Claims

1. A method of switching a subject from a daily oral risperidone therapy to a long acting injectable risperidone formulation, said method comprising:

   i. providing a last dose of a daily oral risperidone therapy to be administered, after which no further oral risperidone therapy is to be administered; and

   ii. the next day, providing to the subject a long acting injectable risperidone formulation to be administered subcutaneously, the long acting injectable risperidone formulation comprising

      (a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

      (b) a biodegradable triblock copolymer having the formula:

      poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$,

      wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

      (c) a biodegradable diblock copolymer having the formula:

      methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$,

      wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

   wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment;

   thereby switching the subject from a daily oral risperidone therapy to a long acting injectable risperidone formulation.

2. A method of switching a subject from a long acting injectable antipsychotic to a long acting injectable risperidone formulation without the need for supplemental oral risperidone therapy, the method comprising:

i. providing a final dose of the long acting injectable antipsychotic to be administered; and

ii. at the next dosing, providing the long acting injectable risperidone formulation to be administered subcutaneously;

wherein the long acting injectable risperidone formulation comprises:

a. risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

b. a biodegradable triblock copolymer having the formula: poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

c. a biodegradable diblock copolymer having the formula: methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$, wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment; and

wherein said method is performed without administering to the subject a supplemental oral risperidone therapy.

3. The method of claim 1 or 2, wherein the long acting injectable risperidone formulation is to be administered once monthly.

4. The method of claim 3, wherein said long acting injectable risperidone formulation comprises from about 50 mg to about 125 mg risperidone in a volume of from about 0.1 mL to about 0.5 mL.

5. The method of claim 1 or 2, wherein the long acting injectable risperidone formulation is to be administered once every two months.

6. The method of claim 5, wherein said long acting injectable risperidone formulation comprises from about 100 mg to about 250 mg risperidone in a volume of from about

0.2 mL to about 1.0 mL.

7. The method of any one of claims 2 to 6, wherein the long acting injectable antipsychotic is a long acting injectable intramuscular product.

8. The method of any one of claims 2 to 6, wherein the long acting injectable antipsychotic is a long acting injectable subcutaneous product.

9. The method of any one of claims 2 to 8, wherein the long acting injectable antipsychotic comprises risperidone, 9-OH-risperidone, or aripiprazole.

10. A method of switching a subject from a once monthly long acting injectable risperidone formulation to a once bimonthly (*i.e.*, once every two months) long acting injectable risperidone formulation without the need for supplemental oral risperidone therapy, said method comprising:

i. providing a final dose of the once monthly long acting injectable risperidone formulation to be administered subcutaneously; and

ii. providing a long acting injectable risperidone formulation to be administered subcutaneously once bimonthly (i.e., once every two months);

wherein each of the once monthly and once bimonthly (i.e., once every two months) long acting injectable risperidone formulations comprise

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula: poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula: methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$, wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to

1:19, in said formulation, which is insoluble in an aqueous environment; and

wherein said method is performed without administering to the subject a supplemental oral risperidone therapy.

11. A method of switching a subject from a once bimonthly (i.e., once every two months) long acting injectable risperidone formulation to a once monthly long acting injectable risperidone formulation without the need for supplemental oral risperidone therapy, said method comprising:

i. providing a final dose of the once bimonthly (i.e., once every two months) long acting injectable risperidone formulation to be administered subcutaneously; and

ii. two months later providing the once monthly long acting injectable risperidone formulation to be administered subcutaneously;

wherein the once monthly and once bimonthly (*i.e.*, once every two months) long acting injectable risperidone formulations comprise

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula: poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula: methoxy poly(ethylene glycol)$_y$-poly(lactic acid)$_z$, wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment; and

wherein said method is performed without administering to the subject a supplemental oral risperidone therapy.

12. A method of switching a risperidone dose in a subject administered once monthly or once bimonthly (*i.e.*, once every two months) long acting injectable risperidone formulation from an initial dose of a long acting injectable risperidone formulation to a subsequent dose of a long acting injectable risperidone formulation, without the need for supplemental oral risperidone therapy, said method comprising:

i. providing a final administration of the initial dose of the long acting injectable risperidone formulation to be administered subcutaneously; and

ii. at the next dosing, providing the subsequent dose of the long acting injectable risperidone formulation to be administered subcutaneously;

wherein the initial dose and the subsequent dose of the long acting injectable risperidone formulations are different doses of a long acting injectable risperidone formulation that comprises

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula:

methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$,

wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment; and

wherein said method is performed without administering to the patient any

supplemental oral risperidone therapy.

13. The method of claim 12, wherein the initial dose of the long acting injectable risperidone formulation comprises a higher dose of risperidone than the subsequent dose of long acting injectable risperidone formulation.

14. The method of claim 12, wherein the initial dose of the long acting injectable risperidone formulation comprises a lower dose of risperidone than the subsequent dose of long acting injectable risperidone formulation.

15. The method of any one of claims 12 to 14, wherein the subsequent dose of the long acting injectable risperidone formulation is to be administered one month after administration of the initial dose of the long acting injectable risperidone formulation.

16. The method of any one of claims 12 to 14, wherein the subsequent dose of the long acting injectable risperidone formulation is to be administered two months after administration of the initial dose of the long acting injectable risperidone formulation.

17. The method of any one of the preceding claims, wherein the subcutaneous administration is into the upper arm of the subject or the abdomen of the subject.

18. The method of claim 17, wherein the subcutaneous administration into the upper arm is into the back of the upper arm of the subject.

19. The method of claim 17, wherein the subcutaneous administration is into the abdomen of the subject.

20. Use of a long acting injectable risperidone formulation in the manufacture of a medicament for the treatment of a psychiatric disease in a subject undergoing long acting injectable risperidone therapy wherein said subject has missed a dose of a long acting injectable risperidone formulation, wherein a dose of a once monthly or once bimonthly (i.e., once every two months) of the formulation is to be subcutaneously administered to the subject;

wherein the long acting injectable risperidone formulation comprises

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula: methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$, wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment; and

wherein said use is performed without administering to the subject any supplemental oral risperidone therapy.

21. The method of any one of claims 10 to 19 or the use of claim 20, wherein the once monthly long acting injectable risperidone formulation comprises from about 50 mg to about 125 mg risperidone and wherein the once bimonthly long acting injectable risperidone formulation comprises from about 100 mg to about 250 mg risperidone .

22. The method of any one of claims 10 to 19 or the use of claim 20 or 21, wherein the long acting injectable risperidone formulation is to be administered from a syringe fitted with a needle having a gauge number equal to or greater than 21 and/or a length equal to or shorter than 5/8 inch, preferably wherein the syringe is a pre-filled syringe.

23. The method of any one of claims 10 to 19 or the use of any one of claims 20 to 22, wherein the subject is suffering from a psychiatric disease selected from schizophrenia, bipolar disorder and irritability associated with autism (IAA).

24. The method of any one of claims 10 to 19 or the use of any one of claims 20 to 23, wherein the subject is suffering from schizophrenia.

25. The method of any one of claims 10 to 19 or the use of any one of claims 20 to 24, wherein the subcutaneous administration of the long acting injectable risperidone formulation results in a post- stabilization decrease in the PANSS total score.

26. The method of any one of claims 10 to 19 or the use of any one of claims 20 to 25,

wherein the subject is an adult from the age of 18 to 65 years old or an adolescent from the age of 13 to 17 years old.

27. The method of any one of claims 10 to 19 or the use of any one of claims 20 to 26, wherein the subcutaneous administration of the long acting injectable risperidone formulation results in a mean exposure of the TAM (AUC0-tau) that is equivalent to that of oral risperidone (2 mg/day to 5 mg/day) administered over an equivalent dosing period.

28. A prefilled syringe (PFS) for subcutaneously administering a long acting injectable risperidone formulation, said prefilled syringe comprising

the long acting injectable risperidone formulation wherein said formulation comprises

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula: poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$, wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula: methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$, wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment; and

a needle having a gauge number equal to or greater than 21 and/or a length equal to or shorter than 5/8 inch.

29. The prefilled syringe of claim 28, wherein the long acting injectable risperidone formulation is stable at 2° to 8°C for at least 12 months, or at least at least 24 months, or at least 36 months.

30. The prefilled syringe of claims 28 or 29, wherein the long acting injectable risperidone

formulation is stable at 20 to 25°C for at least 30 days, at least 60 days or at least 90 days.

31. The prefilled syringe of any one of claims 28 to 30, wherein the long acting injectable risperidone formulation is stable at 25°C and 60% relative humidity (RH) for at least 3 months or at least 6 months.

32. The prefilled syringe of any one of claims 28 to 31, wherein the long acting injectable risperidone formulation is stable upon storage at -20°C for a first period of time, and thawing, by storing at 25°C and 60% relative humidity for a second period of time, optionally repeating the -20°C and thawing twice, wherein the first period of time is at least 2 days, and the second period of time is at least 2 days.

33. The prefilled syringe of any one of claims 28 to 32, wherein the long acting injectable risperidone formulation is stable upon storage at -20°C for a first period of time, and then storing at 5°C for a second period of time, wherein the first period of time is at least 2 weeks, and the second period of time is up to 2 weeks.

34. A kit comprising

the prefilled syringe of any one of claims 28 to 33;
a needle having a gauge number equal to or greater than 21 and/or a length equal to or shorter than 5/8 inch; and optionally
instructions for use.

35. The kit of claim 34, further comprising a means for physically protecting the prefilled syringe.

36. The kit of claim 34 or 35, wherein the long acting injectable risperidone formulation is photostable for up to 36 months.

37. The method of any one of claims 1 to 19, the use of any one of claims 20 to 27, the prefilled syringe of any one of claims 28 to 33 or the kit of any one of claims 34 to 36, wherein the long acting injectable risperidone formulation comprises 10% (w/w %) triblock copolymer and 15% (w/w %) diblock copolymer of the total weight percentage of the formulation.

38. The method, the use, the prefilled syringe or the kit of claim 37, wherein the long

acting injectable risperidone formulation further comprises DMSO.

39. The method, the use, the prefilled syringe or the kit of any of claims 37 or 38, wherein the long acting injectable risperidone formulation comprises 360 mg/mL risperidone base.

40. Use of a long acting injectable risperidone formulation in the manufacture of a medicament for the treatment of a psychiatric disease or disorder in a subject, wherein the medicament is to be administered subcutaneously to the subject once every two months, and wherein administration results in a mean exposure of the TAM (AUC0-tau) that is equivalent to that of oral risperidone (2 mg/day to 5 mg/day) administered over an equivalent dosing period.

41. Use of a long acting injectable risperidone formulation in the manufacture of a medicament for the treatment of a psychiatric disease or disorder in a subject, wherein the risperidone formulation comprises risperidone and a polymer, the medicament is to be administered subcutaneously to the subject and wherein the administration is selected from the subject's upper arm and/or abdomen.

42. The method of any one of claims 1 to 19, the use of any one of claims 20 to 27 or the method or use of any one of claims 37 to 41, wherein:

a subcutaneous administration of the long acting injectable risperidone formulation to the upper arm is to be followed by, at the next dosing, a subcutaneous administration of the long acting injectable risperidone formulation to the abdomen; or

a subcutaneous administration of the long acting injectable risperidone formulation to the abdomen is to be followed by, at the next dosing, a subcutaneous administration of the long acting injectable risperidone formulation to the upper arm.

43. Use of a long acting injectable risperidone formulation in the manufacture of a medicament for the treatment of a psychiatric disease or disorder in a subject, wherein the medicament is to be administered subcutaneously to the subject at a frequency of no more than once every 28 days 1 mL or less and wherein the long acting injectable risperidone formulation comprises

(a) risperidone, or a pharmaceutically acceptable salt thereof, at a concentration of about 250-400 mg/mL, equivalent to risperidone;

(b) a biodegradable triblock copolymer having the formula:

poly(lactic acid)$_v$-poly(ethylene glycol)$_w$-poly(lactic acid)$_x$,

wherein v and x are the number of repeat units ranging from 24 to 682 and w is the number of repeat units ranging from 4 to 273 and v=x or v≠x;

(c) a biodegradable diblock copolymer having the formula:

methoxy-poly(ethylene glycol)$_y$-poly(lactic acid)$_z$,

wherein y and z are the number of repeat units, wherein y is the number of repeat units ranging from 3 to 50 and z is the number of units ranging from 7 to 327; and

wherein the ratio of the biodegradable triblock copolymer of (b) and the biodegradable diblock copolymer of (c) is 1:3 to 1:8 or 1:1 to 1:19 or 3:2 to 1:19, in said formulation, which is insoluble in an aqueous environment;

wherein said formulation provides a therapeutically effective amount of risperidone for at least 28 days.

44. The use of claim 43, wherein said formulation is to be subcutaneously administered once monthly, and wherein said formulation provides a therapeutically effective amount of risperidone for at least one month.

45. The use of claim 43, wherein said formulation is to be subcutaneously administered once bimonthly (i.e., once every two months), and wherein said formulation provides a therapeutically effective amount of risperidone for at least two months.

46. The use of any one of claims 43 to 45, wherein the subject is not administered a loading dose of risperidone.

47. The use of any one of claims 43, 44, or 46, wherein said formulation comprises from about 50 mg to about 125 mg risperidone.

48. The use of any one of claims 43, 45 or 46, wherein said formulation comprises from about 100 mg to about 250 mg risperidone.

49. The use of any one of claims 40 to 48, wherein the psychiatric disease or disorder is

schizophrenia.

50. The use of claim 49, wherein said use results in a reduction in the risk to relapse compared to placebo in subjects having schizophrenia.

51. The use of claim 50, wherein said risk to relapse is reduced by at least 50% or at least 60-80%.

52. The use of any one of claims 49 to 51, wherein said use results in a lower rate of relapse compared to placebo in subjects having schizophrenia.

53. The use of any one of claims 49 to 52, wherein said use extends the time to relapse compared to placebo in subjects having schizophrenia.

54. The use of claim 53, wherein the time to relapse is extended by at least 2 -fold or 2.5 to 5-fold compared to placebo in subjects having schizophrenia.

55. The use of any one of claims 49 to 54, wherein the subject has an increased chance to maintain stability, wherein the increased chance is greater than 80% compared to a subject receiving placebo.

56. The use of claim 55, wherein the stability is maintained for at least 6 months.

57. The use of any one of claims 49 to 56, wherein the subject shows post-stability improvement, as assessed by the PANSS scale, compared to a subject receiving placebo.

58. The use of claim 57, wherein the post-stability improvement is maintained for at least 12 months.

59. A long acting injectable risperidone formulation as defined in any of claims 1 to 27 or 37 to 58, for use in therapy.