and 4.1 μm particles prepared above. The composition is adjusted to have about 40% of the 1 μm particles and about 60% of the 4.1 μm particles to have a desired pharmacokinetics profile.

[115] A fifth ganaxolone composition is produced by mixing the suspensions of the 1 μm particles and 4.1 μm particles prepared above. The composition is adjusted to have about 50% of the 1 μm particles and about 50% of the 4.1 μm particles to have a desired pharmacokinetics profile.

[116] A sixth ganaxolone composition is produced using the suspension of the 4.1 μm particles prepared above to have a desired pharmacokinetics profile.

Example 7: Brexanolone Crystal Form Screening

[117] Brexanolone was purchased from commercial vender and gently grounded prior to dispensing. The brexanolone sample was analyzed by the following analytical techniques: FT-Raman spectroscopy, FT-IR spectroscopy, Differential calorimeter (DSC), Thermogravimetric analysis (TGA-IR), Polarized light microscopy (PLM), and Powder X-ray diffraction (PXRD). The sample was determined to be a white crystalline powder consisting of irregular particles with a wide range of size, including large brittle chunks. The DSC analysis showed a melting endotherm at 174 °C (ΔH=101 J/g). TGA analysis showed negligible (<0.1%) weight loss between 25-175 °C, indicating that the material is non-solvated.

[118] Solubility of the supplied brexanolone was determined by visual assessment of dissolution in various solvents at RT (~22 °C) and 40 °C. Aliquots of solvent were added to a fixed amount of brexanolone (~10 mg) at room temperature until the dissolution point or a maximum volume of 1.8 mL was reached. All samples were then heated to 40 °C for 1 h and dissolution was observed. As shown in **Error! Reference source not found.**, at RT brexanolone exhibited low solubility (<6 mg/mL) in water, moderate solubility (6–52 mg/mL) in MeCN, IPE, MTBE, IPA, MeOH, a mixture of IPA:water (9:1, v:v), toluene, DMSO, EtOAc and high solubility (>96 mg/mL) in THF, and DCM.

Table 1 - Solubility of brexanolone at RT and 40 °C

#	Solvent (v:v)	Solubility at RT [mg/mL]	Solubility at 40 °C [mg/mL]
1	Dichloromethane (DCM)	108-432	>108
2	Tetrahydrofuran (THF)	96-384	>96
3	Ethyl Acetate (EtOAc)	21-52	>21
4	Dimethyl sulfoxide (DMSO)	20-49	>20
5	Toluene	20-50	>20
6	2-Propanol:water (9:1)	20-51	>20
7	Methanol (MeOH)	19-49	>19
8	2-Propanol (IPA)	19-49	>19
9	Methyl t-butyl ether (MTBE)	10-20	>10
10	Isopropyl ether (IPE)	6-11	>6
11	Acetonitrile (MeCN)	6-10	>6
12	Water	<6	<6

[119] Crystallization experiments were conducted in three modes, including: 1) Temperature-cycled ripening of brexanolone slurries between 40-5 °C for two days (TC) (n=48); 2) Heating slurries to 40 °C followed by hot filtration, then storing of brexanolone solutions at 4 °C for up to two days (RC) (n=48); 3) Evaporation of brexanolone solutions at ambient conditions for up to 7 days (EV) (n=48). A total of 48 solvent systems were involved in the crystal-form screen. The solvents were utilized as neat and binary mixtures to provide a diverse set of polarities, dielectric constants, dipole moments, and hydrogen-bond donor/acceptor attributes. Water-containing solvents with a variety of water activities were also included to probe for the formation of hydrates.

[120] All crystalline outputs from the screen were isolated and analyzed by FT-Raman spectroscopy. The samples were then sorted into groups based on Raman spectral match. Representative samples from each of the groups were further analyzed by additional techniques (PXRD, DSC, TGA, PLM), as appropriate and as sample quantity permitted. These data were used to support the form assignment which is shown in **Fig. 4**.

[121] As shown in **Fig. 4**, 27 crystalline solids were obtained from TC, 14 crystalline solids from RC, and 28 crystalline solids from EV crystallization modes for a total of 69 crystalline solids (shaded). **Fig. 5** shows a PXRD pattern overlay of the input brexanolone with a representative Form A pattern from the screen. Polymorph of brexanolone, Form A, was observed in 68 of 69 samples that produced solids. The description of Form A is exemplified by Batch 103260-TC-01. The DSC onset for the melting/decomposition of Lot 103260-TC-01 was 174 °C (ΔH=127 J/g). The TGA % weight loss was < 0.1% prior to the melt/decomposition event. Form A

is a non-solvated form. The characterization data for Form A along with PXRD peak list are provided in Table 2.

Table 2: Ten most intense PXRD peak list of Form A (Batch 103260-TC-01)

Position [°2Theta]*	d-spacing [Å]	Relative Intensity [%]
18.15	4.9	100
7.25	12.2	91
18.32	4.8	40
18.61	4.8	31
17.77	5.0	19
14.78	6.0	18
19.99	4.4	18
14.50	6.1	16
11.46	7.7	16
8.88	10.0	14

*Data collected with copper K-alpha radiation. K-alpha II mathematically stripped from data prior to peak determination based on copper K-alpha I radiation (1.540598 Å).

Instruments and Methods

[122] FT-Raman Spectroscopy. Raman spectra were collected with a Nicolet NXR9650 or NXR 960 spectrometer (Thermo Electron) equipped with 1064 nm Nd:YVO_4 excitation laser, InGaAs and liquid-N_2 cooled Ge detectors, and a MicroStage. All spectra were acquired at 4 cm^{-1} resolution, 64 to 256 scans, using a neutral density filter and Happ-Genzel apodization function and 2-level zero-filling.

[123] Polarized-light Microscopy (PLM). The photomicrographs were collected using Olympus BX60 polarized-light microscope equipped with Olympus DP70 camera.

[124] Powder X-Ray Diffraction (PXRD). PXRD diffractograms were acquired on PANalytical X'Pert Pro diffractometer using Ni-filtered Cu Ka (45 kV/40 mA) radiation and a step size of 0.02° 2θ and X'celerator™ RTMS (Real Time Multi-Strip) detector. Configuration on the incidental beam side: fixed divergence slit (0.25°), 0.04 rad Soller slits, anti-scatter slit (0.25°), and 10mm beam mask. Configuration on the diffracted beam side: fixed divergence slit (0.25°) and 0.04 rad Soller slit. Samples were mounted flat on zero-background Si wafers and covered with Kapton film to comply with safety policies.

[125] Powder X-Ray Diffraction (PXRD) Bruker. PXRD diffractograms were acquired on a Bruker D8 Advance system (SN:2631) using Cu Ka (40 kV/40 mA)

radiation and a step size of 0.017° 2θ and LynxEye detector. Configuration on the incidental beam side: fixed divergence slit (0.2mm), 4mm Soller slits, beam knife. Configuration on the diffracted beam side: anti-scatter slit (8mm) and 2.5 deg. Soller slit. Samples were mounted flat on zero-background Si wafers.

[126] Differential Scanning Calorimetry (DSC). DSC was conducted with a TA Instruments Q100 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms were obtained at 15°C/min in crimped Al pans. Unless noted otherwise.

[127] Thermogravimetric Analysis (TGA). TGA thermograms were obtained with a TA Instruments Q500 thermogravimetric analyzer under 40 mL/min N_2 purge at 15°C/min in Pt or Al pans. Unless noted otherwise.

Example 8: Unit Dose of Injectable Brexanolone Pharmaceutical Composition

[128] A first unit dose of injectable brexanolone composition was packaged as 100 mg/mL injectable solution in a 1 mL via.

[129] A second unit dose of injectable brexanolone composition was packaged as 200 mg/mL injectable solution in a 1 mL via.

[130] A third unit dose of injectable brexanolone composition was packaged as 300 mg/mL injectable solution in a 1 mL via.

[131] A fourth unit dose of injectable brexanolone composition was packaged as 350 mg/mL injectable solution in a 1 mL via.

[132] A fifth unit dose of injectable brexanolone composition was packaged as 400 mg/mL injectable solution in a 1 mL via.

[133] A sixth unit dose of injectable brexanolone composition was packaged as 500 mg/mL injectable solution in a 1 mL via.

[134] A seventh unit dose of injectable brexanolone composition was packaged as 550 mg/mL injectable solution in a 1 mL via.

[135] An eighth unit dose of injectable brexanolone composition was packaged as 600 mg/mL injectable solution in a 1 mL via.

Numbered Embodiments of the Disclosure

[136] Other subject matter contemplated by the present disclosure is set out in the following numbered embodiments:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid, wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and wherein said neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains a plasma concentration of more than about 5% of said C_{max} for at least about 5 days, after a single dose of said pharmaceutical composition by intramuscular or subcutaneous injection.

2. The pharmaceutical composition of embodiment 1, wherein said single dose is about 0.5-50 mg per kilogram of body weight.

3. The pharmaceutical composition of embodiment 2, wherein said single dose is in a range of from about 1 to 8 mg per kilogram of body weight.

4. The pharmaceutical composition of embodiment 2, wherein said single dose is in a range of from about 2 to 6 mg per kilogram of body weight.

5. The pharmaceutical composition of embodiment 2, wherein said single dose is in a range of from about 3 to 5 mg per kilogram of body weight.

6. The pharmaceutical composition of any one of embodiments 1-5, wherein said single dose is about 50 mg to 800 mg per unit dose.

7. The pharmaceutical composition of embodiment 6, wherein said single dose is in a range of from about 50 mg to about 450 mg per unit dose.

8. The pharmaceutical composition of any one of embodiments 1-7, wherein said pharmaceutical composition has a neuroactive steroid concentration of at least about 100 mg/mL.

9. The pharmaceutical composition of embodiment 8, wherein said neuroactive steroid concentration is in a range of from about 100 mg/mL to about 800 mg/mL.

10. The pharmaceutical composition of any one of embodiments 1-7, wherein said neuroactive steroid reaches said C_{max} in about 30 minutes to 1 hour, 1 to 2 hours, 2 to 4 hours, or 4 to 6 hours.

11. The pharmaceutical composition of embodiment 10, wherein said neuroactive steroid reaches said C_{max} in about 1 to 2 hours.

12. The pharmaceutical composition of any one of embodiments 1-11, wherein said neuroactive steroid maintains a plasma concentration of more than about 10%, 15%, 20%, 25%, or 30% of said C_{max} for at least about 10, 20, 30, 40, 50, or 60 days.

13. The pharmaceutical composition of embodiment 12, wherein said neuroactive steroid maintains a plasma concentration of more than about 15% of said C_{max} for at least about 30 days.

14. The pharmaceutical composition of any one of embodiments 1-13, wherein said C_{max} is more than 10 ng/mL.

15. The pharmaceutical composition of embodiment 5, wherein said single dose is in a range of from 3 to about 5 mg per kilogram of body weight, and wherein said neuroactive steroid maintains a plasma concentration of more than about 10 ng/mL for at least about 5 days.

16. The pharmaceutical composition of embodiment 15, wherein said neuroactive steroid maintains a plasma concentration of more than 10, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 ng/mL for at least about 10, 20, 30, 40, 50, or 60 days.

17. The pharmaceutical composition of any one of embodiments 15-16, wherein said neuroactive steroid maintains a plasma concentration of more than 20 ng/mL for at least about 30 days.

18. The pharmaceutical composition of any one of embodiments 1-15, wherein said pharmaceutical composition releases less than about 5%-50% of said neuroactive steroid within about 1 hour of said single dose of said pharmaceutical composition by intramuscular or subcutaneous injection.

19. The pharmaceutical composition of any one of embodiments 1-18, wherein said pharmaceutical composition has a relative bioavailability of about 2%-50% at 24 hours after said single dose by intramuscular or subcutaneous injection, in comparison to the same dose by intravenous administration.

20. The pharmaceutical composition of any one of embodiments 1-19, wherein said pharmaceutical composition comprises a population of particles comprising said neuroactive steroid, wherein said particles have an average particle size of about 0.2-15 μm.

21. The pharmaceutical composition of embodiment 20, wherein said particles have an average particle size of about 1.5-15 μm.

22. The pharmaceutical composition of embodiment 21, wherein said particles have an average particle size of about 3-5 μm.

23. The pharmaceutical composition of embodiment 20, wherein said particles have an average particle size of about 0.2-1.5 μm.

24. The pharmaceutical composition of embodiment 23, wherein said particles have an average particle size of about 0.5-0.9 μm.

25. The pharmaceutical composition of any one of embodiments 20-24, wherein at least 50%, 60%, 70%, 80%, or 90% by weight of said particles have a particle size of about 0.2-15 μm.

26. The pharmaceutical composition of any one of embodiments 20-25, wherein about 0.01%-50% by weight of said particles have an average particle size of about 1.5-15 μm and about 50% to 99.99% by weight of said particles have an average particle size of about 0.2-1.5 μm.

27. The pharmaceutical composition of any one of embodiments 1-26, wherein said neuroactive steroid comprises tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, eltanolone, brexanolone, ganaxolone, zuranolone, or any combination thereof.

28. The pharmaceutical composition of embodiment 27, wherein said neuroactive steroid is brexanolone.

29. The pharmaceutical composition of any one of embodiments 1-28, wherein said pharmaceutical composition is substantially free of cyclodextrins.

30. The pharmaceutical composition of embodiment 29, wherein said pharmaceutical composition is substantially free of sulfobutyl ether β-cyclodextrin.

31. The pharmaceutical composition of any one of embodiments 1-30, further comprising one or more pharmaceutically acceptable excipients.

32. The pharmaceutical composition of embodiment 31, wherein said one or more pharmaceutically acceptable excipients comprise a binder, lubricant, glidant, disintegrant, diluent, coloring agent, surfactant, emulsifier, filler, carrier, isotonicfier, dispersing agent, viscosity modifier, resuspending agent, buffer, or any combination thereof.

33. The pharmaceutical composition of embodiment 31 or 32, wherein said one or more pharmaceutically acceptable excipients comprise acacia, animal oil, benzyl alcohol, benzyl benzoate, calcium stearate, carbomer, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate, glyceryl monooleate, glyceryl monostearate, hydrous, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin,

medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyyethylene glycol, polyoxyethylene-polyoxypropylene copolymer (poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oil, water, xanthan gum, or any combination thereof.

34. The pharmaceutical composition of any one of embodiments 1-33, comprising a brexanolone polymorph Form A, characterized by having at least three of the following peaks in an X-ray Powder Diffraction (XRPD) diffractogram, at 7.25, 8.88, 11.46, 14.50, 14.78, 17.77, 18.15, 18.32, 18.61, and 19.99 ± 0.1 °2θ.

35. The pharmaceutical composition of any one of embodiments 1-33, wherein said pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.

36. The pharmaceutical composition of embodiment 35, wherein the liquid suspension comprises the brexanolone polymorph Form A.

37. The pharmaceutical composition of any one of embodiments 34-36, wherein the brexanolone polymorph Form A has a chemical purity of greater than 90%.

38. The pharmaceutical composition of any one of embodiments 34-37, wherein the brexanolone polymorph Form A has a melting point of about 170-180 °C.

39. The pharmaceutical composition of embodiment 38, wherein the brexanolone polymorph Form A has a melting point of about 174 °C.

40. The pharmaceutical composition of any one of embodiments 34-39, wherein the brexanolone polymorph Form A has the following peaks in an X-ray Powder Diffraction (XRPD) diffractogram, at 7.25, 8.88, 11.46, 14.50, 14.78, 17.77, 18.15, 18.32, 18.61, and 19.99 ± 0.1 °2θ.

41. The pharmaceutical composition of any one of embodiments 34-40, wherein the brexanolone polymorph Form A is crystalized from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl

acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), and water.

42. A method of treating a disease in a subject in need thereof, comprising: administering said pharmaceutical composition of any one of embodiments 1-41 to said subject by intramuscular or subcutaneous injection.

43. A method of treating a disease in a subject in need thereof, comprising: administering a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid to said subject by intramuscular or subcutaneous injection with a single dose in a range of from 0.5 to 10 mg per kilogram of body weight, wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A (GABAA) receptor; and wherein said neuroactive steroid reaches a maximum plasma concentration (Cmax) in about 30 minutes to 6 hours and maintains a plasma concentration of more than about 5% of said Cmax for at least about 5 days, after said intramuscular or subcutaneous injection.

44. The method of any one of embodiments 42-43, wherein said disease is selected from the group consisting of anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome.

45. The method of embodiment 44, wherein said disease is postpartum depression.

46. The method of embodiment 45, wherein said subject has prior history of depression.

47. The method of embodiment 45 or 46, wherein said subject has prior history of postpartum depression.

48. The method of any one of embodiments 42-47, wherein said administering is by a single intramuscular or subcutaneous injection.

49. The method of any one of embodiments 42-47, wherein said pharmaceutical composition is administered to said subject within a time period in a range of from 1 second to about 180 minutes.

50. The method of embodiment 49, wherein said pharmaceutical composition is administered to said subject within a time period in a range of from 1 second to about 30 minutes.

51. The method of any one of embodiments 43-50, wherein said pharmaceutical composition is the pharmaceutical composition of any one of embodiments 1-41.

52. Use of a composition comprising a neuroactive steroid for manufacturing a medicament for treating a disease, wherein said composition is the pharmaceutical composition in any one of embodiments 1-41.

53. Composition comprising a neuroactive steroid for use in a method for the treatment of a disease, wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A (GABAA) receptor; and wherein said neuroactive steroid reaches a maximum plasma concentration (Cmax) in about 30 minutes to 6 hours and maintains a plasma concentration of more than about 5% of said Cmax for at least about 5 days, after a single dose of said neuroactive steroid by intramuscular or subcutaneous injection.

54. Composition according to embodiment 53, wherein said composition is the pharmaceutical composition of any one of embodiments 1-41.

55. Composition according to embodiment 53, wherein said method is the method of any one of embodiments 42-51.

56. A process for producing the pharmaceutical composition of any one of embodiments 1-41, comprising:

a) mixing a composition comprising said neuroactive steroid with one or more pharmaceutically acceptable excipients; and

b) milling said composition to produce a population of particles of said pharmaceutical composition.

57. A process for producing the pharmaceutical composition of any one of embodiments 1-41, comprising:

a) milling a composition comprising said neuroactive steroid to produce a population of particles; and

b) mixing said composition with one or more pharmaceutically acceptable excipients to produce said pharmaceutical composition.

58. A process for producing the pharmaceutical composition of any one of embodiments 34-40, comprising: crystalizing the brexanolone polymorph Form A from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), and water.

59. The process of embodiment 58, further comprising:

a) mixing the brexanolone polymorph Form A with one or more pharmaceutically acceptable excipients to form a composition; and

b) milling said composition to produce a population of particles of said pharmaceutical composition.

60. The process of embodiment 58, further comprising:

a) milling a composition comprising the brexanolone polymorph Form A to produce a population of particles; and

b) mixing said composition with one or more pharmaceutically acceptable excipients to produce said pharmaceutical composition.

61. The process of any one of embodiments 56-60, wherein the pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.

[137] The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent application, foreign patents, foreign patent application and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, application and publications to provide yet further embodiments.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid,

wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and

wherein said neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains a plasma concentration of more than about 5% of said C_{max} for at least about 5 days, after a single dose of said pharmaceutical composition by intramuscular or subcutaneous injection.

2. The pharmaceutical composition of claim 1, wherein said single dose is about 0.5-50 mg per kilogram of body weight.

3. The pharmaceutical composition of claim 2, wherein said single dose is in a range of from about 1 to 8 mg per kilogram of body weight.

4. The pharmaceutical composition of claim 2, wherein said single dose is in a range of from about 2 to 6 mg per kilogram of body weight.

5. The pharmaceutical composition of claim 2, wherein said single dose is in a range of from about 3 to 5 mg per kilogram of body weight.

6. The pharmaceutical composition of any one of claims 1-5, wherein said single dose is about 50 mg to 800 mg per unit dose.

7. The pharmaceutical composition of claim 6, wherein said single dose is in a range of from about 50 mg to about 450 mg per unit dose.

8. The pharmaceutical composition of any one of claims 1-7, wherein said pharmaceutical composition has a neuroactive steroid concentration of at least about 100 mg/mL.

9. The pharmaceutical composition of claim 8, wherein said neuroactive steroid concentration is in a range of from about 100 mg/mL to about 800 mg/mL.

10. The pharmaceutical composition of any one of claims 1-7, wherein said neuroactive steroid reaches said C_{max} in about 30 minutes to 1 hour, 1 to 2 hours, 2 to 4 hours, or 4 to 6 hours.

11. The pharmaceutical composition of claim 10, wherein said neuroactive steroid reaches said C_{max} in about 1 to 2 hours.

12. The pharmaceutical composition of any one of claims 1-11, wherein said neuroactive steroid maintains a plasma concentration of more than about 10%, 15%, 20%, 25%, or 30% of said C_{max} for at least about 10, 20, 30, 40, 50, or 60 days.

13. The pharmaceutical composition of claim 12, wherein said neuroactive steroid maintains a plasma concentration of more than about 15% of said C_{max} for at least about 30 days.

14. The pharmaceutical composition of any one of claims 1-13, wherein said C_{max} is more than 10 ng/mL.

15. The pharmaceutical composition of claim 5, wherein said single dose is in a range of from 3 to about 5 mg per kilogram of body weight, and wherein said neuroactive steroid maintains a plasma concentration of more than about 10 ng/mL for at least about 5 days.

16. The pharmaceutical composition of claim 15, wherein said neuroactive steroid maintains a plasma concentration of more than 10, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 ng/mL for at least about 10, 20, 30, 40, 50, or 60 days.

17. The pharmaceutical composition of any one of claims 15-16, wherein said neuroactive steroid maintains a plasma concentration of more than 20 ng/mL for at least about 30 days.

18. The pharmaceutical composition of any one of claims 1-15, wherein said pharmaceutical composition releases less than about 5%-50% of said neuroactive steroid within about 1 hour of said single dose of said pharmaceutical composition by intramuscular or subcutaneous injection.

19. The pharmaceutical composition of any one of claims 1-18, wherein said pharmaceutical composition has a relative bioavailability of about 2%-50% at 24 hours after said single dose by intramuscular or subcutaneous injection, in comparison to the same dose by intravenous administration.

20. The pharmaceutical composition of any one of claims 1-19, wherein said pharmaceutical composition comprises a population of particles comprising said neuroactive steroid, wherein said particles have an average particle size of about 0.2-15 μm.

21. The pharmaceutical composition of claim 20, wherein said particles have an average particle size of about 1.5-15 μm.

22. The pharmaceutical composition of claim 21, wherein said particles have an average particle size of about 3-5 μm.

23. The pharmaceutical composition of claim 20, wherein said particles have an average particle size of about 0.2-1.5 μm.

24. The pharmaceutical composition of claim 23, wherein said particles have an average particle size of about 0.5-0.9 μm.

25. The pharmaceutical composition of any one of claims 20-24, wherein at least 50%, 60%, 70%, 80%, or 90% by weight of said particles have a particle size of about 0.2-15 μm.

26. The pharmaceutical composition of any one of claims 20-25, wherein about 0.01%-50% by weight of said particles have an average particle size of about 1.5-15

μm and about 50% to 99.99% by weight of said particles have an average particle size of about 0.2-1.5 μm.

27. The pharmaceutical composition of any one of claims 1-26, wherein said neuroactive steroid comprises tetrahydrodeoxycorticosterone (THDOC), androstane, androstane 3α-androstanediol, cholestane cholesterol, pregnane, eltanolone, brexanolone, ganaxolone, zuranolone, or any combination thereof.

28. The pharmaceutical composition of claim 27, wherein said neuroactive steroid is brexanolone.

29. The pharmaceutical composition of any one of claims 1-28, wherein said pharmaceutical composition is substantially free of cyclodextrins.

30. The pharmaceutical composition of claim 29, wherein said pharmaceutical composition is substantially free of sulfobutyl ether β-cyclodextrin.

31. The pharmaceutical composition of any one of claims 1-30, further comprising one or more pharmaceutically acceptable excipients.

32. The pharmaceutical composition of claim 31, wherein said one or more pharmaceutically acceptable excipients comprise a binder, lubricant, glidant, disintegrant, diluent, coloring agent, surfactant, emulsifier, filler, carrier, isotonicfier, dispersing agent, viscosity modifier, resuspending agent, buffer, or any combination thereof.

33. The pharmaceutical composition of claim 31 or 32, wherein said one or more pharmaceutically acceptable excipients comprise acacia, animal oil, benzyl alcohol, benzyl benzoate, calcium stearate, carbomer, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate, glyceryl monooleate, glyceryl monostearate, hydrous, histidine, hydrochloric acid, hydroxpropyl cellulose, hydroxypropyl-β-cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin,

medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyyethylene glycol, polyoxyethylene-polyoxypropylene copolymer (poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oil, water, xanthan gum, or any combination thereof.

34. The pharmaceutical composition of any one of claims 1-33, comprising a brexanolone polymorph Form A, characterized by having at least three of the following peaks in an X-ray Powder Diffraction (XRPD) diffractogram, at 7.25, 8.88, 11.46, 14.50, 14.78, 17.77, 18.15, 18.32, 18.61, and 19.99 ± 0.1 °2θ.

35. The pharmaceutical composition of any one of claims 1-34, wherein said pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.

36. The pharmaceutical composition of claim 35, wherein the liquid suspension comprises the brexanolone polymorph Form A.

37. The pharmaceutical composition of any one of claims 34-36, wherein the brexanolone polymorph Form A has a chemical purity of greater than 90%.

38. The pharmaceutical composition of any one of claims 34-37, wherein the brexanolone polymorph Form A has a melting point of about 170-180 °C.

39. The pharmaceutical composition of claim 38, wherein the brexanolone polymorph Form A has a melting point of about 174 °C.

40. The pharmaceutical composition of any one of claims 34-39, wherein the brexanolone polymorph Form A has the following peaks in an X-ray Powder Diffraction (XRPD) diffractogram, at 7.25, 8.88, 11.46, 14.50, 14.78, 17.77, 18.15, 18.32, 18.61, and 19.99 ± 0.1 °2θ.

41. The pharmaceutical composition of any one of claims 34-40, wherein the brexanolone polymorph Form A is crystalized from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), and water.

42. A method of treating a disease in a subject in need thereof, comprising: administering said pharmaceutical composition of any one of claims 1-41 to said subject by intramuscular or subcutaneous injection.

43. A method of treating a disease in a subject in need thereof, comprising: administering a pharmaceutical composition comprising a pharmaceutically effective amount of a neuroactive steroid to said subject by intramuscular or subcutaneous injection with a single dose in a range of from 0.5 to 10 mg per kilogram of body weight,

wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and

wherein said neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains a plasma concentration of more than about 5% of said C_{max} for at least about 5 days, after said intramuscular or subcutaneous injection.

44. The method of any one of claims 42-43, wherein said disease is selected from the group consisting of anxiety, mood disorder, massive depression disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, focal onset seizures, PCDH19 pediatric epilepsy, pediatric genetic epilepsies, CDKL5 Deficiency

Disorder (CDD), catamenial epilepsy, infantile spasms, Fragile X syndrome, depression, postpartum depression, and premenstrual syndrome.

45. The method of claim 44, wherein said disease is postpartum depression.

46. The method of claim 45, wherein said subject has prior history of depression.

47. The method of claim 45 or 46, wherein said subject has prior history of postpartum depression.

48. The method of any one of claims 42-47, wherein said administering is by a single intramuscular or subcutaneous injection.

49. The method of any one of claims 42-47, wherein said pharmaceutical composition is administered to said subject within a time period in a range of from 1 second to about 180 minutes.

50. The method of claim 49, wherein said pharmaceutical composition is administered to said subject within a time period in a range of from 1 second to about 30 minutes.

51. The method of any one of claims 43-50, wherein said pharmaceutical composition is the pharmaceutical composition of any one of claims 1-41.

52. Use of a composition comprising a neuroactive steroid for manufacturing a medicament for treating a disease, wherein said composition is the pharmaceutical composition in any one of claims 1-41.

53. Composition comprising a neuroactive steroid for use in a method for the treatment of a disease,

wherein said neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor; and

wherein said neuroactive steroid reaches a maximum plasma concentration (C_{max}) in about 30 minutes to 6 hours and maintains a plasma concentration of more

than about 5% of said C_{max} for at least about 5 days, after a single dose of said neuroactive steroid by intramuscular or subcutaneous injection.

54. Composition according to claim 53, wherein said composition is the pharmaceutical composition of any one of claims 1-41.

55. Composition according to claim 53, wherein said method is the method of any one of claims 42-51.

56. A process for producing the pharmaceutical composition of any one of claims 1-41, comprising:

a) mixing a composition comprising said neuroactive steroid with one or more pharmaceutically acceptable excipients; and

b) milling said composition to produce a population of particles of said pharmaceutical composition.

57. A process for producing the pharmaceutical composition of any one of claims 1-41, comprising:

a) milling a composition comprising said neuroactive steroid to produce a population of particles; and

b) mixing said composition with one or more pharmaceutically acceptable excipients to produce said pharmaceutical composition.

58. A process for producing the pharmaceutical composition of any one of claims 34-40, comprising: crystalizing the brexanolone polymorph Form A from one or more solvents selected from the group consisting of dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO), toluene, 2-propanol:water (9:1), methanol (MeOH), 2-propanol (IPA), methyl t-butyl ether (MTBE), isopropyl ether (IPE), and water.

59. The process of claim 58, further comprising:

a) mixing the brexanolone polymorph Form A with one or more pharmaceutically acceptable excipients to form a composition; and

b) milling said composition to produce a population of particles of said pharmaceutical composition.

60. The process of claim 58, further comprising:

a) milling a composition comprising the brexanolone polymorph Form A to produce a population of particles; and

b) mixing said composition with one or more pharmaceutically acceptable excipients to produce said pharmaceutical composition.

61. The process of any one of claims 56-60, wherein the pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.

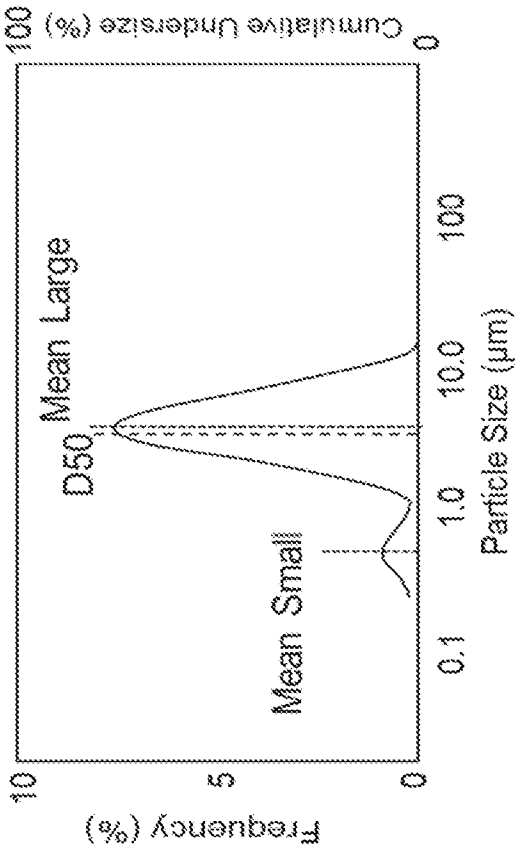

FIG. 1B

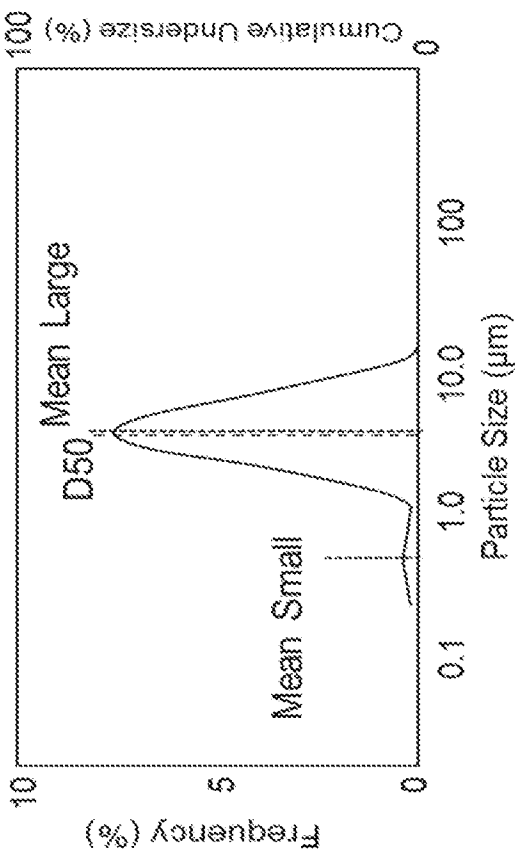

FIG. 1A

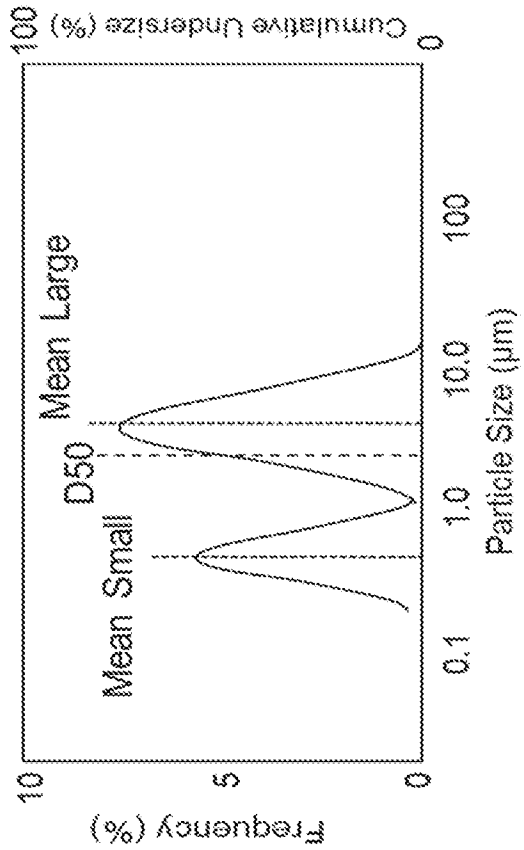

FIG. 1D

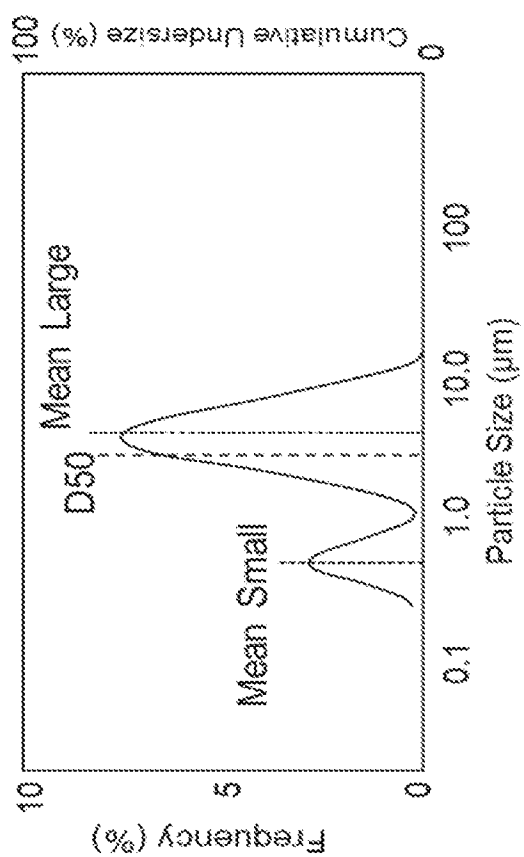

FIG. 1C

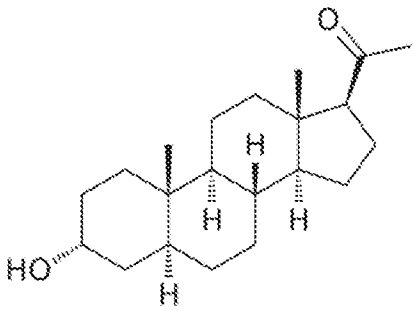

FIG. 2A

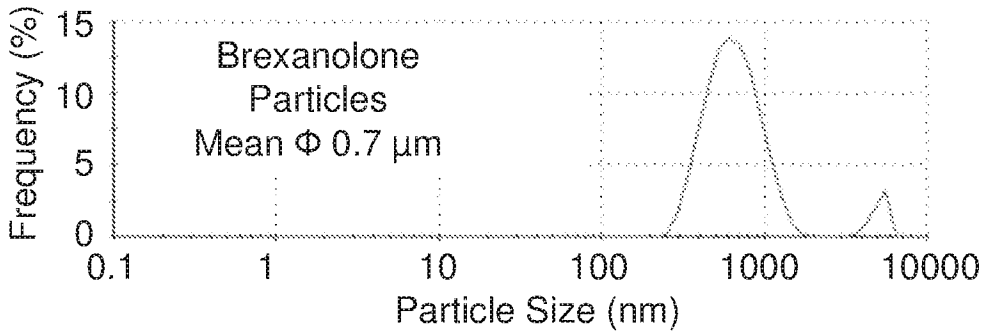

FIG. 2B

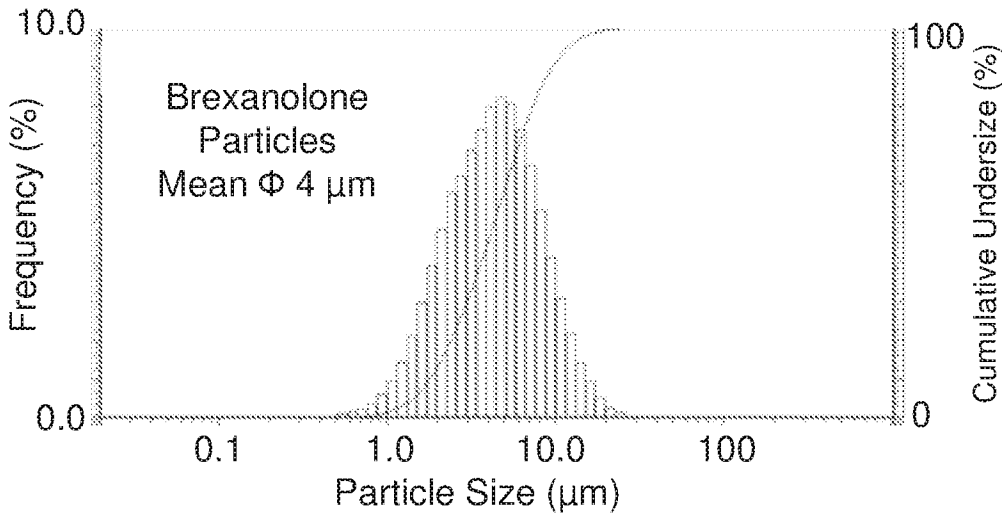

FIG. 2C

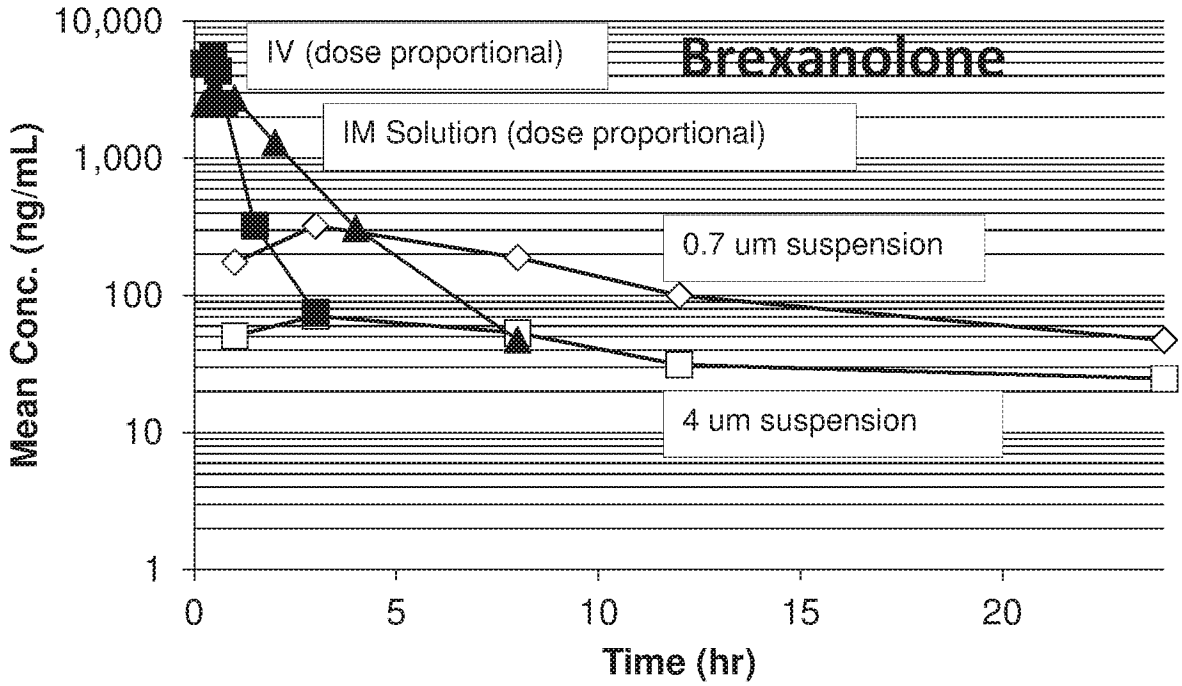
Brexanolone
IV (dose proportional)
IM Solution (dose proportional)
0.7 um suspension
4 um suspension
Mean Conc. (ng/mL)
10,000
1,000
100
10
1
0
5
10
15
20
Time (hr)

FIG. 2D

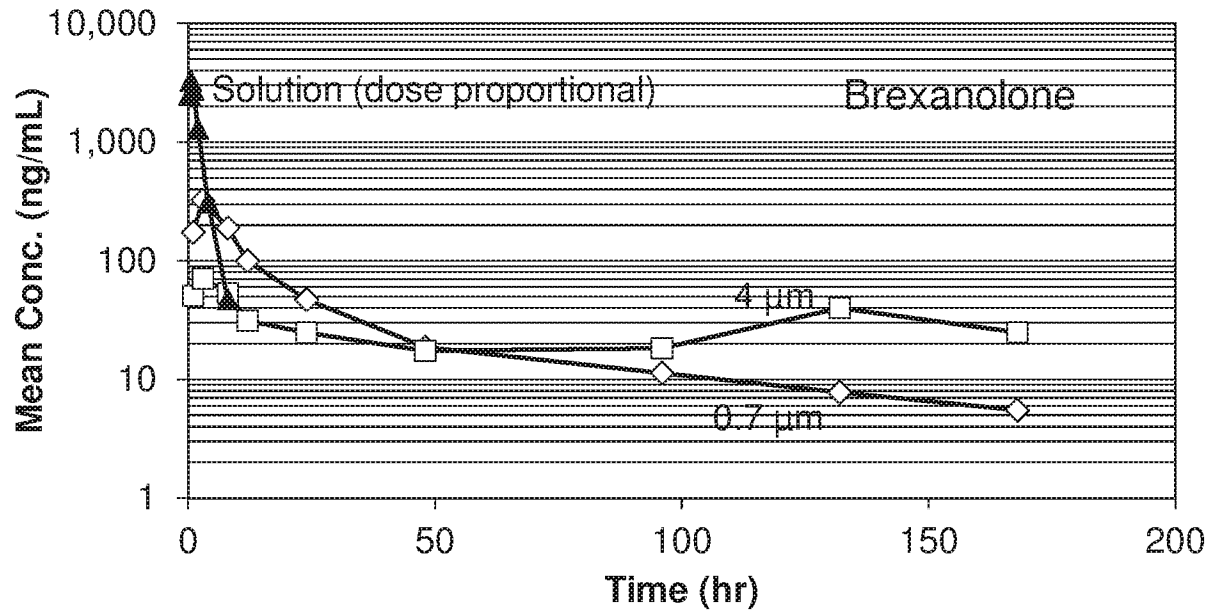
Solution (dose proportional)
Brexanolone
4 µm
0.7 µm
Mean Conc. (ng/mL)
10,000
1,000
100
10
1
0
50
100
150
200
Time (hr)

FIG. 2E

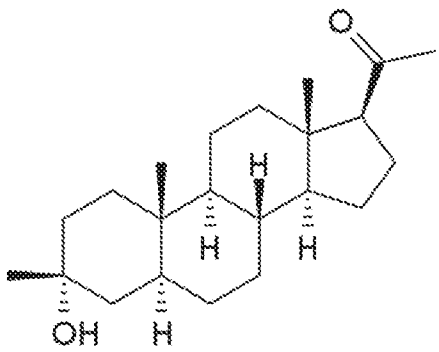

FIG. 3A

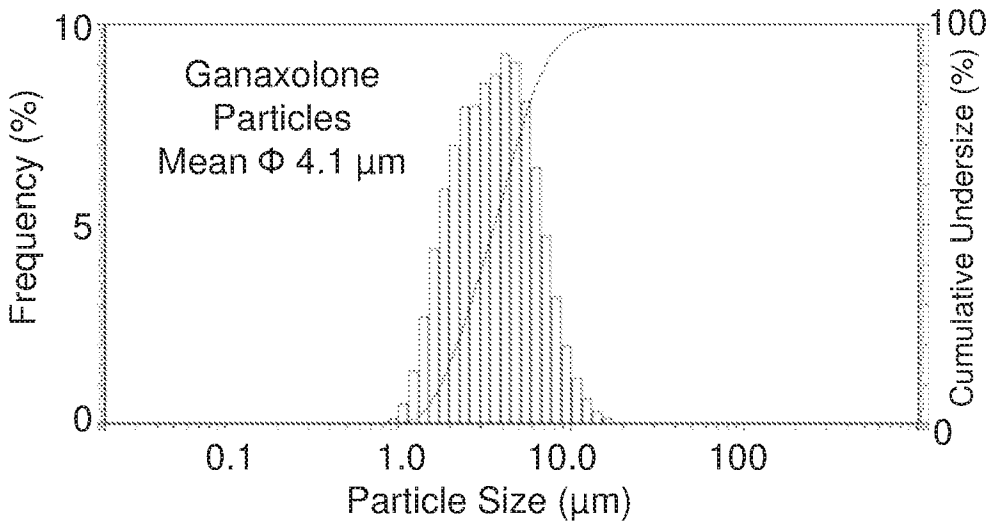

FIG. 3B

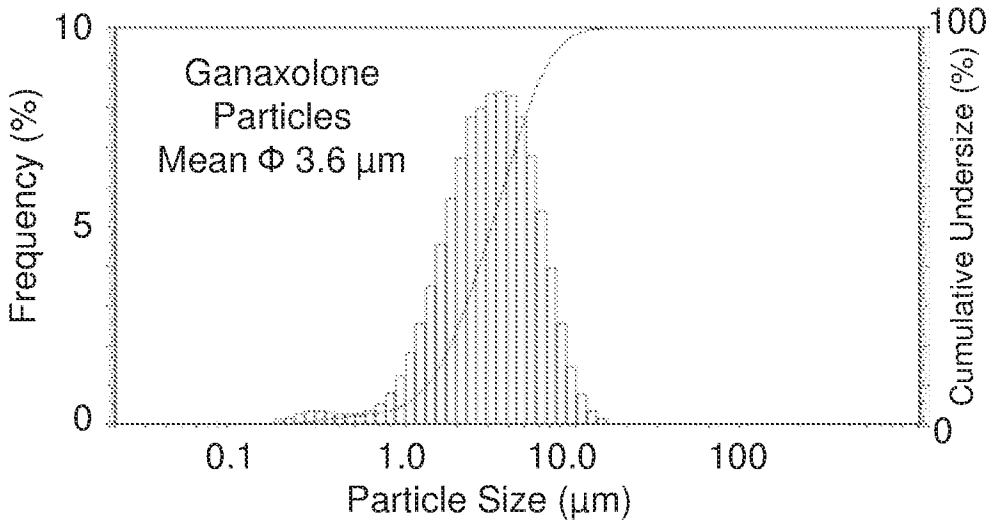

FIG. 3C

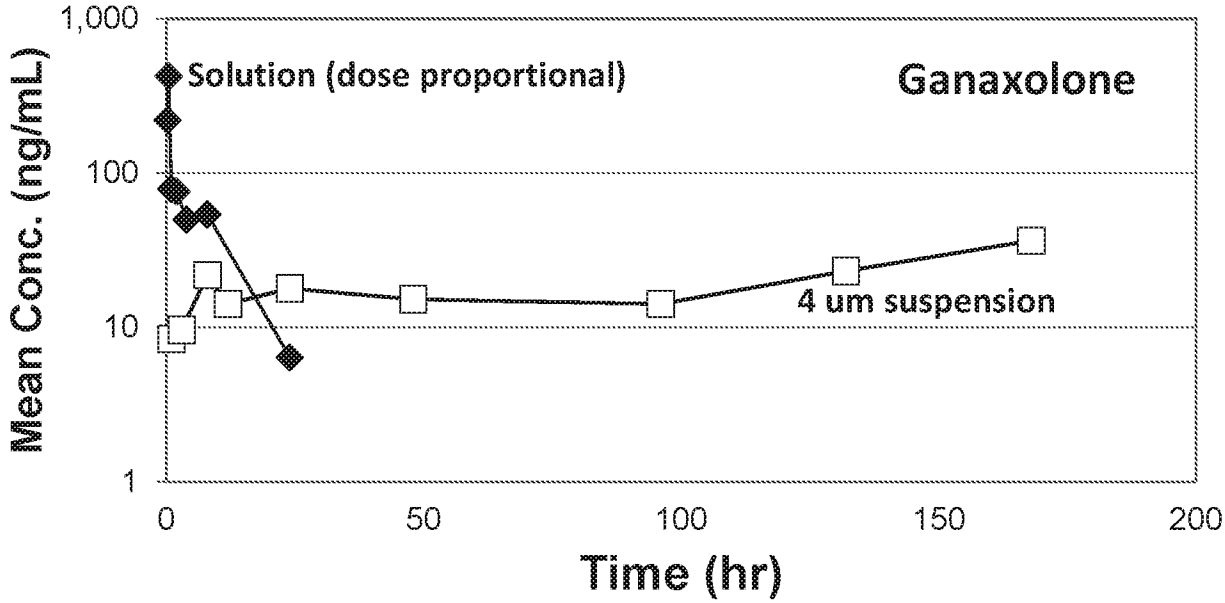
Ganaxolone
Solution (dose proportional)
4 um suspension
Mean Conc. (ng/mL)
1,000
100
10
1
0
50
100
150
200
Time (hr)

FIG. 3D

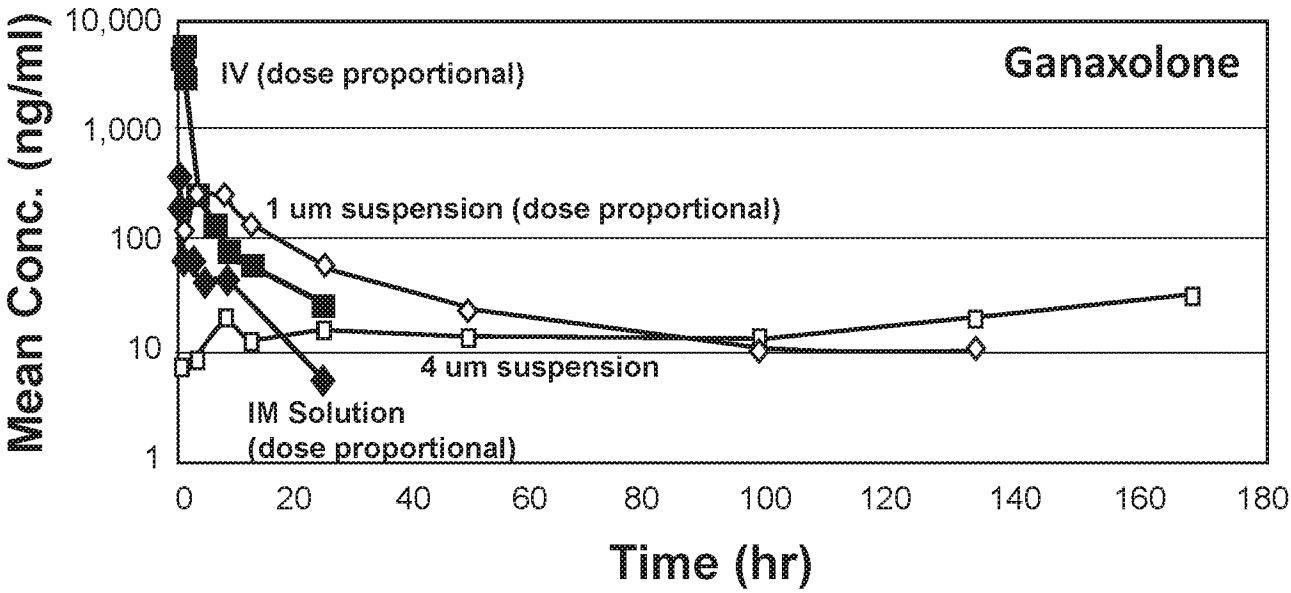
Ganaxolone
IV (dose proportional)
1 um suspension (dose proportional)
4 um suspension
IM Solution
(dose proportional)
Mean Conc. (ng/ml)
10,000
1,000
100
10
1
0
20
40
60
80
100
120
140
160
180
Time (hr)

FIG. 3E

#	Solvent	TC	RC	EV	Water Activity
1	Water				1.00
2	Methanol				
3	2-Methoxyethanol				
4	1-Propanol				
5	Nitromethane				
6	Acetonitrile				
7	Dimethylsulfoxide				
8	Acetone				
9	2-Butanone				
10	Dichloromethane				
11	Methyl acetate				
12	4-Methyl-2-pentanone				
13	Chloroform				
14	Ethyl acetate				
15	Chlorobenzene				
16	Tetrahydrofuran				
17	1,4-Dioxane				
18	Isopropyl ether				
19	Toluene				
20	Cyclohexane				
21	Heptane				
22	1-Butanol				
23	2-Propanol				
24	Trifluoroethanol				
25	Dimethyl carbonate				

FIG. 4

26	t-Butyl methyl ether				
27	Isopropyl acetate				
28	Ethanol				
29	1-Methoxy-2-propanol				
30	Cyclohexanone				
31	N,N-Dimethylformamide				
32	2-Methoxyethyl ether				
33	Methanol: Water (95:5)				0.20
34	Acetonitrile: Water (95:5)				0.60
35	Acetone: Water (95:5)				0.63
36	Tetrahydrofuran: Water (95:5)				0.88
37	2-propanol: Water (95:5)				0.54
38	Methanol: Water (90:10)				0.33
39	Acetonitrile: Water (90:10)				0.76
40	Acetone: Water (90:10)				0.77
41	Tetrahydrofuran: Water (90:10)				0.94
42	1,4-Dioxane: Water (90:10)				0.69
43	2-propanol: Water (90:10)				0.76
44	Acetone: Water (80:20)				0.86
45	Ethanol: Water (20:80)				0.95
46	2-Propanol: Dimethylsulfoxide (80:20)				
47	Acetonitrile: Dimethylsulfoxide (80:20)				
48	N-Methyl-2-pyrrolidone				

FIG. 4 CONT.

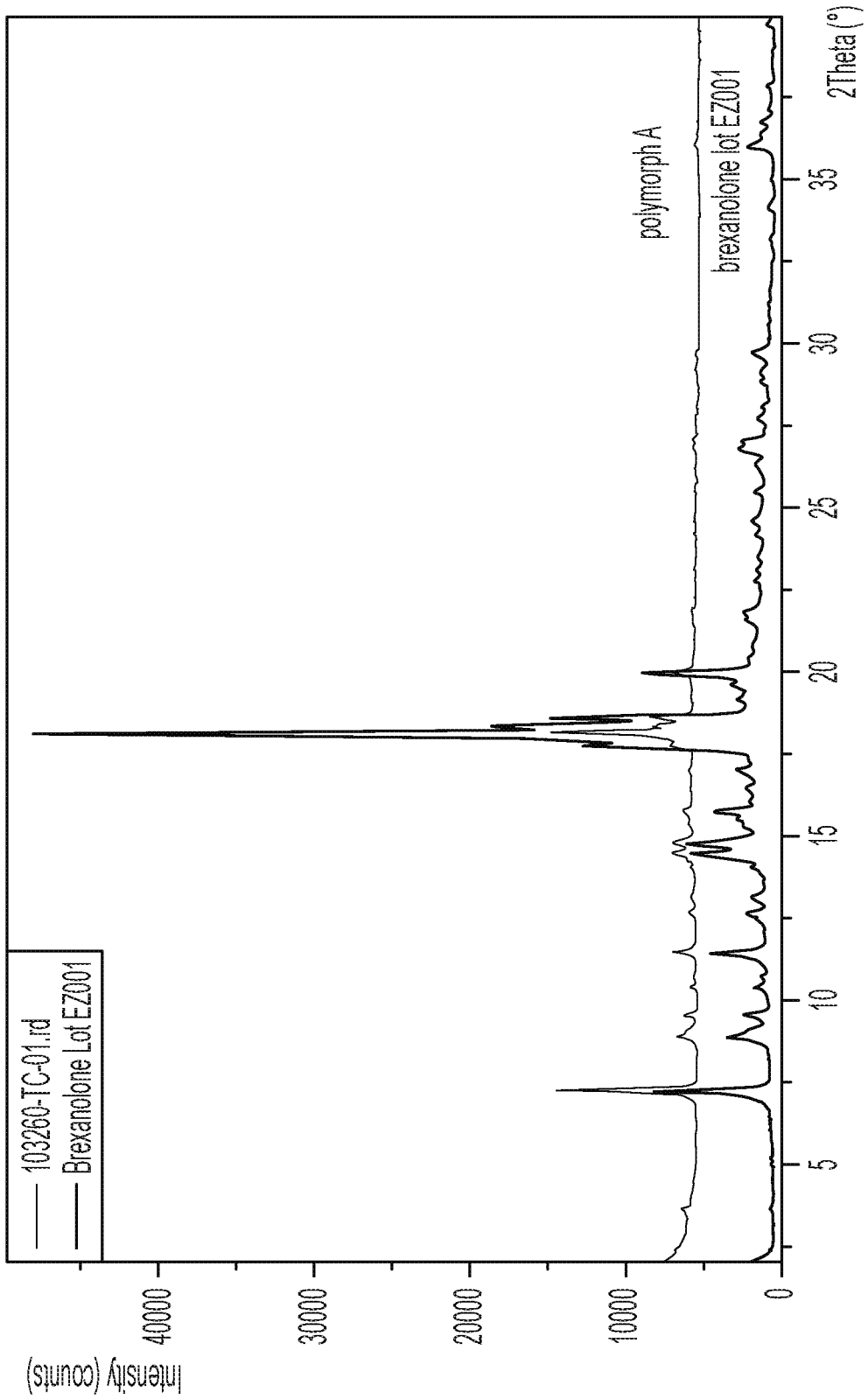
103260-TC-01.rd
Brexanolone Lot EZ001
Intensity (counts)
40000
30000
20000
10000
0
5
10
15
20
25
30
35
2Theta (°)
polymorph A
brexanolone lot EZ001

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/032172

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/56; A61K 31/568; A61P 25/08; A61P 25/24 (2020.01)
CPC - A61K 31/56; A61K 9/0019; A61K 31/568; A61K 31/57; A61K 31/58; A61P 25/08 (2020.05)

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)
see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016/127170 A1 (MARINUS PHARMACEUTICALS INC) 11 August 2016 (11.08.2016) entire document	1-7, 15-17, 43, 53
Y	US 2018/0296487 A1 (MARINUS PHARMACEUTICALS INC) 18 October 2018 (18.10.2018) entire document	1-7, 15-17, 43, 53
Y	US 2019/0117673 A1 (MARINUS PHARMACEUTICALS INC) 25 April 2019 (25.04.2019) entire document	6, 7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
26 June 2020	31 JUL 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/032172

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-14, 18-42, 44-52, 54-61
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.