CLAIMS

1. Use of ~~A method for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy comprising administering to a subject in need thereof~~ a therapeutically effective amount of a pharmaceutically acceptable pregnenolone neurosteroid or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy comprising in a subject in need thereof.

2. The ~~method~~ use of claim 1, wherein the pregnenolone neurosteroid is ganaxolone.

3. The ~~method~~ use of any one of the preceding claims, wherein the pregnenolone neurosteroid is to be administered three times per day.

4. The ~~method~~ use of any one of claims 1-2, wherein the pregnenolone neurosteroid is to be administered twice per day.

5. The ~~method~~ use of any one of the preceding claims, wherein ~~the subject is administered~~ from about 200 mg per day to about 1,800 mg per day of ganaxolone is to be administered to the subject.

6. The ~~method~~ use of any one of claims 1-4, wherein ~~the subject is administered~~ up to about 1,800 mg per day of ganaxolone is to be administered to the subject.

7. The ~~method~~ use of any preceding claim, wherein ~~ganaxolone is administered~~ about 1,500 mg per day of ganaxolone is to be administered.

8. The ~~method~~ use of any one of the preceding claims, wherein ganaxolone is to be administered in an amount of up to 63 mg/kg/day.

9. The ~~method~~ use of any one of the preceding claims, wherein the pregnenolone neurosteroid is to be administered orally.

10. The ~~method~~ use of any one of the preceding claims, wherein the pregnenolone neurosteroid is to be administered as an oral suspension.

11. The ~~method~~ use of any one of the preceding claims, wherein the pregnenolone neurosteroid is to be administered as an oral capsule.

12. The ~~method~~ use of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a infantile spasm.

13. The ~~method~~ use of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a focal impaired awareness seizure.

14. The ~~method~~ use of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a focal seizure.

15. The ~~method~~ use of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a generalized seizure.

16. The ~~method~~ use of any one of the preceding claims, wherein ~~administering~~ the administered pregnenolone neurosteroid reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

17. The ~~method~~ use of any one of the preceding claims, wherein ~~administering~~ the administered pregnenolone neurosteroid results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

18. The ~~method~~ use of any one of the preceding claims, wherein ~~administering~~ the administered pregnenolone neurosteroid results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

19. The ~~method~~ use of any one of the preceding claims, wherein the subject is monitored by electroencephalogram (EEG).

20. The ~~method~~ use of any one of the preceding claims, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

21. The ~~method~~ use of any one of the preceding claims, wherein ganaxolone is to be administered in amount sufficient to provide a ganaxolone plasma concentration in the subject of about 100 ng/mL for approximately 70% or more for a 24 hour-day .

22. The ~~method~~ use of claim 21, wherein ganaxolone is to be administered three times a day.

23. The ~~method~~ use of any one the preceding claims, further comprising:

measuring the level of an endogenous neurosteroid in the subject prior to administering the pregnanolone neurosteroid, wherein a subject having a low endogenous neurosteroid indicates that the subject will respond to the pregnanolone neurosteroid; and

wherein ~~administering~~ a therapeutically effective amount of the pregnenolone neurosteroid is to be administered to the subject having a low endogenous neurosteroid level.

24. The ~~method~~ use of claim 23, wherein the endogenous neurosteroid is allopregnanolone-sulfate.

25. The ~~method~~ use of any one of claims 23 or 24, wherein the low endogenous neurosteroid level is an amount of 2500 pg mL^{-1} or less.

26. The ~~method~~ use of claim 25, wherein the pregnenolone neurosteroid is ganaxolone.

27. ~~A method for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy comprising administering to a subject in need thereof~~ Use of ganaxolone in the manufacture of a medicament for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy in a subject in need thereof, wherein ~~in~~ the ganaxolone is to be administered in a therapeutically effective amount that produces a ganaxolone

plasma concentration of at least about 100 ng/ml for at least about 70% or more for a period of a 24 hour-day.

28. The ~~method~~ use of claim 27, wherein ganaxolone is to be administered three times per day.

29. The ~~method~~ use of any one of claims 27 or 28, wherein ganaxolone is to be administered orally.

30. The ~~method~~ use of any one of claims 27-29, wherein ganaxolone is to be administered as an oral suspension.

31. The ~~method~~ use of any one of claims 27-29, wherein ganaxolone is to be administered as an oral capsule.

32. The ~~method~~ use of any one of claims 27-31, wherein ganaxolone is to be administered in an amount of up to 63 mg/kg/day.

33. The ~~method~~ use of any one of claims 27-32, wherein ganaxolone is to be administered in an amount of up to 1,800 mg per day.

34. The ~~method~~ use of any one of claims 27-32, wherein ganaxolone is to be administered in an amount of up to 1,500 mg per day.

35. The ~~method~~ use of any one of claims 27-34, wherein the tuberous sclerosis complex-related epilepsy is a infantile spasm, a focal impaired awareness seizure, a focal seizure, or a generalized seizure.

36. The ~~method~~ use of any one of claims 27-35, wherein ~~administering~~ the administered ganaxolone reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

37. The ~~method~~ use of any one of claims 27-35, wherein ~~administering~~ the administered ganaxolone reduces major motor frequency in the subject relative to baseline.

38. The ~~method~~ use of any one of claims 27-35, wherein ~~administering~~ the administered ganaxolone results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

39. The ~~method~~ use of any one of claims 27-35, wherein ~~administering~~ the administered ganaxolone results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

40. The ~~method~~ use of any one of claims 27-39, wherein the subject is monitored by electroencephalogram (EEG).

41. The ~~method~~ use of any one of claims 27-39, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

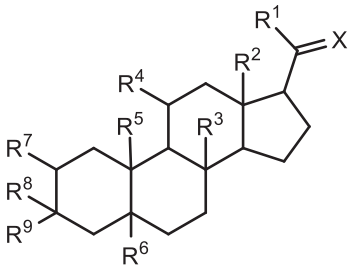
42. Use of a pharmaceutically acceptable pregnenolone neurosteroid or a pharmaceutically acceptable salt thereof in the manufacture of a medicament ~~A method of~~ for treating a subject having or suspected of having tuberous sclerosis-related epilepsy, ~~comprising determining~~ wherein ~~whether~~ the subject is determined to ~~has~~ have a low level of an endogenous neurosteroid; and

wherein ~~administering~~ a therapeutically effective amount of ~~a~~ the pharmaceutically acceptable pregnenolone neurosteroid or a pharmaceutically acceptable salt thereof is to be administered to the subject ~~if the subject has a low level of the endogenous neurosteroid~~.

43. The ~~method~~ use of claim 42, wherein the endogenous neurosteroid is allopregnanolone-sulfate, and the pregnenolone neurosteroid is ganaxolone.

44. The ~~method~~ use of any one of claims 42 or 43, wherein the endogenous neurosteroid is allopregnanolone-sulfate, and the low level of the endogenous stereoid is a level of 2500 pg mL^{-1} or less.

45. The ~~method~~ use of any one of claims 42-44, wherein the pregnenolone neurosteroid is a compound of Formula IA:



Formula IA

or a pharmaceutically acceptable salt thereof, wherein:

X is O, S, or NR^{10};

R^1 is hydrogen, hydroxyl, $-CH_2A$, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, or optionally substituted arylalkyl;

A is hydroxyl, O, S, NR^{11}, optionally substituted nitrogen-containing five-membered heteroaryl, optionally substituted nitrogen-containing five-membered heteroaryl or optionally substituted nitrogen-containing bicyclic heteroaryl or bicyclic heterocyclyl,

R^4 is hydrogen, hydroxyl, oxo, optionally substituted alkyl, or optionally substituted heteroalkyl,

R^2, R^3, R^5, R^6, and R^7 are each independently absent, hydrogen, hydroxyl, halogen, optionally substituted a C_1-C_6 alkyl, optionally substituted a C_1-C_6alkoxyl (e.g., methoxyl) or optionally substituted heteroalkyl;

R^8 and R^9 are each independently selected from a group consisting of hydrogen, a C_1-C_6 alkyl (e.g., methyl), a halogenated C_1-C_6 alkyl (e.g., trifluoromethyl) or C_1-C_6alkoxyl (e.g., methoxyl), or R^8 and R^9 form an oxo group;

R^{10} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, or optionally substituted arylalkyl where each alkyl is a C_1-C_{10}alkyl, C_3-C_6cycloalkyl, (C_3-C_6cycloalkyl)C_1-C_4alkyl, and optionally contains a single bond replaced by a double or triple bond;

each heteroalkyl group is an alkyl group in which one or more methyl group is replaced by an independently chosen -O-, -S-, -N(R^{10})-, -S(=O)- or -S(=O)$_2$-, where R^{10} is hydrogen, alkyl, or alkyl in which one or more methylene group is replaced by -O-, -S-, -NH, or -N-alkyl;

R^{11} is -H_2 or –$HR^{12;}$

R^{12} is C_1-C_6 alkyl or C_1-C_6 alkoxy.

46. The ~~method~~ use of claim 45, wherein the pregnenolone neurosteroid is selected from the group consisting of allopregnanolone, pregnenolone, 5-alphaDHP (5-alphadihydroprogesterone), pregnanolone, dehydroepiandrosterone (DHEA), ganaxolone, 3α-Hydroxy-3β-methyl-21-(4-cyano-1*H*-pyrazol-1'-yl)-19-nor-5β-pregnan-20-one, pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing.

47. The ~~method~~ use of any one of claims 42-46, wherein the pregnenolone neurosteroid is to be administered orally.

48. The ~~method~~ use of any one of claims 42-47, wherein ~~the subject is administered~~ up to about 63 mg/kg/day of ganaxolone is to be administered to the subject.

49. The ~~method~~ use of claim 48, wherein ~~the subject is administered~~ up to about 33 mg/kg/day of ganaxolone is to be administered to the subject.

50. The ~~method~~ use of any one of claims 42-47, wherein ~~the subject is administered~~ up to about 1,800 mg per day of ganaxolone is to be administered to the subject.

51. The ~~method~~ use of any one of claims 42-47, wherein ~~the subject is administered~~ up to about 1,500 mg per day of ganaxolone is to be administered to the subject.

52. The ~~method~~ use of claim 42-51, wherein the tuberous sclerosis complex-related epilepsy is selected from the group consisting of a focal motor seizure, a focal seizure, and a generalized seizure.

53. The ~~method~~ use of any one of claims 42-52, wherein ~~administering~~ the administered ganaxolone reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

54. The ~~method~~ use of any one of claims 42-53, wherein the administered ~~administering~~ ganaxolone reduces major motor frequency in the subject relative to baseline.

55. The ~~method~~ use of any one of claims 42-53, wherein the administered ~~administering~~ ganaxolone results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

56. The ~~method~~ use of any one of claims 42-53, wherein the administered ~~administering~~ ganaxolone results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

57. The ~~method~~ use of any one of claims 42-56, wherein the subject is monitored by electroencephalogram (EEG).

58. The ~~method~~ use of any one of claims 42-56, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

59. The ~~method~~ use of claim 42, wherein the endogenous neurosteroid is allopregnanolone, and a low level of allopregnanolone is a 200 pg mL^{-1} or less.

60. The ~~method~~ use of claim 42, wherein the endogenous neurosteroid comprises allopregnanolone, allopregnanolone-sulfate, pregnenolone, pregnenolone-sulfate, and mixtures thereof.