

WHAT IS CLAIMED IS:

1. A method for treating suicidality in a subject in need thereof, the method comprising intranasally administering a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof, to the subject.
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2. A method for treating suicidal ideation in a subject in need thereof, the method comprising intranasally administering a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof, to the subject.
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3. A method for treating major depressive disorder in a subject in need thereof, the method comprising intranasally administering a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof, to the subject.
- 15 4. The method of any one of claims 1-3, further comprising administering one or more additional therapies consisting of typical antipsychotics, atypical antipsychotics, antidepressants, electroconvulsive therapy, transcranial magnetic stimulation, benzodiazepines, mood stabilizers, and pramipexole.
- 20 5. The method of any one of claims 1-4, wherein the subject has previously been administered one or more additional therapies consisting of typical antipsychotics, atypical antipsychotics, antidepressants, electroconvulsive therapy, transcranial magnetic stimulation, benzodiazepines, mood stabilizers, and pramipexole; wherein the subject was not responsive to the previous one or more therapies.
- 25 6. The method of claim 4 or 5, wherein the typical antipsychotic is chlorpromazine, chlorprothixene, levomepromazine, mesoridazine, periciazine, promazine, loxapine, molindone, perphenazine, thiothixene, droperidol, flupentixol, fluphenazine, haloperidol, pimozide, prochlorperazine, thioproperazine, trifluoperazine, or
30 zuclopenthixol.

7. The method of claim 5 or 6, wherein the atypical antipsychotic is aripiprazole, risperidone, olanzapine, quetiapine, asenapine, paliperidone, ziprasidone, or lurasidone.

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8. The method of claim 4 or 5, wherein the antidepressant consists of atypical antidepressants, selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and selective norepinephrine reuptake inhibitors.

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9. The method of claim 8, wherein the atypical antidepressant is mirtazapine, mianserin, bupropion, trazodone, nefazodone, tianeptine, opipramol, agomelatine, vilazodone, or vortioxetine.

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10. The method of claim 8, wherein the selective serotonin reuptake inhibitor is citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline.

11. The method of claim 8, wherein the selective serotonin and norepinephrine reuptake inhibitor is atomoxetine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran, sibutramine, tramadol, or venlafaxine.

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12. The method of claim 8, wherein the monoamine oxidase inhibitor is moclobemide, rasagiline, selegiline, or safinamide.

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13. The method of claim 8, wherein the selective norepinephrine reuptake inhibitor is reboxetine.

14. The method of claim 4 or 5, wherein the benzodiazepine is alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, or triazolam.

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15. The method of claim 4 or 5, wherein the mood stabilizer is lithium, valproic acid, lamotrigine, or carbamazepine.

16. The method of claim 4 or 5, wherein the one or more therapies are
5 electroconvulsive therapy or transcranial magnetic stimulation.

17. The method of any one of claims 4-16, further comprising decreasing the duration of hospitalization of the subject relative to administration of an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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18. The method of any one of claims 4-17, wherein the suicidality of the subject resolves faster relative to administration of an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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19. The method of any one of claims 4-18, wherein the recurrence of suicidality in the subject decreases relative to administration of an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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20. The method of any one of claims 4-16, wherein the depression of the subject resolves faster relative to administration of an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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21. The method of any one of claims 4-20, wherein the dose of the one or more therapies administered in combination with the intranasal racemic ketamine, or a pharmaceutically acceptable salt thereof, is reduced relative to the dose of the one or more therapies administered to the subject prior to treatment with the intranasal racemic ketamine, or a pharmaceutically acceptable salt thereof.

22. The method of any one of claims 17-21, wherein the one or more therapies is a selective serotonin reuptake inhibitor, a selective serotonin and norepinephrine reuptake inhibitor, or a selective norepinephrine reuptake inhibitor.

5 23. The method of any one of claims 17-22, wherein the one or more therapies is sertraline.

24. The method of any one of claims 17-22, wherein the one or more additional therapies is venlafaxine.

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25. The method of any one of claims 4-24, wherein the subject does not experience a clinically significant weight gain relative to the administration of the one or more additional therapies in the absence of intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

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26. The method of any one of claims 1-25, wherein the magnitude of one or more side effects of the intranasal racemic ketamine, or a pharmaceutically acceptable salt thereof, are reduced relative to an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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27. The method of any one of claims 1-26, wherein the subject exhibits reduction in one or more side effects as compared to an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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28. The method of any one of claims 1-27, wherein one or more side effects of the one or more additional therapies are reduced relative to an equivalent dose of the one or more additional therapies in the absence of intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

29. A method for reducing one or more side effects of ketamine in a subject in need thereof, the method comprising intranasally administering a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof, to the subject.

5 30. The method of claim 29, wherein the one or more side effects are reduced relative to the one or more side effects observed after intranasal administration of an equivalent dose of (S)-ketamine, or a pharmaceutically acceptable salt thereof.

10 31. The method of claim 29, wherein the one or more side effects are reduced relative to the one or more side effects observed after administration of an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof

15 32. The method of any one of claims 29-31 wherein the one or more side effects comprise cognitive impairment, motor impairment, vertigo, nausea, vomiting, sweating, increased blood pressure, ulcerative cystitis, or interstitial cystitis.

20 33. The method of claim 32, wherein the cognitive impairment comprises one or more of psychotomimetic effects, dizziness, dysgeusia, sedation, dissociation, euphoria, changes in hearing, changes in vision, and hallucinations.

34. The method of claim 33, wherein the cognitive impairment comprises sedation.

25 35. The method of claim 33 or 34, wherein the cognitive impairment is sedation.

36. The method of any one of claims 32-35, wherein the motor impairment comprises tremors, issues with balance, or dystonic movements.

30 37. The method of claims 1, 2, 4-19, or 21-36, wherein the Columbia-Suicide Severity Rating Scale (CSSRS) score is greater than 3 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

38. The method of claims 1, 2, 4-19, or 21-37, wherein the CSSRS score is 6 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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39. The method of claims 1, 2, 4-19, or 21-37, wherein the CSSRS score is 7 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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40. The method of claims 1, 2, 4-19, or 21-39, wherein the CSSRS score is determined about 1 hour to about 24 hours prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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41. The method of claims 1, 2, 4-19, or 21-40, wherein the CSSRS decreases by 1 to 7 units after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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42. The method of claims 1, 2, 4-19, or 21-41, wherein the CSSRS decreases by 1 to 5 units after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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43. The method of claim 41 or 42, wherein a first CSSRS score is determined about 1 hour to about 12 hours prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof; and a second CSSRS score is determined about 1 hour to about 12 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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44. The method of claim 43, wherein the first CSSRS score from the subject is determined about 4 hours to about 8 hours prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

45. The method of any claim 43 or 44, wherein the second CSSRS score from the subject is determined about 4 hours to about 8 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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46. The method of claim any one of claims 1-45, wherein the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score of the subject is 4 or 5, prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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47. The method of claim any one of claims 1-46, wherein the MOAA/S score of the subject is 5, prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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48. The method of claim any one of claims 1-47, wherein the MOAA/S score of the subject is determined about 1 hour to about 24 hours prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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49. The method of claim any one of claims 1-48, wherein the MOAA/S score of the subject is 5, about 10 minutes to about 2 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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50. The method of claim 49, wherein the MOAA/S score of the subject is 1 to 4 units higher about 10 minutes to about 2 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, than a subject administered an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

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51. The method of claim 49, wherein the MOAA/S score of the subject is 1 to 4 units higher after about 10 minutes to about 2 hours after intranasal administration of the

racemic ketamine, or a pharmaceutically acceptable salt thereof, than a subject administered an equivalent dose of (S)-ketamine, or a pharmaceutically acceptable salt thereof.

5 52. The method of claim 50, wherein the rate of increase in the MOAA/S score is greater than the rate of increase in the MOAA/S score in a subject administered an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

10 53. The method of claim 51, wherein the rate of increase in the MOAA/S score is greater than the rate of increase in the MOAA/S score in a subject administered an equivalent dose of (S)-ketamine, or a pharmaceutically acceptable salt thereof.

 54. The method of claim 49, wherein the MOAA/S score of the subject is 2 to
15 4 units higher about 10 minutes to about 2 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, than a subject administered an equivalent dose of (S)-ketamine, or a pharmaceutically acceptable salt thereof, and 2 to 4 units higher about 10 minutes to about 2 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, than
20 a subject administered an equivalent dose of intravenous racemic ketamine, or a pharmaceutically acceptable salt thereof.

 55. The method of any one of claims 1-54, wherein the Bowdle Visual Analog Scale score is about 0 to about 50, about 45 minutes to about 24 hours prior to intranasal
25 administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

 56. The method of any one of claims 1-55, wherein the Bowdle Visual Analog Scale score is about 0 to about 50, about 45 minutes to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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57. The method of any one of claims 1-56, wherein the Bowdle Visual Analog Scale score is reduced by about 10 to about 1300, about 45 minutes to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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58. The method of claim 56 or 57, wherein the Bowdle Visual Analog Scale score is determined about 1 hour to about 4 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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59. The method of any one of claims 1-58, wherein the Clinician Administered Dissociative States Scale score is about 0 to about 10, about 45 minutes to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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60. The method of claim 59, wherein the Clinician Administered Dissociative States Scale score is reduced by about 1 to about 92, about 45 minutes to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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61. The method of claim 60, wherein the Clinician Administered Dissociative States Scale score is determined about 1 hour to about 4 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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62. The method of any one of claims 1-51, wherein the Profile of Mood States score of the subject is substantially the same from about 1 hour to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

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63. The method of any one of claims 1-62, wherein the Profile of Mood States score of the subject is substantially the same about 1 hour to about 12 hours after intranasal

administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

64. The method of any one of claims 1-63, wherein the Profile of Mood States
5 score of the subject is substantially the same from about 1 hour to about 4 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

65. The method of claim any one of claims 1-54, wherein the Choice Reaction
10 Time Test score of the subject is substantially the same from about 1 hour to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

66. The method of claim any one of claims 1-54, wherein the Choice Reaction
15 Time Test score of the subject is substantially the same from about 1 hour to about 12 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

67. The method of claim any one of claims 1-66, wherein the Choice Reaction
20 Time Test score of the subject is substantially the same from about 1 hour to about 4 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

68. The method of claim any one of claims 1-67, wherein the Sternberg Short-
25 Term Memory score of the subject is substantially the same from about 1 hour to about 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

69. The method of claim any one of claims 1-68, wherein the Sternberg Short-
30 Term Memory score of the subject is substantially the same from about 1 hour to about 12

hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof, as prior to the administration.

70. The method of claim any one of claims 1-69, wherein the Sternberg Short-
5 Term Memory score of the subject is substantially the same from about 1 hour to about 4
hours after intranasal administration of the racemic ketamine, or a pharmaceutically
acceptable salt thereof, as prior to the administration.

71. The method of any one of claims 1-70, wherein the subject has a score of 1
10 or 0 on the Subject-Rated Assessment of Intranasal Irritation after intranasal administration
of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

72. The method of any one of claims 1-49 or 58-71, wherein no clinically
meaningful sedation is observed in the subject within about 24 hours after intranasal
15 administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

73. The method of claim 72, wherein no clinically meaningful sedation is
observed in the subject at about 4 hours after intranasal administration of the racemic
ketamine, or a pharmaceutically acceptable salt thereof.

20 74. The method of claim 72, wherein no clinically meaningful sedation is
observed in the subject at about 1 hour after intranasal administration of the racemic
ketamine, or a pharmaceutically acceptable salt thereof.

25 75. The method of any one of claims 1-49 or 58-74, wherein no clinically
meaningful dissociation is observed in the subject within about 24 hours after intranasal
administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

76. The method of claim 75, wherein no clinically meaningful dissociation is
30 observed in the subject at about 4 hours after intranasal administration of the racemic
ketamine, or a pharmaceutically acceptable salt thereof.

77. The method of claim 75, wherein no clinically meaningful dissociation is observed in the subject at about 1 hour after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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78. The method of any one of claims 1-77, wherein the subject has been previously diagnosed with one or more of: suicidality, suicidal ideation, major depressive disorder, treatment-resistant depression, and post-traumatic stress disorder.

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79. The method of any one of claims 1-78, wherein the subject is currently suffering from one or more of: suicidality, suicidal ideation, major depressive disorder, treatment-resistant depression, and post-traumatic stress disorder.

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80. The method of claim 77 or 78, wherein the treatment-resistant depression is Stage I to Stage IV.

81. The method of claim 77 or 78, wherein the treatment resistant depression is Stage V.

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82. The method of claim 77 or 78, wherein the Massachusetts General Hospital Staging Method to Classify Treatment Resistant Depression score of the subject is from 2 and 10, prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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83. The method of claim 77 or 78, wherein the Antidepressant Treatment History Form score of the subject is 1 to 4, prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

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84. The method of claim 77 or 78, wherein the subject exhibits one or more of the following characteristics: unwanted upsetting memories, nightmares, flashbacks, emotional distress after exposure to traumatic reminders, or physical reactivity after exposure to traumatic reminders; and one or more of trauma-related thoughts or feelings

and trauma-related external reminders, prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

85. The method of claim 84, wherein the subject exhibits two or more of the
5 following characteristics: inability to recall key features of a traumatic event, overly negative thoughts and assumptions about oneself or the world, exaggerated blame of self or others for causing a traumatic event, negative affect, decreased interest in activities, feeling isolated, and difficulty experiencing positive affect.

10 86. The method of claim 84 or 85, wherein the subject exhibits one or more of the following characteristics: irritability or aggression, risky or destructive behavior, hypervigilance, heightened startle reaction, difficulty concentrating, and difficulty sleeping.

15 87. The method of any one of claims 84-86, wherein the characteristics are present for more than about 1 month, create distress and/or functional impairment in social or occupational situations, and are not due to medication or substance abuse.

88. The method of any one of claims 1-87, wherein about 30 mg to about 90
20 mg of racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered to the subject.

89. The method of any one of claims 1-88, wherein about 30 mg to about 60
mg of racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally
25 administered to the subject.

90. The method of any one of claims 1-89, wherein about 60 mg to about 90
mg of racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally
administered to the subject.

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91. The method of any one of claims 1-90, wherein about 30 mg, about 60 mg, about 75 mg, or about 90 mg of racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered to the subject, preferably about 60 mg per dose.

5 92. The method of any one of claims 1-91, wherein the $t_{1/2}$ for ketamine is about 2 hours to about 9 hours following intranasal administration of racemic ketamine.

93. The method of any one of claims 1-92, wherein the $t_{1/2}$ for ketamine is about 4 hours to about 7 hours following intranasal administration of racemic ketamine.

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94. The method of any one of claims 1-93, wherein the $t_{1/2}$ for 6-hydroxynorketamine is about 5.5 hours to about 21.5 hours following intranasal administration of racemic ketamine.

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95. The method of any one of claims 1-94, wherein the $t_{1/2}$ for 6-hydroxynorketamine is about 10 hours to about 12 hours following intranasal administration of racemic ketamine.

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96. The method of any one of claims 1-95, wherein the $t_{1/2}$ for norketamine is about 4.5 hours to about 12.5 hours following intranasal administration of racemic ketamine.

97. The method of any one of claims 1-96, wherein the $t_{1/2}$ for norketamine is about 7 hours to about 8 hours following intranasal administration of racemic ketamine.

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98. The method of any one of claims 1-97, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered from about once per day to about once per month.

99. The method of any one of claims 1-98, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered from about once per day to about once every two weeks.

5 100. The method of any one of claims 1-99, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered from about once per day to about once per week.

10 101. The method of any one of claims 1-100, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered from about once per week to about twice per week.

102. The method of any one of claims 1-101, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered twice per week.

15 103. The method of any one of claims 1-102, wherein racemic ketamine, or a pharmaceutically acceptable salt thereof, is intranasally administered once per day, once every other day, three times per week, twice per week, or once per week.

20 104. The method of any one of claims 1-103, wherein the $T_{\max}$ of the ketamine is from about 20 minutes to about 120 minutes following intranasal administration of racemic ketamine.

25 105. The method of any one of claims 1-104, wherein the $T_{\max}$ of the ketamine is from about 30 minutes to about 90 minutes following intranasal administration of racemic ketamine.

30 106. The method of any one of claims 1-105, wherein the $T_{\max}$ of 6-hydroxynorketamine is from about 45 minutes to about 8 hours following intranasal administration of racemic ketamine.

107. The method of any one of claims 1-106, wherein the $T_{\max}$ of norketamine is from about 45 minutes to about 360 minutes following intranasal administration of racemic ketamine.

5 108. The method of any one of claims 1-107, wherein the $C_{\max}$ of ketamine is from about 15 ng/mL to about 225 ng/mL following intranasal administration of racemic ketamine.

10 109. The method of any one of claims 1-108, wherein the $C_{\max}$ of ketamine is from about 70 ng/mL to about 205 ng/mL following intranasal administration of racemic ketamine.

15 110. The method of any one of claims 1-109, wherein the $C_{\max}$ of 6-hydroxynorketamine is from about 15 ng/mL to about 275 ng/mL following intranasal administration of racemic ketamine.

20 111. The method of any one of claims 1-110, wherein the $C_{\max}$ of 6-hydroxynorketamine is from about 80 ng/mL to about 265 ng/mL following intranasal administration of racemic ketamine.

25 112. The method of any one of claims 1-111, wherein the $C_{\max}$ of norketamine is from about 40 ng/mL to about 375 ng/mL following intranasal administration of racemic ketamine.

30 113. The method of any one of claims 1-112, wherein the $C_{\max}$ of norketamine is from about 160 ng/mL to about 195 ng/mL following intranasal administration of racemic ketamine.

30 114. The method of any one of claims 1-113, wherein the AUC_{0-4} for 6-hydroxynorketamine is from about 300 ng*h/mL to about 3,100 ng*h/mL following intranasal administration of racemic ketamine.

115. The method of any one of claims 1-114, wherein the AUC_{0-t} for 6-hydroxynorketamine is from about 850 ng*h/mL to about 950 ng*h/mL following intranasal administration of racemic ketamine.

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116. The method of any one of claims 1-115, wherein the AUC_{0-t} for norketamine is from about 250 ng*h/mL to about 2,200 ng*h/mL following intranasal administration of racemic ketamine.

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117. The method of any one of claims 1-116, wherein the AUC_{0-t} for norketamine is from about 900 ng*h/mL to about 1,550 ng*h/mL following intranasal administration of racemic ketamine.

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118. The method of any one of claims 1-117, wherein the AUC_{0-inf} for 6-hydroxynorketamine is from about 375 ng*h/mL to about 3,700 ng*h/mL following intranasal administration of racemic ketamine.

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119. The method of any one of claims 1-118, wherein the AUC_{0-inf} for 6-hydroxynorketamine is from about 1,200 ng*h/mL to about 1,400 ng*h/mL following intranasal administration of racemic ketamine.

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120. The method of any one of claims 1-119 wherein the AUC_{0-inf} for norketamine is from about 250 ng*h/mL to about 875 ng*h/mL following intranasal administration of racemic ketamine.

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121. The method of any one of claims 1-120, wherein the AUC_{0-inf} for norketamine is from about 450 ng*h/mL to about 675 ng*h/mL following intranasal administration of racemic ketamine.

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122. The method of claim 33, wherein the cognitive impairment comprises dissociation.

123. The method of claim 33 or 34, wherein the cognitive impairment is dissociation.

5 124. The method of any one of claims 1-123, wherein intranasal administration of the racemic ketamine exhibits one or more of:

an AUC_{0-t} of norketamine that is at least 1.5 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

10 an AUC_{0-inf} of norketamine that is at least 1.5 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

a C_{max} of norketamine that is at least 2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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125. The method of any one of claims 1-124, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of norketamine that is about 1.7 to about 2.5 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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126. The method of any one of claims 1-125, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of norketamine that is about 1.9 to about 2.3 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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127. The method of any one of claims 1-126, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-inf} of norketamine that is about 1.5 to about 2.5 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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128. The method of any one of claims 1-127, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of norketamine that is about 1.8 to about 2.2 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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129. The method of any one of claims 1-128, wherein intranasal administration of the racemic ketamine exhibits a C_{max} of norketamine that is about 2.2 to about 3.5 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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130. The method of any one of claims 1-129, wherein intranasal administration of the racemic ketamine exhibits a C_{max} of norketamine that is about 2.4 to about 3.2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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131. The method of any one of claims 1-130, wherein intranasal administration of the racemic ketamine exhibits a T_{max} of norketamine that is about 80% to about 125% of the T_{max} of norketamine exhibited by an intravenous administration of an equivalent dose of racemic ketamine.

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132. The method of any one of claims 1-131, wherein intranasal administration of the racemic ketamine exhibits a T_{max} of norketamine that is about 90% to about 110% of the T_{max} of norketamine exhibited by an intravenous administration of an equivalent dose of racemic ketamine.

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133. The method of any one of claims 1-132, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of norketamine is determined following one dose of racemic ketamine.

134. The method of any one of claims 1-132, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of norketamine is determined following two doses of racemic ketamine.

5 135. The method of any one of claims 1-132, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of norketamine is determined following three doses of racemic ketamine.

10 136. The method of any one of claims 1-135, wherein intranasal administration of the racemic ketamine exhibits one or more of:

an AUC_{0-t} of hydroxynorketamine that is at least 1.5 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

15 an AUC_{0-inf} of hydroxynorketamine that is at least 1.2 times higher than the AUC_{0-inf} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

a C_{max} of hydroxynorketamine that is at least 2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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137. The method of any one of claims 1-136, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of hydroxynorketamine that is about 1.7 to about 2.5 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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138. The method of any one of claims 1-137, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of hydroxynorketamine that is about 1.9 to about 2.3 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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139. The method of any one of claims 1-138, wherein intranasal administration of the racemic ketamine exhibits an $AUC_{0-\infty}$ of hydroxynorketamine that is about 1.5 to about 2.5 times higher than the $AUC_{0-\infty}$ of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

5

140. The method of any one of claims 1-139, wherein intranasal administration of the racemic ketamine exhibits an AUC_{0-t} of hydroxynorketamine that is about 1.7 to about 2.1 times higher than the $AUC_{0-\infty}$ of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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141. The method of any one of claims 1-140, wherein intranasal administration of the racemic ketamine exhibits a C_{max} of hydroxynorketamine that is about 2.2 to about 3.2 times higher than the C_{max} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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142. The method of any one of claims 1-141, wherein intranasal administration of the racemic ketamine exhibits a C_{max} of hydroxynorketamine that is about 2.4 to about 2.8 times higher than the C_{max} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

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143. The method of any one of claims 1-142, wherein intranasal administration of the racemic ketamine exhibits a T_{max} of hydroxynorketamine that is about 80% to about 125% of the T_{max} of hydroxynorketamine exhibited by an intravenous administration of an equivalent dose of racemic ketamine.

25

144. The method of any one of claims 1-143, wherein intranasal administration of the racemic ketamine exhibits a T_{max} of hydroxynorketamine that is about 90% to about 110% of the T_{max} of hydroxynorketamine exhibited by an intravenous administration of an equivalent dose of racemic ketamine.

30

145. The method of any one of claims 1-144, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of hydroxynorketamine is determined following one dose of racemic ketamine.

5 146. The method of any one of claims 1-144, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of hydroxynorketamine is determined following two doses of racemic ketamine.

10 147. The method of any one of claims 1-144, wherein one or more of the AUC_{0-t} , AUC_{0-inf} , C_{max} , and T_{max} of hydroxynorketamine is determined following three doses of racemic ketamine.

15 148. The method of any one of claims 1-147, wherein the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score of the subject is from 20-60 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

20 149. The method of any one of claims 1-148, wherein the MADRS Total Score of the subject is from 30-60 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

25 150. The method of any one of claims 1-149, wherein the MADRS Total Score of the subject is reduced by at least 50% 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

 151. The method of any one of claims 1-150, wherein the MADRS Total Score of the subject is less than or equal to 15 units 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

152. The method of any one of claims 1-151, wherein the MADRS Total Score of the subject is less than or equal to 12 units 48 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

5 153. The method of any one of claims 1-152, wherein the MADRS Item 10 Score of the subject is 4, 5, or 6 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

10 154. The method of any one of claims 1-153, wherein the MADRS Item 10 Score of the subject is 5 or 6 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

15 155. The method of any one of claims 1-154, wherein the MADRS Item 10 Score of the subject is reduced by at least 1 unit 4 hours administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

20 156. The method of any one of claims 1-155, wherein the Clinical Global Impression of Severity for Suicide Ideation and Behavior (CGIS-SI/B) score of the subject is 4 or 5 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

25 157. The method of any one of claims 1-156, wherein the CGIS-SI/B score of the subject is 1 or 2 units 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

30 158. The method of any one of claims 1-157, wherein the Sheehan – Suicidality Tracking Scale (S-STs) Clinically Meaningful Change Measure (CMCM) score of the subject is from 15-52 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

159. The method of any one of claims 1-158, wherein the S-STS CMCM score of the subject is from 20-52 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

5 160. The method of any one of claims 1-159, wherein the -STS CMCM score of the subject is reduced by at least 50% 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

10 161. The method of any one of claims 1-160, wherein the -STS CMCM score of the subject is from 1-3 units 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

15 162. The method of any one of claims 1-161, wherein the Sheehan – Suicidality Tracking Scale (S-STS) Clinically Meaningful Change Measure (CMCM) Risk of Suicide at Within the Next 7 Days score of the subject is from 5 to 10 units prior to intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

20 163. The method of any one of claims 1-162, wherein the S-STS CMCM Risk of Suicide at Within the Next 7 Days score of the subject is reduced by at least 50% 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

25 164. The method of any one of claims 1-163, wherein the S-STS CMCM Risk of Suicide at Within the Next 7 Days score of the subject is from 0-2 units 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

165. The method of any one of claims 1-163, wherein the S-STS CMCM Risk of Suicide at Within the Next 7 Days score of the subject is 0 or 1 unit 96 hours after

intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

166. The method of any one of claims 1-165, wherein the Modified Observer's
5 Assessment of Alertness/Sedation (MOAA/S) score of the subject is 5 units prior to
intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt
thereof.

167. The method of any one of claims 1-166, wherein the MOAA/S score of the
10 subject is 4 or 5 units from 15 minutes to 6 hours after intranasal administration of the
racemic ketamine, or a pharmaceutically acceptable salt thereof.

168. The method of any one of claims 1-167, wherein the Clinician Administered
Dissociative States Scale (CADSS) score of the subject is zero units prior to intranasal
15 administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

169. The method of any one of claims 1-168, wherein the CADSS score of the
subject is zero units from 1 hour to 6 hours after intranasal administration of the racemic
ketamine, or a pharmaceutically acceptable salt thereof.

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170. The method of any one of claims 1-169, wherein the C-SSRS score of the
subject is from 2 units to 9 units prior to intranasal administration of the racemic ketamine,
or a pharmaceutically acceptable salt thereof.

25 171. The method of any one of claims 1-170, wherein the C-SSRS score of the
subject is from 2 units to 5 units prior to intranasal administration of the racemic ketamine,
or a pharmaceutically acceptable salt thereof.

172. The method of any one of claims 1-171, wherein the CSSR-S score of the subject is zero units 24 hours after intranasal administration of the racemic ketamine, or a pharmaceutically acceptable salt thereof.

- 5 173. A method of treating suicidality in a subject in need thereof, comprising:
- (a) determining if the subject has one or more of:
- (i) a MADRS Total Score of at least 20 units;
- (ii) a MADRS Item 10 Score of 4, 5, or 6 units;
- (iii) a CGIS-SI/B score of 4 or 5 units;
- 10 (iv) a S-STS CMCM score of at least 15 units;
- (v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5 units; and
- (vi) a C-SSRS score of at least 2; and
- (b) intranasally administering to the subject a therapeutically effective amount of
- 15 racemic ketamine, or a pharmaceutically acceptable salt thereof;
- wherein intranasal administration of the racemic ketamine exhibits one or more of:
- an AUC_{0-t} of norketamine that is at least 1.5 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of
- 20 racemic ketamine;
- an AUC_{0-inf} of norketamine that is at least 1.5 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and
- a C_{max} of norketamine that is at least 2 times higher than the C_{max} of
- 25 norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

174. A method of treating suicidal ideation in a subject in need thereof, comprising:

- 30 (a) determining if the subject has one or more of:

- (i) a MADRS Total Score of at least 20 units;
(ii) a MADRS Item 10 Score of 4, 5, or 6 units;
(iii) a CGIS-SI/B score of 4 or 5 units;
(iv) a S-STS CMCM score of at least 15 units;
5 (v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5 units; and
(vi) a C-SSRS score of at least 2; and
(b) intranasally administering to the subject a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof;
10 wherein intranasal administration of the racemic ketamine exhibits one or more of:
an AUC_{0-t} of norketamine that is at least 1.5 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;
15 an AUC_{0-inf} of norketamine that is at least 1.5 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and
a C_{max} of norketamine that is at least 2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.
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175. A method of treating major depressive disorder in a subject in need thereof, comprising:

- (a) determining if the subject has one or more of:
25 (i) a MADRS Total Score of at least 20 units;
(ii) a MADRS Item 10 Score of 4, 5, or 6 units;
(iii) a CGIS-SI/B score of 4 or 5 units;
(iv) a S-STS CMCM score of at least 15 units;
(v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5
30 units; and

(vi) a C-SSRS score of at least 2; and

(b) intranasally administering to the subject a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof;

wherein intranasal administration of the racemic ketamine exhibits one or more of:

an AUC_{0-t} of norketamine that is at least 1.5 times higher than the AUC_{0-t} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

an AUC_{0-inf} of norketamine that is at least 1.5 times higher than the AUC_{0-inf} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

a C_{max} of norketamine that is at least 2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

176. A method of treating suicidality in a subject in need thereof, comprising:

(a) determining if the subject has one or more of:

(i) a MADRS Total Score of at least 20 units;

(ii) a MADRS Item 10 Score of 4, 5, or 6 units;

(iii) a CGIS-SI/B score of 4 or 5 units;

(iv) a S-STS CMCM score of at least 15 units;

(v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5 units; and

(vi) a C-SSRS score of at least 2; and

(b) intranasally administering to the subject a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof;

wherein intranasal administration of the racemic ketamine exhibits one or more of:

an AUC_{0-t} of hydroxynorketamine that is at least 1.5 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

an AUC_{0-inf} of hydroxynorketamine that is at least 1.2 times higher than the AUC_{0-inf} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

a C_{max} of hydroxynorketamine that is at least 2 times higher than the C_{max} of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

177. A method of treating suicidal ideation in a subject in need thereof, comprising:

(a) determining if the subject has one or more of:

(i) a MADRS Total Score of at least 20 units;

(ii) a MADRS Item 10 Score of 4, 5, or 6 units;

(iii) a CGIS-SI/B score of 4 or 5 units;

(iv) a S-STS CMCM score of at least 15 units;

(v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5 units; and

(vi) a C-SSRS score of at least 2; and

(b) intranasally administering to the subject a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof;

wherein intranasal administration of the racemic ketamine exhibits one or more of:

an AUC_{0-t} of hydroxynorketamine that is at least 1.5 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

an AUC_{0-inf} of hydroxynorketamine that is at least 1.2 times higher than the AUC_{0-inf} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

a $C_{\max}$ of hydroxynorketamine that is at least 2 times higher than the $C_{\max}$ of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

5 178. A method of treating major depressive disorder in a subject in need thereof, comprising:

(a) determining if the subject has one or more of:

(i) a MADRS Total Score of at least 20 units;

(ii) a MADRS Item 10 Score of 4, 5, or 6 units;

10 (iii) a CGIS-SI/B score of 4 or 5 units;

(iv) a S-STS CMCM score of at least 15 units;

(v) a S-STS CMCM Risk of Suicide at Within the Next 7 Days score of at least 5 units; and

(vi) a C-SSRS score of at least 2; and

15 (b) intranasally administering to the subject a therapeutically effective amount of racemic ketamine, or a pharmaceutically acceptable salt thereof;

wherein intranasal administration of the racemic ketamine exhibits one or more of:

20 an AUC_{0-t} of hydroxynorketamine that is at least 1.5 times higher than the AUC_{0-t} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine;

an AUC_{0-inf} of hydroxynorketamine that is at least 1.2 times higher than the AUC_{0-inf} of hydroxynorketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine; and

25 a $C_{\max}$ of hydroxynorketamine that is at least 2 times higher than the $C_{\max}$ of norketamine exhibited by intravenous administration of an equivalent dose of racemic ketamine.

30 179. The method of any one of claims 173-178, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of

Suicide at Within the Next 7 Days, and C-SSRS scores is reduced by at least 50% 96 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

5 180. The method of any one of claims 173-179, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of Suicide at Within the Next 7 Days, and C-SSRS scores is reduced by at least 50% 48 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

10 181. The method of any one of claims 173-180, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of Suicide at Within the Next 7 Days, and C-SSRS scores is reduced by at least 50% 24 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

15 182. The method of any one of claims 173-181, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of Suicide at Within the Next 7 Days, and C-SSRS scores is below the standard for remission 96 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

20 183. The method of any one of claims 173-182, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of Suicide at Within the Next 7 Days, and C-SSRS scores is below the standard for remission 48 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.

25 184. The method of any one of claims 173-183, wherein one or more of the MADRS Total, MADRS Item 10, CGIS-SI/B, S-STS CMCM, S-STS CMCM Risk of

Suicide at Within the Next 7 Days, and C-SSRS scores is below the standard for remission 24 hours after intranasal administration of racemic ketamine, or a pharmaceutically acceptable salt thereof.