CLAIMS

What is claimed is:

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

100 mg/mL to 800 mg/mL brexanolone polymorph Form A; and

a population of particles comprising said brexanolone polymorph Form A having a mean particle size of 1.5-15 µm, and

wherein said brexanolone polymorph Form A has 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.

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

~~2~~3. The pharmaceutical composition of claim ~~1~~2, wherein said single dose ~~is about~~comprises brexanolone polymorph Form A in a range of 0.5-50 mg per kilogram of body weight.

~~3~~4. The pharmaceutical composition of claim 2, wherein said single dose ~~is~~ comprises brexanolone polymorph Form A in a range of from ~~about~~ 1 to 8 mg per kilogram of body weight.

~~4~~5. The pharmaceutical composition of claim 2, wherein said single dose ~~is~~ comprises brexanolone polymorph Form A in a range of from ~~about~~ 2 to 6 mg per kilogram of body weight.

~~5~~6. The pharmaceutical composition of claim 2, wherein said single dose ~~is~~ comprises brexanolone polymorph Form A in a range of from ~~about~~ 3 to 5 mg per kilogram of body weight.

~~6~~7. The pharmaceutical composition of any one of claims ~~1-5~~2-5, wherein said single dose ~~is about~~ comprises brexanolone polymorph Form A in a range of 50 mg to 800 mg per unit dose.

~~7~~8. The pharmaceutical composition of claim ~~6~~7, wherein said single dose ~~is~~ comprises brexanolone polymorph Form A in a range of from ~~about~~ 50 mg to ~~about~~ 450 mg per unit dose.

~~8~~9. The pharmaceutical composition of any one of claims ~~1-7~~1-8, wherein said pharmaceutical composition has a ~~neuroactive steroid~~ brexanolone polymorph Form A concentration of ~~at least about~~from 100 mg/mL to 400 mg/mL.

~~9~~10. The pharmaceutical composition of claim ~~8~~9, wherein said ~~neuroactive steroid~~ brexanolone polymorph Form A concentration is ~~in a range of from about 100 mg/mL to about 800~~300 mg/mL.

~~10~~11. The pharmaceutical composition of any one of claims ~~1-7~~1-8, wherein said ~~neuroactive steroid~~ brexanolone polymorph Form A reaches ~~said~~ a C_{max} in ~~about~~ 30 minutes to 1 hour, 1 to 2 hours, 2 to 4 hours, or 4 to 6 hours, after a single dose of said pharmaceutical composition by intramuscular or subcutaneous injection.

~~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~~ brexanolone polymorph Form A 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~~ brexanolone polymorph Form A 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~~2-13, wherein said C_{max} is more than 10 ng/mL.

15. The pharmaceutical composition of claim ~~5~~6, 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~~ brexanolone polymorph Form A 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~~ brexanolone polymorph Form A 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~~claim 15 or 16, wherein said ~~neuroactive steroid~~ brexanolone polymorph Form A 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~~1-17, wherein said pharmaceutical composition releases less than ~~about~~ 5%-50% of said ~~neuroactive steroid~~ brexanolone polymorph Form A within ~~about~~ 1 hour of ~~said~~ a 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~~ a 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~~a mean particle size of ~~about 0.2-15~~2-10 µm.

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

~~22~~21. The pharmaceutical composition of claim ~~21~~20, wherein said particles have ~~an average~~a mean 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~~22. The pharmaceutical composition of any one of claims ~~1-28~~1-21, wherein said pharmaceutical composition is substantially free of cyclodextrins.

~~30~~23. The pharmaceutical composition of claim ~~29~~22, wherein said pharmaceutical composition is substantially free of sulfobutyl ether β-cyclodextrin.

~~31~~24. The pharmaceutical composition of any one of claims ~~1-30~~1-23, further comprising one or more pharmaceutically acceptable excipients.

~~32~~25. The pharmaceutical composition of claim ~~31~~24, wherein said one or more pharmaceutically acceptable excipients comprise a binder, lubricant, glidant, disintegrant, diluent, coloring agent, surfactant, emulsifier, filler, carrier, isotonicifier, dispersing agent, viscosity modifier, resuspending agent, buffer, or any combination thereof.

~~33~~26. The pharmaceutical composition of claim ~~31-~~24 or ~~32~~25, 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 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 claim 27 or 28, wherein the brexanolone is 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~~27. The pharmaceutical composition of any one of claims ~~1-34~~1-26, 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~~28. The pharmaceutical composition of any one of claims ~~34-36~~1-27, wherein the brexanolone polymorph Form A has a chemical purity of greater than 90%.

~~38~~29. The pharmaceutical composition of any one of claims ~~34-37~~1-28, wherein the brexanolone polymorph Form A has a melting point of ~~about~~ 170-180 °C.

~~39~~30. The pharmaceutical composition of claim ~~38~~29, wherein the brexanolone polymorph Form A has a melting point of ~~about~~ 174 °C.

~~40~~31. The pharmaceutical composition of any one of claims ~~34-39~~1-30, 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~~32. The pharmaceutical composition of any one of claims ~~34-40~~1-31, 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~~33. Use of a pharmaceutical composition of any one of claims ~~1-41~~1-32 in the manufacture of a medicament for treating a disease in a subject, wherein said disease is selected from the group consisting of anxiety, mood disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, CDKL5 Deficiency Disorder (CDD), Fragile X syndrome, depression, and premenstrual syndrome.

~~43~~34. Use of a pharmaceutical composition comprising a pharmaceutically effective amount of ~~a neuroactive steroid~~ brexanolone polymorph Form A in the manufacture of a medicament for treating a disease in a subject,

wherein said disease is selected from the group consisting of anxiety, mood disorder, postpartum disorder, Alzheimer disease, Parkinson disease, epilepsy, CDKL5 Deficiency Disorder (CDD), Fragile X syndrome, depression, and premenstrual syndrome,

wherein said pharmaceutical composition comprises 100 mg/mL to 800 mg/mL brexanolone polymorph Form A and a population of particles comprising said brexanolone polymorph Form A having a mean particle size of 1.5-15 µm,

wherein said brexanolone polymorph Form A has 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,~~neuroactive steroid is a positive modulator of gamma-aminobutyric acid type A ($GABA_A$) receptor;~~

wherein the pharmaceutical composition is to be administered by intramuscular or subcutaneous injection with a single dose in a range of from 0.5 to 10 mg per kilogram of body weight to the subject; and

wherein said ~~neuroactive steroid~~ brexanolone polymorph Form A 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~~35. The use of claim ~~42~~33 or ~~43~~34, wherein said depression is massive depression disorder or postpartum depression.

~~45~~36. The use of claim ~~42~~ 33 or ~~43~~34, wherein said epilepsy comprises focal onset seizures, PCDH19 pediatric epilepsy, catamenial epilepsy, infantile spasms, or pediatric genetic epilepsies.

~~46~~37. The use of claim ~~42~~ 33 or ~~43~~34, wherein said disease is postpartum depression.

~~47~~38. The use of claim ~~46~~37, wherein said subject has prior history of depression.

~~48~~39. The use of claim ~~46~~37, wherein said subject has prior history of postpartum depression.

~~49~~40. The use of any one of claims ~~42~~ 33 and ~~44-48~~35-39, wherein said pharmaceutical composition is to be administered to said subject by a single intramuscular or subcutaneous injection.

~~50~~41. The use of any one of claims ~~42-49~~33-40, wherein said pharmaceutical composition is to be administered to said subject within a time period in a range of from 1 second to ~~about~~ 180 minutes.

~~51~~42. The use of claim ~~50~~41, wherein said pharmaceutical composition is to be administered to said subject within a time period in a range of from 1 second to ~~about~~ 30 minutes.

~~52~~43. The use of any one of claims ~~42~~ 33 and ~~44-51~~35-42, wherein said pharmaceutical composition is to be administered to the subject in a single dose ranging from 0.5 to 10 mg per kilogram of body weight.~~.~~

~~53~~44. A process for producing the pharmaceutical composition of any one of claims ~~1-41~~1-32, comprising:

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

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

~~54~~45. A process for producing the pharmaceutical composition of any one of claims ~~1-41~~1-32, comprising:

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

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

~~55~~46. A process for producing the pharmaceutical composition of any one of claims ~~34-40~~1-31, comprising: crystallizing 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.

~~56~~47. The process of claim ~~55~~46, further comprising:

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

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

~~57~~48. The process of claim ~~55~~46, further comprising:

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

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

~~58~~49. The process of any one of claims ~~53-57~~44-48, wherein the pharmaceutical composition is a liquid suspension for intramuscular or subcutaneous injection.