TREATMENT OF ESSENTIAL TREMOR

CROSS REFERENCE TO RELATED APPLICATION

[0001] This PCT application claims the benefit of U.S. provisional application no. 63/173,867, filed on 12 April 2021, the entire content of which is hereby incorporate by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods of treating essential tremor in a subject in need thereof.

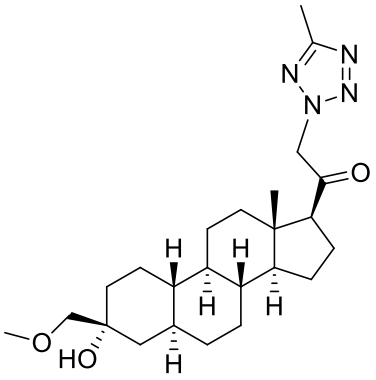
BACKGROUND

[0003] Progesterone and its metabolites have been demonstrated to have profound effects on brain excitability (Backstrom, T. *et al., Acta Obstet. Gynecol. Scand. Suppl.* 130:19-24 (1985); Pfaff, D.W and McEwen, B. S., *Science* 219:808-814 (1983); Gyermek *et al., J Med Chem.* 11: 117 (1968); Lambert, J. *et al., Trends Pharmacol. Sci.* 8:224-227 (1987)). Additionally, several lines of evidence suggest that cerebellar dysfunction through the cerebello-thalamocortical pathway play a key role in essential tremor (ET) (McAuley 2000; Pinto 2003; Elble 2009; Schnitzler 2009; Deuschl 2009). Activation studies with positron emission tomography (PET) indicate abnormally increased regional cerebral blood flow in the cerebellus both at rest and when tremor is provoked by unilateral arm extension (Boechker 1994, Wills 1996). Post-mortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22-31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella from ET patients (Paris-Robidas 2012).

[0004] There is increasing evidence to support the use of neuroactive steroids, e.g., a neuroactive steroid as described herein, in the treatment and prevention of tremor (e.g., essential tremor).

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a use of **Compound 1**

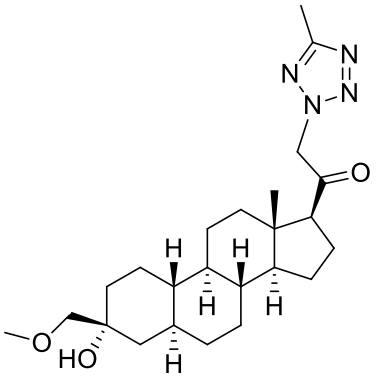


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein a dose of from about 5 mg to about 80 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

[0004b] In another aspect of the present disclosure, there is provided a use of **Compound 1**

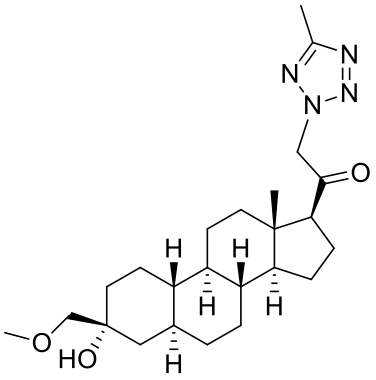


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject experiences a reduction in tremor amplitude of at least about 5% following treatment onset.

[0004c] In yet another aspect of the present disclosure, there is provided a use of **Compound 1**

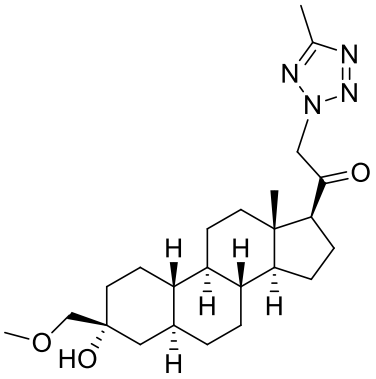


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject experiences a reduction in TETRAS activities of daily living (ADL) subscale total score following treatment onset.

[0004d] In a further aspect of the present disclosure, there is provided a use of **Compound 1**

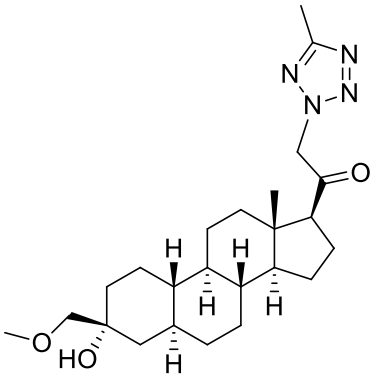


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein an initial dose of from about 50 mg to about 80 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

[0004e] In another aspect of the present disclosure, there is provided a use of **Compound 1**

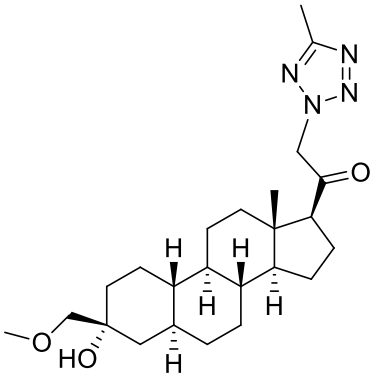


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 100 ng/mL to about 450 ng/mL about 8 days following treatment onset.

[0004f] In yet another aspect of the present disclosure, there is provided a **u**se of **Compound 1**

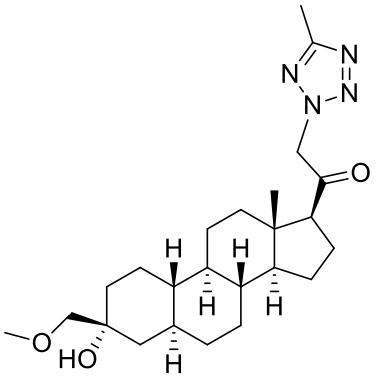


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 475 ng/mL about 15 days following treatment onset.

[0004g] In a further aspect of the present disclosure, there is provided a use of **Compound 1**

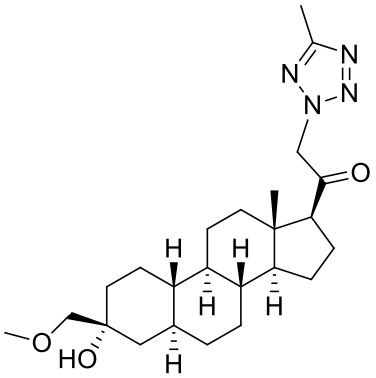


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 230 ng/mL to about 390 ng/mL about 22 days following treatment onset.

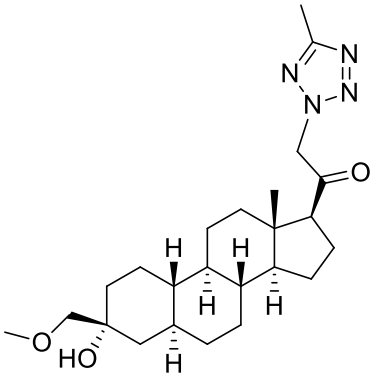
[0005] The present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof.

[0006] In one example, the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a dose of from about 5 mg to about 80 mg amount of **Compound 1**



(**Compound 1**),

or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

[0007] In some implementations, the subject is administered a dose of from about 35 mg to about 70 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID). For instance, the subject is administered a dose of from about 30 mg to about 60 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

[0008] In some implementations, the subject is administered a dose of from about 10 mg to about 35 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID). For instance, the subject is administered a dose of from about 15 mg to about 30 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

[0009] In some implementations, the subject is administered a dose of from about 10 mg to about 20 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

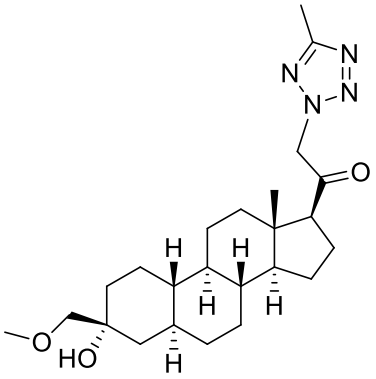
[0010] In some implementations, the subject is administered a dose of from about 25 mg to about 35 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

[0011] In some implementations, the subject is administered a dose of from about 40 mg to about 50 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

[0012] In some implementations, the subject is administered a dose of from about 55 mg to about 65 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof at least once per day (e.g., QD, BID, TID, or QID).

[0013] In some implementations, such as any of the implementations described herein, wherein **Compound 1** or a dose equivalent or a pharmaceutically acceptable salt thereof is administered to the subject once per day, the administration is at night (e.g., before bed).

[0014] In one example, the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of **Compound 1**

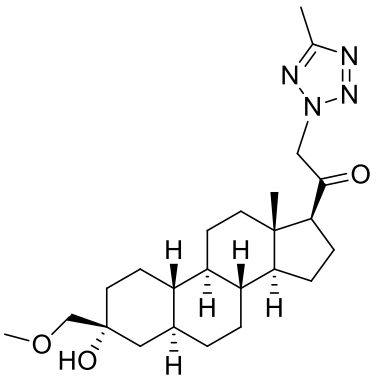


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, wherein the subject experiences a reduction in tremor amplitude of at least about 5% following treatment onset.

[0015] In some implementations, the subject experiences a reduction in tremor amplitude of at least about 10% following treatment onset. For example, the subject experiences a reduction in tremor amplitude of at least about 12% (e.g., at least about 15%, at least about 20%, or at least about 25%) following treatment onset. For example, the subject experiences a reduction in

[0018] Another example of the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, wherein the subject experiences a reduction in TETRAS activities of daily living (ADL) subscale total score following treatment onset.

[0019] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score of at least about 5% following treatment onset. For example, the subject experiences a reduction in TETRAS ADL subscale total score of at least about 10% following treatment onset. In other examples, the subject experiences a reduction in TETRAS ADL subscale total score of at least about 15% following treatment onset. In other examples, the subject experiences a reduction in TETRAS ADL subscale total score of at least about 20% following treatment onset.

[0020] In some implementations, the subject experiences the reduction in TETRAS ADL subscale total score about 8 days following treatment onset.

[0021] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score about 10 days following treatment onset.

[0022] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score about 15 days following treatment onset.

[0023] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score about 20 days following treatment onset.

[0024] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score about 25 days following treatment onset.

[0025] In some implementations, the subject experiences a reduction in TETRAS ADL subscale total score about 30 days following treatment onset.

[0035] In some implementations, the subject is administered a dose of from about 20 mg to about 40 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

[0036] In some implementations, **Compound 1**, or the pharmaceutically acceptable salt thereof, is administered once per day.

[0037] In some implementations, **Compound 1**, or a pharmaceutically acceptable salt thereof, is administered once per day for at least about 28 days.

[0038] In some implementations, **Compound 1**, or a pharmaceutically acceptable salt thereof, is administered once per day chronically.

[0039] In some implementations, the subject has a plasma concentration of **Compound 1** of at least about 175 ng/mL about 8 days following treatment onset. For example, the subject has a plasma concentration of **Compound 1** of about 200 ng/mL about 8 days following treatment onset. In other examples, the subject has a plasma concentration of **Compound 1** of from about 200 ng/mL to about 250 ng/mL about 8 days following treatment onset. In some examples, the subject has a plasma concentration of **Compound 1** of at least about 210 ng/mL about 15 days following treatment onset. In some examples, the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 450 ng/mL about 15 days following treatment onset. In another example, the subject has a plasma concentration of **Compound 1** of at least about 230 ng/mL about 22 days following treatment onset. In some examples, the subject has a plasma concentration of **Compound 1** of from about 230 ng/mL to about 390 ng/mL about 22 days following treatment onset. And, in some examples, the subject has a plasma concentration of **Compound 1** of greater than about 250 ng/mL about 29 days following treatment onset.

[0040] In some implementations, **Compound 1**, or the pharmaceutically acceptable salt thereof, is administered orally. For example, **Compound 1**, or the pharmaceutically acceptable salt thereof, is administered as a tablet or capsule.

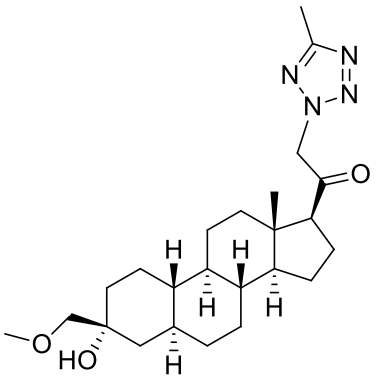
[0041] Another example of the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject an initial dose of from about 5 mg to about 80 mg of **Compound 1**

to about 20 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof. In other examples, the third dose comprises from about 7.5 mg to about 17.5 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof.

[0049] In some implementations, the third dose is administered at least once per day. For instance, the third dose is administered once per day.

[0050] In some implementations, **Compound 1,** or the pharmaceutically acceptable salt thereof, is administered orally. For example, **Compound 1,** or the pharmaceutically acceptable salt thereof, is administered as a tablet or capsule.

[0051] Another example of the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of **Compound 1**

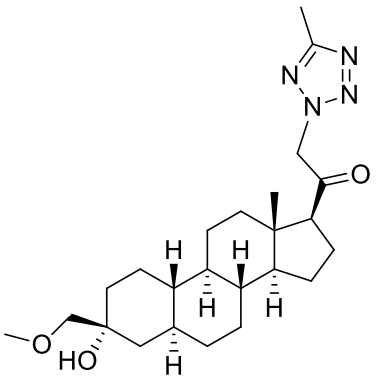


(**Compound 1**),

or a pharmaceutically acceptable salt thereof, wherein the subject has a plasma concentration of **Compound 1** of from about 100 ng/mL to about 450 ng/mL about 8 days following treatment onset.

[0052] In some implementations, the subject has a plasma concentration of **Compound 1** of from about 150 ng/mL to about 400 ng/mL about 8 days following treatment onset. For example, the subject has a plasma concentration of **Compound 1** of from about 175 ng/mL to about 400 ng/mL about 8 days following treatment onset. In other examples, the subject has a plasma concentration of **Compound 1** of from about 175 ng/mL to about 250 ng/mL about 8 days following treatment onset. In other examples, the subject has a plasma concentration of **Compound 1** of from about 200 ng/mL to about 250 ng/mL about 8 days following treatment onset. In some examples, the plasma concentration as described herein is the plasma concentration, C_{trough}.

[0053] Another example of the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of **Compound 1**



(**Compound 1**),

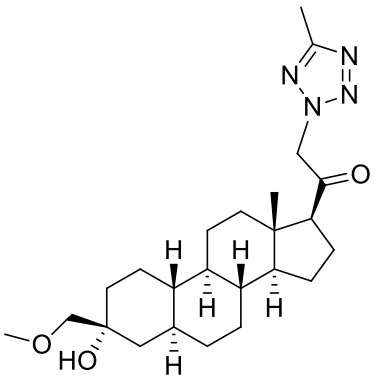
or a pharmaceutically acceptable salt thereof, wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 475 ng/mL about 15 days following treatment onset.

[0054] In some implementations, the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 450 ng/mL about 15 days following treatment onset. For example, the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 350 ng/mL about 15 days following treatment onset. For example, the subject has a plasma concentration of the compound of **Compound 1** of from about 210 ng/mL to about 280 ng/mL about 15 days following treatment onset. In other examples, the subject has a plasma concentration of **Compound 1** of from about 320 ng/mL to about 420 ng/mL about 15 days following treatment onset. And, in some examples, the subject has a plasma concentration of **Compound 1** of from about 275 ng/mL to about 490 ng/mL about 15 days following treatment onset. In some examples, the plasma concentration as described herein is the plasma concentration, C_{trough}.

[0055] Another example of the present disclosure provides a method of treating essential tremor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of **Compound 1**

WHAT IS CLAIMED IS:

1. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein a dose of from about 5 mg to about 80 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

2. The use of claim 1, wherein a dose of from about 50 mg to about 70 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

3. The use of claim 1, wherein a dose of from about 10 mg to about 30 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

4. The use of claim 1, wherein a dose of from about 20 mg to about 40 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

5. The use of claim 1, wherein a dose of about 10 mg, about 15 mg, about 30 mg, about 45 mg, or about 60 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

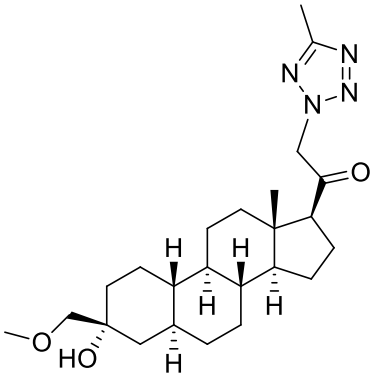
6. The use of claim 1, wherein a dose of about 60 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

7. The use of claim 1, wherein a dose of about 45 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

8. The use of claim 1, wherein a dose of about 30 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

9. The use of claim 1, wherein a dose of about 15 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

10. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject experiences a reduction in tremor amplitude of at least about 5% following treatment onset.

11. The use of any one of claims 1-10, wherein the subject experiences a reduction in tremor amplitude of at least about 15% following treatment onset.

12. The use of claim 11, wherein the subject experiences a reduction in tremor amplitude of at least about 30% following treatment onset.

13. The use of claim 12, wherein the subject experiences a reduction in tremor amplitude of at least about 50% following treatment onset.

14. The use of claim 13, wherein the subject experiences a reduction in tremor amplitude of at least about 75% following treatment onset.

15. The use of any one of claims 1-14, wherein the subject experiences a reduction in tremor amplitude about 8 days following treatment onset.

16. The use of any one claims 1-15, wherein the subject experiences a reduction in tremor amplitude about 28 days following treatment onset.

17. The use of any one of claims 1-16, wherein the subject has an initial The Essential Tremor Assessment Scale (TETRAS) performance subscale part 4 upper limb tremor total score of at least about 10 or greater prior to treatment onset.

18. The use of any one of claims 1-16, wherein the subject has an initial TETRAS performance subscale part 4 upper limb tremor total score of at least about 4 prior to treatment onset.

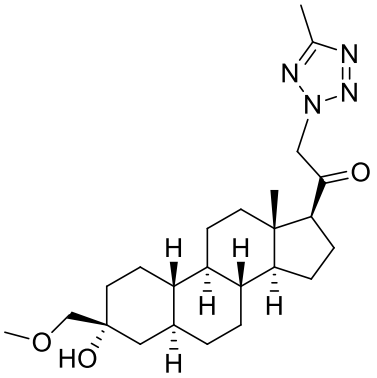
19. The use of any one of claims 1-16 or 18, wherein the subject has an initial TETRAS performance subscale part 4 upper limb tremor total score of at least about 6 prior to treatment onset.

20. The use of any one of claims 1-16, 18, or 19, wherein the subject has an initial TETRAS performance subscale part 4 upper limb tremor total score of at least about 8 prior to treatment onset.

21. The use of any one of claims 1-16 or 18-20, wherein the subject has an initial TETRAS performance subscale part 4 upper limb tremor total score of at least about 10 prior to treatment onset.

22. The use of any one of claims 1-16 or 18-21, wherein the subject has an initial TETRAS performance subscale part 4 upper limb tremor total score of at least about 12 prior to treatment onset.

23. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject experiences a reduction in TETRAS activities of daily living (ADL) subscale total score following treatment onset.

24. The use of claim 23, wherein the subject experiences a reduction in TETRAS ADL subscale total score of at least about 5% following treatment onset.

25. The use of claims 23 or 24, wherein the subject experiences a reduction in TETRAS ADL subscale total score of at least about 10% following treatment onset.

26. The use of any one of claims 23-25, wherein the subject experiences a reduction in TETRAS ADL subscale total score of at least about 15% following treatment onset.

27. The use of any one of claims 23-26, wherein the subject experiences a reduction in TETRAS ADL subscale total score of at least about 20% following treatment onset.

28. The use of any one of claims 23-27, wherein the subject experiences the reduction in TETRAS ADL subscale total score about 8 days following treatment onset.

29. The use of any one of claims, 23-28, wherein the subject experiences a reduction in TETRAS ADL subscale total score about 28 days following treatment onset.

30. The use of any one of claims 23-29, wherein the subject has an initial TETRAS ADL subscale total score of at least 12 prior to treatment onset.

31. The use of any one of claims 23-29, wherein the subject has an initial TETRAS ADL subscale total score of at least about 20 prior to treatment onset.

32. The use of any one of claims 23-29 or 31, wherein the subject has an initial TETRAS ADL subscale total score of at least about 24 prior to treatment onset.

33. The use of any one of claims 23-29, 31, or 32, wherein the subject has an initial TETRAS ADL subscale total score of at least about 28 prior to treatment onset.

34. The use of any one of claims 23-33, wherein the subject is to be administered a dose of from about 5 mg to about 80 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

35. The use of claim 36, wherein the subject is to be administered a dose of from about 10 mg to about 70 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

36. The use of claim 36, wherein the subject is to be administered a dose of from about 50 mg to about 70 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

37. The use of claim 36, wherein the subject is to be administered a dose of from about 10 mg to about 30 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

38. The use of claim 36, wherein the subject is to be administered a dose of about 10 mg, about 15 mg, about 30 mg, about 45 mg, or about 60 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

39. The use of claim 38, wherein the subject is to be administered a dose of about 60 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

40. The use of claim 36, wherein the subject is to be administered a dose of from about 30 mg to about 50 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

41. The use of claim 40, wherein the subject is to be administered a dose of about 45 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

42. The use of claim 36, wherein the subject is to be administered a dose of from about 20 mg to about 40 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof, at least once per day.

43. The use of any one of claims 1-42, wherein **Compound 1**, or the pharmaceutically acceptable salt thereof, is to be administered to the subject once per day.

44. The use of any one of claims 1-42, wherein **Compound 1**, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day for at least about 28 days.

45. The use of any one of claims 1-44, wherein the subject has a plasma concentration of **Compound 1** of at least about 175 ng/mL about 8 days following treatment onset.

46. The use of any one of claims 1-45, wherein the subject has a plasma concentration of **Compound 1** of from about 200 ng/mL to about 250 ng/mL about 8 days following treatment onset.

47. The use of any one of claims 1-46, wherein the subject has a plasma concentration of **Compound 1** of at least about 210 ng/mL about 15 days following treatment onset.

48. The use of any one of claims 1-47, wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 450 ng/mL about 15 days following treatment onset.

49. The use of any one of claims 1-48, wherein the subject has a plasma concentration of **Compound 1** of at least about 230 ng/mL about 22 days following treatment onset.

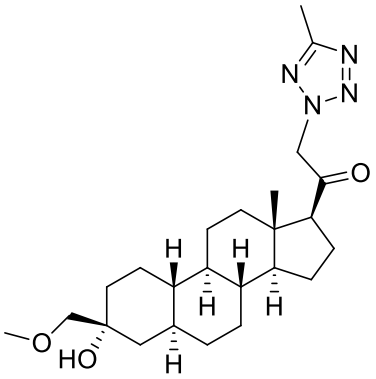
50. The use of any one of claims 1-49, wherein the subject has a plasma concentration of **Compound 1** of from about 230 ng/mL to about 390 ng/mL about 22 days following treatment onset.

51. The use of any one of claims 1-50, wherein the subject has a plasma concentration of **Compound 1** of greater than about 250 ng/mL about 29 days following treatment onset.

52. The use of any one of claims 1-51, wherein **Compound 1** or the pharmaceutically acceptable salt thereof, is to be administered to the subject orally.

53. The use of any one of claims 1-52, wherein **Compound 1** or the pharmaceutically acceptable salt thereof, is to be administered to the subject as a tablet or capsule.

54. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein an initial dose of from about 50 mg to about 80 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt thereof, is to be administered to the subject at least once per day.

55. The use of claim 54, wherein the initial dose is to be administered to the subject from onset of treatment for a duration of from about 1 to about 30 days.

56. The use of claim 55, wherein the initial dose is to be administered to the subject from onset of treatment for a duration of about 28 days.

57. The use of any one of claims 54-56, wherein the initial dose is from about 55 mg to about 70 mg of **Compound 1** or a dose equivalent of a pharmaceutically acceptable salt thereof.

58. The use of any one of claims 54-57, wherein a second dose comprising from about 25 mg to about 50 mg of **Compound 1**, or a dose equivalent of a pharmaceutically acceptable salt

thereof, is to be administered to the subject on the day following the last administration of the initial dose.

59. The use of claim 58, wherein the second dose comprises from about 30 mg to about 45 mg of **Compound 1**, or a dose equivalent of the pharmaceutically acceptable salt thereof.

60. The use of claim 58 or claim 59, wherein the second dose comprises from about 25 mg to about 35 mg of **Compound 1**, or a dose equivalent of the pharmaceutically acceptable salt thereof.

61. The use of any one of claims 58-60, wherein the second dose is to be administered to the subject for a duration of about 60 days or less.

62. The use of any one of claims 58-61, wherein a third dose comprising from about 5 mg to about 24 mg of **Compound 1**, or a dose equivalent of the pharmaceutically acceptable salt thereof, is to be administered to the subject on the day following the last administration of the second dose.

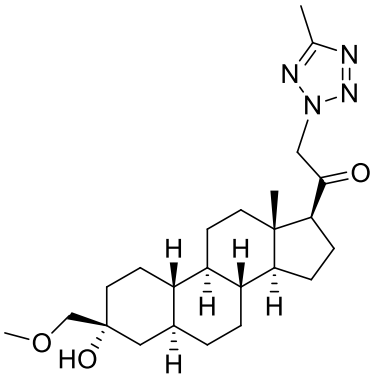
63. The use of claim 62, wherein the third dose comprises from about 5 mg to about 20 mg of **Compound 1**, or a dose equivalent of the pharmaceutically acceptable salt thereof.

64. The use of claim 62 or claim 63, wherein the third dose comprises from about 7.5 mg to about 17.5 mg of **Compound 1**, or a dose equivalent of the pharmaceutically acceptable salt thereof.

65. The use of any one of claims 54-64, wherein **Compound 1**, or the pharmaceutically acceptable salt thereof, is to be administered to the subject orally.

66. The use of any one of claims 54-65, wherein **Compound 1**, or the pharmaceutically acceptable salt thereof, is to be administered to the subject as a tablet or capsule.

67. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 100 ng/mL to about 450 ng/mL about 8 days following treatment onset.

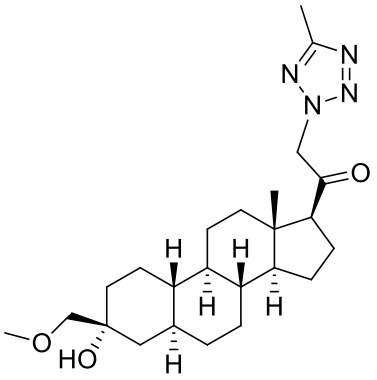
68. The use of claim 67, wherein the subject has a plasma concentration of **Compound 1** of from about 150 ng/mL to about 400 ng/mL about 8 days following treatment onset.

69. The use of claim 68, wherein the subject has a plasma concentration of **Compound 1** of from about 175 ng/mL to about 400 ng/mL about 8 days following treatment onset.

70. The use of claim 69, wherein the subject has a plasma concentration of **Compound 1** of from about 175 ng/mL to about 250 ng/mL about 8 days following treatment onset.

71. The use of claim 69, wherein the subject has a plasma concentration of **Compound 1** of from about 200 ng/mL to about 250 ng/mL about 8 days following treatment onset.

72. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 475 ng/mL about 15 days following treatment onset.

73. The use of claim 72, wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 450 ng/mL about 15 days following treatment onset.

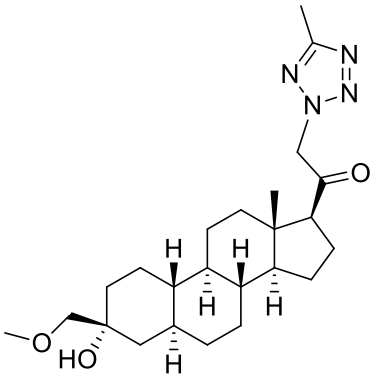
74. The use of claim 72, wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 350 ng/mL about 15 days following treatment onset.

75. The use of claim 72, wherein the subject has a plasma concentration of **Compound 1** of from about 210 ng/mL to about 280 ng/mL about 15 days following treatment onset.

76. The use of claim 72, wherein the subject has a plasma concentration of **Compound 1** of from about 320 ng/mL to about 420 ng/mL about 15 days following treatment onset.

77. The use of claim 72, wherein the subject has a plasma concentration of **Compound 1** of from about 275 ng/mL to about 490 ng/mL about 15 days following treatment onset.

78. Use of **Compound 1**



(**Compound 1**),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating essential tremor in a subject in need thereof,

wherein the subject has a plasma concentration of **Compound 1** of from about 230 ng/mL to about 390 ng/mL about 22 days following treatment onset.

79. The use of any one of claims 66-78, wherein **Compound 1**, or the pharmaceutically acceptable salt thereof, is to be administered to the subject orally.

80. The use of any one of claims 66-79, wherein **Compound 1**, or the pharmaceutically acceptable salt thereof, is to be administered to the subject as a tablet or capsule.

81. The use of any one of claims 66-80, wherein the plasma concentration is C_{trough}.