CLAIMS

1. A modified release pharmaceutical granulation comprising a plurality of coated granules, wherein,

the coated granules comprise a core and a modified release coating surrounding the core;

the modified release coating comprises:

from 80 wt% to 90 wt% of a matrix polymer; and

from 10 wt% to 20 wt% an antistatic agent;

wherein wt% is based on the total weight of the modified release coating. and

the core comprises greater than 85 wt% of 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the core.

2. The pharmaceutical granulation of claim 1, wherein the pharmaceutical granulation is characterized by a particle size distribution (PSD) (D50) from 200 μm to 400 μm, wherein PSD is determined by sieve analysis.

3. The pharmaceutical granulation of any one of claims 1 to 2, wherein the pharmaceutical granulation comprises from 50 wt% to 90 wt% of 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the pharmaceutical granulation.

4. The pharmaceutical granulation of any one of claims 1 to 3, wherein the matrix polymer comprises a water-insoluble polymer.

5. The pharmaceutical granulation of claim 4, wherein the water-insoluble polymer comprises ethylcellulose.

6. The pharmaceutical granulation of any one of claims 1 to 5, wherein the matrix polymer comprises from 0 wt% to 10 wt% of a pore forming polymer, wherein wt% is based on the total weight of the matrix polymer.

7. The pharmaceutical granulation of claim 6, wherein the pore forming polymer comprises a water-soluble polymer.

8. The pharmaceutical granulation of claim 7, wherein the water-soluble polymer comprises hydroxypropylcellulose.

9. The pharmaceutical granulation of any one of claims 1 to 8, wherein the antistatic agent comprises talc, magnesium stearate, or a combination thereof.

10. The pharmaceutical granulation of any one of claims 1 to 9, wherein,
the core represents from 65 wt% to 85 wt% of the total weight of the coated granulation; and
the modified release coating represents from 15 wt% to 40 wt% of the total weight of the coated granulation.

11. The pharmaceutical granulation of any one of claims 1 to 10, wherein the modified release coating has a thickness from 5 μm to 30 μm.

12. The pharmaceutical granulation of any one of claims 1 to 11, wherein the pharmaceutical granulation has a water content less than 2 wt%, wherein wt% is based on the total weight of the pharmaceutical granulation.

13. The pharmaceutical granulation of any one of claims 1 to 12, further comprising a seal coating surrounding the core, and wherein the modified release coating surrounds the seal coating.

14. The pharmaceutical granulation of claim 13, wherein the seal coating comprises:
hydroxypropyl cellulose;
hydroxypropylmethyl cellulose;
hydroxypropylcellulose and talc; or
hydroxypropylmethyl cellulose and talc.

15. The pharmaceutical granulation of any one of claims 13 to 14, wherein the pharmaceutical granulation comprises from 2 wt% to 15 wt% of the seal coating, wherein wt% is based on the total weight of the pharmaceutical granulation.

16. The pharmaceutical granulation of any one of claims 1 to 15, wherein from 30% to 80% of the 4-((*L*-valyl)oxy)butanoic acid is released from the pharmaceutical granulation within 2 hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 100 rpm.

17. The pharmaceutical granulation of any one of claims 1 to 16, wherein from 50% to 90% of the 4-((*L*-valyl)oxy)butanoic acid is released from the pharmaceutical granulation within 4

hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 100 rpm.

18. The pharmaceutical granulation of any one of claims 1 to 17, wherein from 60% to 100% of the 4-((*L*-valyl)oxy)butanoic acid is released from the pharmaceutical granulation within 6 hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 100 rpm.

19. The pharmaceutical granulation of any one of claims 1 to 18, wherein the modified release pharmaceutical granulation exhibits a dissolution profile when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 100 rpm that is bioequivalent to a dissolution profile as shown in any one of FIGS. 6, 12, and 15.

20. The pharmaceutical granulation of any one of claims 1 to 18, wherein the modified release pharmaceutical granulation exhibits a dissolution profile when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 100 rpm that is bioequivalent to a dissolution profile as shown in any one of FIGS. 6, 12, and 15.

21. The pharmaceutical granulation of any one of claims 1 to 20, wherein the pharmaceutical granulation does not comprise a plasticizer.

22. A pharmaceutical composition comprising the pharmaceutical granulation of any one of claims 1 to 20.

23. The pharmaceutical composition of claim 22, wherein the pharmaceutical composition is an oral composition.

24. The pharmaceutical composition of any one of claims 22 to 23, wherein the oral composition comprises:

a modified release component, wherein the modified release portion comprises the pharmaceutical granulation; and

an immediate release component.

25. The pharmaceutical composition of claim 24, wherein the immediate release component dissolves in water within less than 5 minutes.

26. The pharmaceutical composition of any one of claims 23 to 25, wherein the oral composition is a BID formulation.

27. The pharmaceutical composition of any one of claims 23 to 25, wherein the oral composition is a QD formulation.

28. The pharmaceutical composition of any one of claims 22 to 27, wherein the pharmaceutical composition comprises from 500 mg equivalents to 12 g equivalents of 4-((*L*-valyl)oxy)butanoic acid.

29. The pharmaceutical composition of any one of claims 22 to 28, wherein the pharmaceutical composition comprises a sustained release oral composition, a delayed release composition, an immediate release composition, or a combination of any of the foregoing.

30. The pharmaceutical composition of any one of claims 22 to 29, wherein the pharmaceutical composition comprises a therapeutically effective amount of 4-((*L*-valyl)oxy)butanoic acid for treating a disease in a patient, wherein the disease is selected from narcolepsy, cataplexy, excessive daytime sleepiness, fibromyalgia, chronic fatigue, and tardive dyskinesia.

31. A method of treating a disease in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 22 to 30, wherein the disease is selected from narcolepsy, cataplexy, excessive daytime sleepiness, fibromyalgia, chronic fatigue, and tardive dyskinesia.

32. The method of claim 31, wherein the disease is cataplexy associated with narcolepsy.

33. The method of claim 31, wherein the disease is excessive daytime sleepiness associated with narcolepsy.

34. The method of claim 31, wherein the disease is excessive daytime sleepiness in a patient with Parkinson's disease.

35. The method of claim 31, wherein the disease is chronic fatigue in a patient with Parkinson's disease.

36. The method of any one of claims 31 to 35, wherein administering comprises orally administering.

37. The method of claim 36, wherein administering orally administering in the fasted state.

38. The method of claim 36, wherein administering orally administering in the fed state.

39. A method of coating a granulation comprising applying a coating composition to a pharmaceutical granulation comprising a plurality of granules comprising 4-((*L*-valyl)oxy)butanoic acid, wherein the coating composition comprises:

from 6 wt% to 14 wt% solids;

from 0 wt% to 20 wt% water; and

from 70 wt% to 95 wt% ethanol

wherein wt% is based on the total weight of the coating formulation.

40. The method of claim 39, wherein the solids comprise:

a matrix polymer selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, or a combination thereof; and

an antistatic agent selected from talc, magnesium stearate, or a combination thereof.

41. The method of any one of claims 39 to 40, wherein applying comprises spraying.

42. A pharmaceutical composition comprising;

an immediate release (IR) component, wherein the immediate release component comprises from 1.2 g-equivalents γ-hydroxybutyrate to 4.0 g-equivalents γ-hydroxybutyrate; and

a modified release (MR) component, wherein the modified release component comprises:

from 3 g-equivalents γ-hydroxybutyrate to 9 g-equivalents γ-hydroxybutyrate; and

the modified release granulation of any one of claims 1 to 21.

43. The pharmaceutical composition of claim 42, wherein each of the immediate release component and the modified release component comprise 4-((*L*-valyl)oxy)butanoic acid.

44. The pharmaceutical composition of any one of claims 42 to 43, wherein the γ-hydroxybutyrate equivalents is in the form of γ-((*L*-valyl)oxy)butanoic acid.

45. The pharmaceutical composition of any one of claims 43 to 44, wherein,

the immediate release component comprises from 10 wt% to 50 wt% of the 4-((*L*-valyl)oxy)butanoic acid; and

the modified release component comprises from 50 wt% to 90 wt% of the 4-((*L*-valyl)oxy)butanoic acid,

wherein wt% is based on the total weight of 4-((*L*-valyl)oxy)butanoic acid in the pharmaceutical composition.

46. The pharmaceutical composition of any one of claims 43 to 45, wherein,

the immediate release component comprises form 2 g to 7 g of 4-((*L*-valyl)oxy)butanoic acid; and

the modified release component comprises from 7 g to 15 g of 4-((*L*-valyl)oxy)butanoic acid.

47. The pharmaceutical composition of any one of claims 42 to 46, wherein,

the immediate release component comprises form 1 g-equivalents to 4 g-equivalents γ-hydroxybutyrate; and

the modified release component comprises from 3.5 g-equivalents to 8.5 g-equivalents γ-hydroxybutyrate.

48. The pharmaceutical composition of any one of claims 42 to 47, wherein a weight ratio of the gm-equivalents γ-hydroxybutyrate in the immediate release component to the gm-equivalents γ-hydroxybutyrate in the modified release component is from 1.5 to 3.5.

49. The pharmaceutical composition of any one of claims 42 to 48, wherein the immediate release component comprises a plurality of immediate release microparticles.

50. The pharmaceutical composition of claim 49, wherein the immediate release microparticles comprise greater than 90 wt% 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the immediate release microparticles.

51. The pharmaceutical composition of any one of claims 49 to 50, wherein the immediate release microparticles have a volume mean diameter D(4.3) from 200 μm to 500 μm.

52. The pharmaceutical composition of any one of claims 42 to 51, wherein the immediate release component comprises a solution suitable for oral administration.

53. The pharmaceutical composition of any one of claims 42 to 52, wherein the modified release component comprises a plurality of modified release microparticles.

54. The pharmaceutical composition of any one of claims 42 to 53, wherein the modified release component comprises a suspension of modified release microparticles suitable for oral administration.

55. The pharmaceutical composition of any one of claims 53 to 54, wherein the modified release microparticles comprise a core and a modified release coating surrounding the core.

56. The pharmaceutical composition of claim 55, wherein the core comprises greater than 85 wt% of 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the core.

57. The pharmaceutical composition of claim 55, wherein the core comprises greater than 90 wt% of 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the core.

58. The pharmaceutical composition of any one of claims 55 to 57, wherein the core comprises immediate release macroparticles comprising 4-((*L*-valyl)oxy)butanoic acid.

59. The pharmaceutical composition of any one of claims 53 to 58, wherein the modified release microparticles comprise from 10 wt% to 50 wt% of the modified release coating, wherein wt% is based on the total weight of the modified release microparticles.

60. The pharmaceutical composition of any one of claims 53 to 59, wherein the modified release microparticles comprise:

from 24 wt% to 34 wt% of the modified release coating (MR2);

from 28 wt% to 38 wt% of the modified release coating (MR3); or

from 32 wt% to 42 wt% of the modified release coating (MR1);

wherein wt% is based on the total weight of the modified release microparticles.

61. The pharmaceutical composition of any one of claims 42 to 60, wherein following oral administration of an IR component comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ of from 0.3 hours to 0.5 hours, a mean T_{max} from 0.8 hours to 1.0 hours, a mean C_{max} from 14 µg/mL to 18 µg/mL, a mean AUC_{0-6} from 14 h×µg/mL to 18 h×µg/mL, an AUC_{0-inf} from 14 h×µg/mL to 18 h×µg/mL, and a CL/F of 44 L/h to 52 L/h).

62. The pharmaceutical composition of any one of claims 42 to 61, wherein following oral administration of an IR composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 0.4 hours to 0.8 hours, a mean T_{max} from 1.1 hours to 1.5 hours, a mean C_{max} from 76 µg/mL to 96 µg/mL, an AUC_{0-6} from 219 h×µg/mL to 259 h×µg/mL, an AUC_{0-inf} from 226 h×µg/mL to 266 h×µg/mL, and a CL/F from 21 L/h to 41 L/h.

63. The pharmaceutical composition of any one of claims 42 to 62, wherein following oral administration of an IR composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile is characterized by a C_{max} ratio from 4.9 to 6.9, and an AUC_{0-inf} ratio from 14 to 26, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the 4-((*L*-valyl)oxy)butanoic acid value.

64. The pharmaceutical composition of any one of claims 42 to 63, wherein following oral administration of a modified release (MR1) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ from 0.5 hours to 0.9 hours, a mean T_{max} from 1.4 hours to 1.8 hours, a mean C_{max} from 2 µg/mL to 6 µg/mL, a mean AUC_{0-6} from 7 h×µg/mL to 11 h×µg/mL, a mean AUC_{0-inf} from 7 h×µg/mL to 11 h×µg/mL, and a mean CL/F from 818 L/h to 858 L/h.

65. The pharmaceutical composition of any one of claims 42 to 64, wherein following oral administration of a modified release (MR1) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 0.9 hours to 1.3 hours, a mean T_{max} from, 2.2 hours to 2.6 hours, a mean C_{max} from 17 µg/mL to 37 µg/mL, a mean AUC_{0-6} from 76 h×µg/mL to 96 h×µg/mL, a mean AUC_{0-inf} from 75 h×µg/mL to 115 h×µg/mL, and a mean CL/F from 85 L/h to 105 L/h.

66. The pharmaceutical composition of any one of claims 42 to 65, wherein following oral administration of a modified release (MR1) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile is characterized by a C_{max} ratio from 6.2 to 7.2, and AUC_{0-inf} ratio from 9.0 to 11.0, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the 4-((*L*-valyl)oxy)butanoic acid value.

67. The pharmaceutical composition of any one of claims 42 to 66, wherein following oral administration of a modified release (MR2) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ from 0.5 hours to 0.9 hours, a mean T_{max} from 1.2 hours to 1.6 hours, a mean C_{max} from 4 µg/mL to 8 µg/mL, a mean AUC_{0-6} from 8 h×µg/mL to 12 h×µg/mL, a mean AUC_{0-inf} from 8 h×µg/mL to 12 h×µg/mL, and a mean CL/F from 720 L/h to 800 L/h.

68. The pharmaceutical composition of any one of claims 42 to 66, wherein following oral administration of a modified release (MR2) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 0.8 hours to 1.0 hour, a mean T_{max} from 2.2 hours to 2.6 hours, a mean C_{max} from 34 µg/mL to 38 µg/mL, a mean AUC_{0-6} from 102 h×µg/mL to 122 h×µg/mL, a mean AUC_{0-inf} from 110 h×µg/mL to 130 h×µg/mL, and a mean CL/F from 62 L/h to 82 L/h.

69. The pharmaceutical composition of any one of claims 42 to 68, wherein following oral administration of a modified release (MR2) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile is characterized by a C_{max} ratio from 5.9 to 6.7, and AUC_{0-inf} ratio from 11.5 to 12.3, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the 4-((*L*-valyl)oxy)butanoic acid value.

70 The pharmaceutical composition of any one of claims 42 to 69, wherein following oral administration of a modified release (MR3) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ from 0.6 hours to 1.0 hours, a mean T_{max} from 0.9 hours to 1.3 hours, a mean C_{max} from 3 µg/mL to 7 µg/mL, a mean AUC_{0-6} from 8 h×µg/mL to 12 h×µg/mL, a mean AUC_{0-inf} from 10 h×µg/mL to 12 h×µg/mL, and a mean CL/F from 760 L/h to 840 L/h.

71. The pharmaceutical composition of any one of claims 42 to 69, wherein following oral administration of a modified release (M3) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 0.9 hours to 1.1 hours, a mean T_{max} from 1.7 hours to 2.1 hours, a mean C_{max} from 26 µg/mL to 34 µg/mL, a mean AUC_{0-6} from 82 h×µg/mL to

122 h×µg/mL, a mean $AUC_{0\text{-}inf}$ from 90 h×µg/mL to 130 h×µg/mL, and a mean CL/F from 69 L/h to 89 L/h.

72. The pharmaceutical composition of any one of claims 42 to 71, wherein following oral administration of a modified release (MR3) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile is characterized by a C_{max} ratio from 6.1 to 6.9, and $AUC_{0\text{-}inf}$ ratio from 11.0 to 11.8, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the 4-((*L*-valyl)oxy)butanoic acid value.

73. The pharmaceutical composition of any one of claims 42 to 72, wherein following oral administration of an immediate release (IR) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 6 and 7 or shown in FIGS. 17 and 18.

74. The pharmaceutical composition of any one of claims 42 to 73, wherein following oral administration of a modified release (M1) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 6 and 7 or shown in FIGS. 17 and 18.

75. The pharmaceutical composition of any one of claims 42 to 74, wherein following oral administration of a modified release (M2) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 6 and 7 or shown in FIGS. 17 and 18.

76. The pharmaceutical composition of any one of claims 43 to 74, wherein following oral administration of a modified release (M3) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 6 and 7 or shown in FIGS. 17 and 18.

77. The pharmaceutical composition of any one of claims 42 to 76, wherein,

the immediate release component comprises from 2 g to 8 g 4-((*L*-valyl)oxy)butanoic acid; and

the modified release component comprises form 8 g to 16 g 4-((*L*-valyl)oxy)butanoic acid.

78. The pharmaceutical composition of any one of claims 42 to 77, wherein,

the immediate release component comprises from 20 wt% to 40 wt% 4-((*L*-valyl)oxy)butanoic acid; and

the modified release component comprises form 60 wt% to 80 wt% 4-((*L*-valyl)oxy)butanoic acid

wherein wt% is based on the total weight of 4-((*L*-valyl)oxy)butanoic acid.

79. The pharmaceutical composition of any one of claims 42 to 78, wherein a weight ratio of 4-((*L*-valyl)oxy)butanoic acid in the immediate release component to 4-((*L*-valyl)oxy)butanoic acid in the modified release component is from 1:2 to 1:3.

80. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of a combined release composition (CR1) comprising:

the IR component comprises 4.1 g 4-((*L*-valyl)oxy)butanoic acid; and

the modified release (MR1) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects,

following oral administration of the pharmaceutical composition to a population to a population of patients the plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ from 1.0 hours to 1.2 hours, a mean T_{max} from 1.3 hours to 1,5 hours, a mean C_{max} from 12 µg/mL to 18µg/mL, a mean $AUC_{0\text{-}6}$ from 20 h×µg/mL to 30 h×µg/mL, a mean $AUC_{0\text{-}inf}$ from 22 h×µg/mL to 32 h×µg/mL, and a mean CL/F from 536 L/h to 576 L/h.

81. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of a combined release composition (CR1) comprising:

an IR component comprising 4.1 g 4-((*L*-valyl)oxy)butanoic acid; and a

a modified release (MR1) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects,

following oral administration of the pharmaceutical composition to a population to a population of patients the plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 1.0 hours to 1.2 hours, a mean T_{max} from 2.5 to 2.9 hours, a mean C_{max} from 88 µg/mL to 128 µg/mL, a mean $AUC_{0\text{-}6}$ from 380 h×µg/mL to 420 h×µg/mL, a mean $AUC_{0\text{-}inf}$ from 514 h×µg/mL to 554 h×µg/mL, and a mean CL/F from 22 L/h to 42 L/h.

82. The pharmaceutical composition of any one of claims 80 to 81, wherein following oral administration of a combined release composition (CR1) comprising:

an IR component comprising 4.1 g 4-((*L*-valyl)oxy)butanoic acid; and

a modified release (MR1) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects,

following oral administration of the pharmaceutical composition to a population to a population of patients the plasma pharmacokinetic profile is characterized by a C_{max} ratio from 7.0 to 9.0, and $AUC_{0\text{-}inf}$ ratio from 18.3 to 20.3, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the corresponding 4-((*L*-valyl)oxy)butanoic acid value.

83. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of the combined release (CR1) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 10 and 11 or shown in FIGS. 19 and 20.

84. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of a combined release composition (CR2) comprising:

an IR component comprising 4.5 g 4-((*L*-valyl)oxy)butanoic acid; and

a modified release (MR2) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects,

following oral administration of the pharmaceutical composition to a population to a population of patients the plasma pharmacokinetic profile of 4-((*L*-valyl)oxy)butanoic acid is characterized by a mean $t_{1/2}$ from 0.9 hours to 1.1 hours, a mean T_{max} from 1.1 hours to 1.5 hours, a mean C_{max} from 10 µg/mL to 14 µg/mL, a mean $AUC_{0\text{-}6}$ from 16 h×µg/mL to 24 h×µg/mL, a mean $AUC_{0\text{-}inf}$ from 11 h×µg/mL to 31 h×µg/mL, and a mean CL/F of 660 L/h to 740 L/h.

85. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of a combined release composition (CR2) comprising:

an IR component comprising 4.5 g 4-((*L*-valyl)oxy)butanoic acid; and

a modified release (MR2) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects,

following oral administration of the pharmaceutical composition to a population to a population of patients the plasma pharmacokinetic profile of γ-hydroxybutyrate is characterized by a mean $t_{1/2}$ from 0.8 hours to 1.0 hours, a mean T_{max} from 2.0 hours to 2.4 hours, a mean C_{max} from 73

µg/mL to 93 µg/mL, a mean AUC_{0-6} from 302 h×µg/mL to 342 h×µg/mL, a mean AUC_{0-inf} from 366 h×µg/mL to 406 h×µg/mL, and a mean CL/F from 33 L/h to 53 L/h.

86. The pharmaceutical composition of any one of claims 84 to 85, wherein following oral administration of a combined release composition (CR2) comprising:

an IR component comprising 4.5 g 4-((*L*-valyl)oxy)butanoic acid; and

following oral administration of the pharmaceutical composition to a population to a population of patients a modified release (MR2) component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects, the plasma pharmacokinetic profile is characterized by a C_{max} ratio from 6.8 to 8.8, and AUC_{0-inf} ratio from 16.3 to 20.3, where the ratio refers to the ratio of the γ-hydroxybutyrate value to the corresponding 4-((*L*-valyl)oxy)butanoic acid value.

87. The pharmaceutical composition of any one of claims 42 to 79, wherein following oral administration of the combined release (CR2) composition comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects a plasma pharmacokinetic profile 4-((*L*-valyl)oxy)butanoic acid and γ-hydroxybutyrate is bioequivalent to the plasma pharmacokinetic profile as presented in Tables 10 and 11 or shown in FIGS. 19 and 20.

88. The pharmaceutical composition of any one of claims 42 to 87, wherein, at 6 hours following oral administration of the pharmaceutical composition to a population of fasted, healthy subjects, the concentration of γ-hydroxybutyrate in the plasma of the subjects is less than 15 µg /mL, less than 10 µg/mL, or less than 5 µg /mL.

89. The pharmaceutical composition of any one of claims 42 to 88, wherein following oral administration of a pharmaceutical composition comprising from 10 g to 20 g of 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects, the γ-hydroxybutyrate concentration in the plasma of the subjects is greater than the sum of: (a) the AUC_{inf} of γ-hydroxybutyrate following oral administration of the immediate release component; and (b) the AUC_{inf} of γ-hydroxybutyrate following oral administration of the modified release component to the population of fasted, healthy subjects.

90. The pharmaceutical composition of any one of claims 42 to 89, wherein between 6 hours and 8 hours following oral administration of a pharmaceutical composition comprising from 10 g to 20 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects, the γ-hydroxybutyrate concentration in the plasma of the subjects is greater than the sum of: (a) the γ-hydroxybutyrate concentration between 6 hours and 8 hours following oral administration of the

immediate release component; and (b) the γ-hydroxybutyrate concentration between 6 hours and 8 hours following oral administration of the modified release component to the population of fasted, healthy subjects.

91. The pharmaceutical composition of any one of claims 42 to 90, wherein following oral administration of a pharmaceutical composition comprising from 10 g to 20 g 4-((*L*-valyl)oxy)butanoic acid to a population of healthy, fasted subjects, concentration from 6 hours to 8 hours following administration is greater than the concentration of γ-hydroxybutyrate in the plasma of the subjects following administration of the modified release component alone.

92. The pharmaceutical composition of any one of claims 42 to 91, wherein the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of the immediate release component and the modified release component to a population of fasted, healthy subjects is greater than the sum of the sum of the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of the immediate release component alone, and the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of the modified release component alone.

93. The pharmaceutical composition of any one of claims 42 to 92, wherein the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of the immediate release component and the modified release component to a population of subjects is substantially the same as than the sum of the sum of the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of the immediate release component alone, and the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of the modified release component alone.

94. The pharmaceutical composition of any one of claims 42 to 92, wherein the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of a pharmaceutical composition comprising an immediate release component comprising 4.52 g 4-((*L*-valyl)oxy)butanoic acid and a modified release component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects is greater than the sum of the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of an immediate release component comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid alone, and the mean γ-hydroxybutyrate $AUC_{0\text{-}inf}$ following oral administration of a modified release component comprising 7.25 4-((*L*-valyl)oxy)butanoic acid alone.

95. The pharmaceutical composition of any one of claims 42 to 93, wherein the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of a pharmaceutical composition comprising an immediate release component comprising 4.52 g 4-((*L*-valyl)oxy)butanoic acid and a

modified release component comprising 10 g 4-((*L*-valyl)oxy)butanoic acid to a population of fasted, healthy subjects is substantially the same as than the sum of the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of an immediate release component comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid alone, and the mean 4-((*L*-valyl)oxy)butanoic acid $AUC_{0\text{-}inf}$ following oral administration of a modified release component comprising 7.25 g 4-((*L*-valyl)oxy)butanoic acid alone.

96. A method of treating fatigue or excessive daytime sleepiness associated with narcolepsy in a patient comprising orally administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

97. A method of treating narcolepsy, excessive daytime sleepiness, cataplexy, excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with Parkinson's disease, excessive daytime sleepiness associated with multiple sclerosis, cataplexy associated with narcolepsy, fatigue, fatigue associated with Parkinson's diseases, fatigue associated with multiple sclerosis, or fibromyalgia in a patient comprising orally administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

98. A method of treating a symptom associated with narcolepsy, excessive daytime sleepiness, cataplexy, excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with Parkinson's disease, excessive daytime sleepiness associated with multiple sclerosis, cataplexy associated with narcolepsy, fatigue, fatigue associated with Parkinson's diseases, fatigue associated with multiple sclerosis, or fibromyalgia in a patient comprising orally administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

99. A method of treating REM sleep behavior disorder, spasmodic dystonia, schizophrenia, insomnia, insomnia associated with schizophrenia, idiopathic hypersomnia, chronic fatigue syndrome, cluster headache, Alzheimer's disease, essential tremor, post-traumatic stress syndrome, insomnia associated with post-traumatic stress syndrome, or anxiety in a patient comprising orally administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

100. A method of treating a symptom associated with REM sleep behavior disorder, spasmodic dystonia, schizophrenia, insomnia, insomnia associated with schizophrenia, idiopathic

hypersomnia, chronic fatigue syndrome, cluster headache, Alzheimer's disease, essential tremor, post-traumatic stress syndrome, insomnia associated with post-traumatic stress syndrome, or anxiety in a patient comprising orally administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

101. A method of treating a sleep disorder associated with a bacterial infection in a patient comprising orally administering to a patient in need of such treatment, a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

102. The method of claim 101, wherein the bacterial infection is a COVID-19 infection.

103. A method of enhancing cognitive function in a patent having a neurological disorder comprising orally administering to a patient in need of such treatment, a therapeutically effective amount of the pharmaceutical composition of any one of claims 42 to 95.

104. The method of any one of claims 97 to 103, wherein administering comprises administering QD.

105. The method of any one of claims 97 to 103, wherein administering comprises administering BID.

106. The method of any one of claims 97 to 103, wherein administering comprising administering once nightly.

107. A kit comprising the pharmaceutical composition of any one of claims 42 to 95.

CLAIMS

1. A modified release pharmaceutical granulation comprising a plurality of coated granules, wherein,

the granules comprise a core and a modified release coating surrounding the core, wherein,

the modified release coating comprises:

from 50 wt% to 85 wt% of a matrix polymer; and

from 10 wt% to 20 wt% an antistatic agent;

wherein wt% is based on the total weight of the modified release coating;

the core comprises greater than 85 wt% of 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the core; and

the modified release pharmaceutical granulation is characterized by an average particle size (D50) from 150 μm to 400 μm, wherein PSD is determined by sieve analysis.

2. The pharmaceutical granulation of claim 1, wherein the matrix polymer comprises ethylcellulose and hydroxypropyl cellulose.

3. The modified release pharmaceutical granulation of any one of claims 1 and 2, wherein the modified release coating comprises:

from 72 wt% to 92 wt% of the water-insoluble polymer; and

from 0.1 wt% to 10 wt% of the water-soluble polymer,

wherein wt% is based on the total weight of the modified release coating.

4. The modified release pharmaceutical granulation of any one of claims 1 to 3, wherein the antistatic agent comprises talc, magnesium stearate, or a combination thereof.

5. The modified release pharmaceutical granulation of any one of claims 1 to 4, wherein,

the core represents from 65 wt% to 85 wt% of the total weight of the coated granules; and

the modified release modified release coating represents from 15 wt% to 40 wt% of the total weight of the coated granules.

6. The modified release pharmaceutical granulation of any one of claims 1 to 5, wherein the modified release coating has a thickness from 5 μm to 30 μm.

7. The modified release pharmaceutical granulation of any one of claims 1 to 6, wherein the modified release pharmaceutical granulation has a water content less than 2 wt%, wherein wt% is based on the total weight of the modified release pharmaceutical granulation.

8. A pharmaceutical composition comprising:

(a) an immediate release component, wherein the immediate release component comprises: from 2 g to 8 g 4-((*L*-valyl)oxy)butanoic acid; and

(b) the modified release component, wherein the modified release component comprises: from 8 g to 16 g 4-((*L*-valyl)oxy)butanoic acid, and
the modified release pharmaceutical granulation of any one of claims 1 to 7.

9. The pharmaceutical composition of claim 8, wherein the immediate release component comprises a plurality of immediate release microparticles.

10. The pharmaceutical composition of any one of claims 8 to 9, wherein the immediate release microparticles comprise greater than 90 wt% 4-((*L*-valyl)oxy)butanoic acid, wherein wt% is based on the total weight of the immediate release microparticles.

11. The pharmaceutical composition of any one of claims 8 to 9, wherein the immediate release microparticles have a volume mean diameter D(4.3) from 200 μm to 500 μm.

12. The pharmaceutical composition any one of claims 8 to 11, wherein the immediate release microparticles have an average particle diameter (D50) from 75 μm to 450 μm as determined by sieve analysis or by laser diffraction.

13. The pharmaceutical composition any one of claims 8 to 12, wherein,

the immediate release component comprises from 20 wt% to 40 wt% 4-((*L*-valyl)oxy)butanoic acid; and

the modified release component comprises form 60 wt% to 80 wt% 4-((*L*-valyl)oxy)butanoic acid

wherein wt% is based on the total weight of 4-((*L*-valyl)oxy)butanoic acid in the pharmaceutical composition.

14. The pharmaceutical composition any one of claims 8 to 13, wherein a weight ratio of 4-((*L*-valyl)oxy)butanoic acid in the immediate release component to 4-((*L*-valyl)oxy)butanoic acid in the modified release component is from 1:2 to 1:3.

15. The pharmaceutical composition any one of claims 8 to 14, wherein the immediate release component comprises a solution suitable for oral administration.

16. The pharmaceutical composition of claim 15, wherein the modified release component comprises the modified release granules suspended in the solution.

17. Use of the pharmaceutical granulation of any one of claims 1 to 7 or the pharmaceutical composition of any one of claims 8 to 16 for use in the manufacture of a medicament for the treatment of narcolepsy, excessive daytime sleepiness, cataplexy, excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with Parkinson's disease, excessive daytime sleepiness associated with multiple sclerosis, cataplexy associated with narcolepsy, fatigue, fatigue associated with Parkinson's diseases, fatigue associated with multiple sclerosis, or fibromyalgia.

18. Use of the pharmaceutical granulation of any one of claims 1 to 7 or the pharmaceutical composition of any one of claims 8 to 16 for use in the manufacture of a medicament for the treatment of a REM sleep behavior disorder, spasmodic dystonia, schizophrenia, insomnia, insomnia associated with schizophrenia, idiopathic hypersomnia, chronic fatigue syndrome, cluster headache, Alzheimer's disease, essential tremor, post-traumatic stress syndrome, insomnia associated with post-traumatic stress syndrome, or anxiety.

19. Use of the pharmaceutical granulation of any one of claims 1 to 7 or the pharmaceutical composition of any one of claims 8 to 16 for use in the manufacture of a medicament for the treatment of a sleep disorder associated with a bacterial infection.

20. Use of the pharmaceutical granulation of any one of claims 1 to 7 or the pharmaceutical composition of any one of claims 8 to 16 for use in the manufacture of a medicament for enhancing cognitive function.