

METHODS OF TREATING PSYCHIATRIC DISORDERS OR PAIN USING (R)-2-(4-FLUOROPHENYL)-2-(METHYLAMINO)CYCLOHEXAN-1-ONE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

FIELD OF THE DISCLOSURE

The present disclosure relates to dosing regimens of (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or pharmaceutically acceptable salts thereof for effectively treating psychiatric disorders or pain in a subject in need thereof.

BACKGROUND OF THE DISCLOSURE

Approximately one third of patients with major depressive disorder (MDD) fail to achieve remission of their symptoms, even after multiple rounds of treatment with several known classes of antidepressants, including selective serotonin reuptake inhibitors. This high prevalence of treatment-resistant depression (TRD) highlights the need for new, more efficacious pharmacotherapies for depression that will target new mechanisms and/or patient populations. In recent years, ketamine, a drug long used as a dissociative anesthetic, has attracted considerable attention for its secondary use as a rapid-acting antidepressant with robust efficacy, even in patients with TRD. Importantly, the *S* enantiomer of ketamine (S-ketamine; esketamine; S-ket) has recently been approved by the United States Food and Drug Administration as a treatment for depression.

Unfortunately, the potent dissociative anesthetic effects of ketamine and S-ket make these drugs attractive to recreational drug users and limit the broad clinical utility of these compounds by restricting their use to circumstances under the direct supervision of a medical provider. Given that the primary molecular target of ketamine is the *N*-methyl-D-aspartate receptor (NMDAR), inhibition of which is responsible for the drug's anesthetic effects, many have proposed that inhibition of this target is also responsible for the antidepressant effects of ketamine. Such a mechanism suggests that the antidepressant and dissociative effects of ketamine might be inseparable at the mechanistic level. However, a number of lines of evidence question this hypothesis. First, the *R* enantiomer of ketamine (R-ketamine; R-ketamine; R-ket) has been found to be more efficacious and longer lasting as an antidepressant in rodent models than S-ket, despite the fact that R-ket has a weaker binding affinity for NMDAR than S-ket. Similarly, the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine (HNK) has been shown to induce antidepressant effects in rodent models, but only weakly binds NMDAR and does not engage this receptor *in vivo* at dose

levels that induce antidepressant effects. Accordingly, both R-ket and HNK may induce antidepressant effects while causing less dissociation than ketamine.

However, other strategies proposed to target NMDAR with less dissociative effects than ketamine (for example, by targeting the NR2B subunit of NMDAR or utilizing a compound with low-trapping properties) have met with poor results. For example, a number of such structurally distinct NMDAR antagonists (e.g., memantine, MK-0657, and lanicemine), although in some cases reducing dissociation, have been found to be less efficacious and/or shorter acting than ketamine in treating depression. Likewise, antagonists with higher affinity for NMDAR (e.g., MK-801) or targeting alternative binding sites on the channel (e.g., rapastinel), have also met with failure. Accordingly, the precise molecular mechanisms underpinning the antidepressant effects of ketamine remain poorly understood and may involve other as-yet-unidentified targets. Further, the antidepressant effects of NMDAR modulators and the magnitude of their concomitant dissociative effects are in general unpredictable. At the same time, these findings have raised the exciting possibility that the antidepressant effects of ketamine might in fact be separable from its dissociative anesthetic effects.

In addition to its dissociative side effects, the use of ketamine for depression treatment is further limited by the drug's poor oral bioavailability. Accordingly, for the treatment of MDD (major depressive disorder), ketamine is used almost entirely by the intravenous (IV) route. The practical challenges of IV administration further necessitate the use of ketamine under the supervision of a medical provider in a clinic or hospital setting. The inability to use ketamine by an oral route of administration is thus a major shortcoming that has limited the drug's broad adoption and increased medical costs associated with its use. Although other NMDAR antagonists have been developed that are orally bioavailable, to date none have reached the market, nor have they demonstrated the robust clinical efficacy of ketamine as an antidepressant. Therefore, there remains an acute need for novel antidepressants of the ketamine class that possess robust efficacy, decreased dissociative side effects, and increased oral bioavailability. A drug that retained the antidepressant efficacy of ketamine while producing less dissociative effects and having improved oral bioavailability would provide a treatment option that would be simpler to administer and potentially viable for at home use by virtue of its reduced dissociative effects and concomitant reduced abuse potential.

The present disclosure relates to an antidepressant compound, (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one, which has increased oral bioavailability relative to ketamine and its stereoisomers and exhibits reduced dissociative and ataxic side effects compared to ketamine at exposures that are effective in treating depression and related disorders. It achieves improvement and/or remission of the symptoms associated with depression and related disorders with the dosing regimens described herein. It also improves pain symptoms when administered according to the dosing regimens described herein.

SUMMARY OF THE DISCLOSURE

The present disclosure relates, in part, to a method of treating a patient having a psychiatric disorder comprising administering orally to a patient in need thereof a base compound or a pharmaceutically acceptable salt thereof at a dose ranging from about 40 to about 360 mg relative to the base compound at each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method of treating a patient having a psychiatric disorder or pain comprising administering to a patient in need thereof a base compound or a pharmaceutically acceptable salt thereof in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 3,600 h·ng/mL subsequent to each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL subsequent to each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method of treating a patient having a psychiatric disorder comprising administering a base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to a patient in need thereof on a daily basis, wherein the base compound or a pharmaceutically acceptable salt thereof is administered orally at a dose level ranging from about 20 to about 140 mg per day relative to the base compound, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method of treating a patient having pain comprising administering orally to a patient in need thereof a base compound or a pharmaceutically acceptable salt thereof at a dose ranging from about 40 to about 360 mg relative to the base compound at each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method of treating a patient having pain comprising administering a base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to a patient in need thereof orally on a daily basis, wherein the base compound or a pharmaceutically acceptable salt thereof is administered at a dose level ranging from about 20 to about 140 mg per day relative to the base compound during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a dosing kit comprising unit doses of a first pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a first pharmaceutical carrier therefor and unit doses of a second pharmaceutical composition comprising a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor and a second pharmaceutical carrier therefor and instructions for administering the first pharmaceutical composition and the second pharmaceutical composition to a patient suffering from a psychiatric disorder or pain, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a first component of about 20 to about 140 mg of a base compound or a pharmaceutically acceptable salt thereof relative to the base compound and a second component that is one of the following: about 10 to about 80 mg of fluoxetine, about 10 to about 60 mg of paroxetine, about 10 to about 40 mg of citalopram, about 5 to about 20 mg of escitalopram, about 25 to about 300 mg of fluvoxamine, about 50 to about 200 mg of sertraline, about 5 to about 20 mg of vortioxetine, about 30 to about 120 mg of duloxetine, about 37.5 to about 375 mg of venlafaxine, about 25 to about 200 mg of desvenlafaxine, about 12.5 to about 200 mg of milnacipran, or about 20 to about 120 mg of levomilnacipran, along with a pharmaceutically

acceptable carrier therefor, wherein all doses are relative to the free base form, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method for treating a psychiatric disorder or pain in a subject comprising administering a base compound or a pharmaceutically acceptable salt thereof as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 13 to about 120 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL subsequent to each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

In another embodiment, the present disclosure relates to a method for treating a psychiatric disorder or pain in a subject comprising administering a base compound or a pharmaceutically acceptable salt thereof as an intramuscular (IM) injection in an amount ranging from about 20 to about 180 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL subsequent to each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects, features, and advantages of the present disclosure will become apparent to one of ordinary skill in the art, in view of the following detailed description, taken in combination with the attached drawings. In the drawings, BC and base cmpd refer to base compound, as defined herein. In addition, the terms FIG. denotes Figure, and the terms FIG. and Figure are used herein interchangeably.

Figure 1A graphically shows the mean plasma concentration of base compound after administration thereof in six human subject at various dosages in SAD trial.

Figure 1B is the semilog plot of Figure 1A.

Figure 2 graphically shows the mean change from baseline in body sway (in millimeters) at the indicated dose of base compound (or placebo) and time relative to drug administration in SAD trial. Each body sway measurement was recorded over 2 minutes.

Figure 3 graphically shows the mean CADSS score in SAD trial at the indicated dose of base compound (or placebo) and time relative to drug administration to human subjects.

Figure 4 tabulates some TEAEs reported by at least one human subject in each of the various groups that were administered different dosage amounts of base compound in SAD trial.

Figure 5 tabulates other TEAEs relative to the TEAEs listed in Figure 4 reported by at least one human subject in each of the various groups that were administered different dosage amounts of base compound in SAD trial.

Figure 6 graphically shows the percentage of human subjects in each of the groups who were orally administered base compound at different dosages having a CADSS greater than 4 in SAD trial. In the figure, n=6 is the total number of human subject that were tested at each dosage of the base compound.

Figure 7 graphically shows the dose dependent and time dependent effect from the administration of base compound to human subjects at different dosages thereof in SAD trial.

Figure 8A shows the spectral EEG changes when base compound is administered to human subject at dose levels of 20, 60, 100, 140, 220, and 360 mg across Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-25 Hz), Slow Gamma (GammaS; 30-50 Hz), and Fast Gamma (GammaF; 65-95 Hz) EEG bands in SAD trial, while Figure 8B graphically shows the effect of administration of base compound on human subjects over time on EEG signals relative to baseline at -2 and -1 hours before dosing, and 1, 3 and 8 hours after dosing at dose levels of 20, 60, 100, 140, 220, and 360 mg across Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-25 Hz), Slow Gamma (GammaS; 30-50 Hz), and Fast Gamma (GammaF; 65-95 Hz) EEG bands in SAD trial. Separate scales were used for lower EEG bands (Delta, Theta, Alpha and Beta) and higher EEG bands (GammaS and GammaF). Data are from Eyes Open condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 8C show the spectral EEG changes when base compound is administered to human subject at dose levels of 20, 60, 100, 140, 220, and 360 mg across Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-25 Hz), Slow Gamma (GammaS; 30-50 Hz), and Fast Gamma (GammaF; 65-95 Hz) EEG bands in SAD trial. Figure 8D graphically shows the effect

of administration of base compound on human subjects over time on EEG signals relative to baseline at -2 and -1 hours before dosing, and 1, 3 and 8 hours after dosing at dose levels of 20, 60, 100, 140, 220, and 360 mg across Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-25 Hz), Slow Gamma (GammaS; 30-50 Hz), and Fast Gamma (GammaF; 65-95 Hz) EEG bands in SAD trial. Separate scales were used for lower EEG bands (Delta, Theta, Alpha and Beta) and higher EEG bands (GammaS and GammaF). Data from Eyes Closed condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 9 graphically depicts the dose dependent increase of Real Time Intensity Score of human subjects ingesting different dosages of base compound in SAD trial.

Figure 10 is a bar graph of 5D-ASC scores of human subject after administration of various dosages of base compound to the human subject in SAD trial.

Figure 11 graphically depicts the dose- dependent sedative effects of oral administration of base compound to human subjects at different dosages over time with respect to saccadic peak velocity in SAD trial.

Figure 12 graphically depicts the dose dependent increase in systolic blood pressure relative to baseline at different dosages of orally administered base compound to humans at rest in SAD trial.

Figure 13 tabulates the dose dependent increase in systolic blood pressure relative to baseline at different dosages of orally administered base compound to humans at rest at 30 minutes post administration thereof in SAD trial.

Figure 14 graphically depicts the dose dependent increased QTcF when base compound is orally administered to human subjects in SAD trial.

Figure 15 graphically depicts the dose dependent increase in heart rate when base compound is orally administered to human subjects in SAD trial.

Figure 16 graphically depicts the VAS alertness effect when base compound is orally administered to human subjects in SAD trial.

Figure 17 depicts an overview of the schedule of comprehensive pharmacodynamic measures including subjective effects from SAD trial and EEG (including MAD trial and Food Effects when the human subject fasted or is fed).

Figure 18A graphically shows the mean plasma concentration of base compound in MAD trial after administration thereof in nine human subjects on day 1 when orally administered at 140 and 220 mg.

Figure 18B is the semi-log plot of Figure 18a.

Figure 18C graphically shows the mean plasma concentration of base compound in MAD trial after administration thereof in nine human subjects on day 7 when orally administered at 140 and 220 mg.

Figure 18D is the semi-log plot of Figure 18c.

Figure 19A shows the spectral EEG changes when placebo is administered to human subjects and when base compound is administered to human subject at dose level of 140 mg across Alpha (8-13 Hz) and Fast Gamma (65-95 Hz) EEG bands on days 1 and 7 of MAD trial. Data is from eyes open condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 19B shows the spectral EEG changes when placebo is administered to human subjects and when base compound is administered to human subject at dose level of 220 mg across Alpha (8-13 Hz) and Fast Gamma (65-95 Hz) EEG bands on days 1 and 7 of MAD trial. Data is from eyes open condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 19C shows the spectral EEG changes when placebo is administered to human subjects and when base compound is administered to human subject at dose level of 140 mg across Alpha (8-13 Hz) and Fast Gamma (65-95 Hz) EEG bands on days 1 and 7 of MAD trial. Data is from eyes closed condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 19D shows the spectral EEG changes when placebo is administered to human subjects and when base compound is administered to human subject at dose levels of 220 mg across Alpha (8-13 Hz) and Fast Gamma (65-95 Hz) EEG bands on days 1 and 7 of MAD trial. Data is from eyes closed condition. Data were averaged across subjects at each dose level with placebo subjects shown separately.

Figure 20A graphically shows the effect of administration of base compound on human subjects over time on EEG signals relative to baseline at 2 hours before administration of the base compound, at 1 hour before administration of the base compound, at 1 hour after

administration of base compound, at 3 hours after administration of base compound and 8 hours after administration of base compound at dose levels of 140 and 220 mg across Alpha (8-13 Hz), and Fast Gamma (65-95 Hz) EEG bands on day 1 of MAD trial. Data are from Eyes Open condition. Data were averaged across subjects at each dose level with placebo subjects shown separately. Separate scales were used for Alpha and Fast Gamma EEG bands.

Figure 20B graphically shows the effect of administration of base compound on human subjects over time on EEG signals relative to baseline at 2 hours before administration of the base compound, at 1 hour before administration of the base compound, at 1 hour after administration of base compound, at 3 hours after administration of base compound and 8 hours after administration of base compound at dose levels of 140 and 220 mg across Alpha (8-13 Hz), and Fast Gamma (65-95 Hz) EEG bands on day 7 of MAD trial. Data are from Eyes Open condition. Data were averaged across subjects at each dose level with placebo subjects shown separately. Separate scales were used for Alpha And Fast Gamma EEG bands.

Figure 20C graphically shows the effect of administration of base compound on human subjects over time on EEG signals relative to baseline at 2 hours before administration of the base compound, at 1 hour before administration of the base compound, at 1 hour after administration of base compound, at 3 hours after administration of base compound and 8 hours after administration of base compound at dose levels of 140 and 220 mg across Alpha (8-13 Hz), and Fast Gamma (65-95 Hz) EEG bands on day 1 of MAD trial. Data are from Eyes Closed condition. Data were averaged across subjects at each dose level with placebo subjects shown separately. Separate scales were used for Alpha and Fast Gamma EEG bands.

Figure 20D graphically shows the effect of administration of base compound on human subjects over time on EEG signals relative to baseline at 2 hours before administration of the base compound, at 1 hour before administration of the base compound, at 1 hour after administration of base compound, at 3 hours after administration of base compound and 8 hours after administration of base compound at dose levels of 140 and 220 mg across Alpha (8-13 Hz), and Fast Gamma (65-95 Hz) EEG bands on day 7 of MAD trial. Data are from Eyes Closed condition. Data were averaged across subjects at each dose level with placebo subjects shown separately. Separate scales were used for Alpha and Fast Gamma EEG bands.

Figure 21 tabulates some TEAEs reported by at least one human subject at the conclusion of the 7-day MAD trial in each of the two groups that were administered the two dosage amounts of base compound relative to the administration of placebo.

Figure 22 graphically shows the percentage of human subjects in the two groups who were orally administered base compound at 140 mg and 220 mg and in the groups to which placebo were administered having a CADSS greater than 4 at the end of the MAD trial.

Figure 23 graphically depicts the dose dependent increase of Real Time Intensity Scale for Total Score from the administration of 140 mg and 220 mg dosages of base compound to human subjects on the first day of the trial and the seventh day of the MAD trial.

Figures 24A and 24B graphically depict the dose dependent effect on the VAS alertness scale on subjects relative to baseline (from placebo administration) from the administration of 140 mg and 220 mg dosages, respectively, of base compound to human subjects on the first day of the MAD trial and the seventh day of the MAD trial. The measurements were taken 1 hour before administration, at the start of the MAD trial when the base compounds were administered to subjects, 1 hour after administration of base compounds, 2 hours after administration of base compounds, 3 hours after administration of base compounds, 4 hours after administration of base compounds, 6 hours after administration of base compounds, 8 hours after administration of base compounds, and 24 hours after administration of base compounds. Data were averaged across subjects at each dose level.

Figure 25A and Figure 25B graphically depicts the dose dependent increase in systolic blood pressure relative to baseline at 140 mg and 220 mg dosages, respectively, of orally administered base compound to humans at rest on the first day of the MAD trial and the seventh day of the MAD trial. Measurements were taken 24 hours prior to administration of the base compound, 2 hours before administration of base compounds, when the base compounds were administered, 2 hours after administration of base compounds, 6 hours after administration of base compounds, 8 hours after administration of base compounds, and 24 hours after administration of base compounds. Measurements were also taken 72 hours after administration of base compounds on the seventh day of the MAD trial. Data were averaged across subjects at each dose level.

Figure 26A shows graphically the effect of acute administration of base compound (1-32 mg/kg, s.c.) on immobility time as compared to desipramine (20 mg/kg, s.c., t.i.d.) in naïve rats

tested in the FST 24 h after dosing ($n \geq 10/\text{group}$). Asterisks indicate a significant difference from the vehicle-treated group using Dunnett's post-hoc test.

Figure 26B depicts an overview of the experimental schedule for CMS studies. Small unlabeled arrows represent weekly sucrose drinking tests (Tuesdays every week of the study). Large arrows show when animals received weekly treatments (Mondays). Small, labelled arrows show the timing for the Elevated Plus Maze (EPM) assay (Wednesday) and the Novel Object Recognition (NOR) task (Thursday), as indicated.

Figures 26 C-E show graphically data collected in the first chronic mild stress (CMS) trial in Wistar Han rats ($n=8/\text{group}$).

Figure 26C graphically shows the effect of base compound (0.75-9 mg/kg, i.p.) and (*rac*)-ketamine (10 mg/kg, i.p.) on sucrose intake over the course of the study.

Figure 26D graphically shows the percent time spent in the open arms of the EPM, which was conducted 48 h after the first treatment. Open bars show data from unstressed control rats, while filled bars show data from rats exposed to CMS for each treatment group.

Figure 26E graphically shows the results from the NOR task. The NOR task was conducted 72 h after the first treatment. Open bars show data from unstressed control rats, while filled bars show data from rats exposed to CMS for each treatment group.

Figures 26F and 26G graphically show the effects of a single administration of (*rac*)-ketamine or base compound on sucrose intake in Wistar Kyoto (WKY) rats ($n=8/\text{group}$) as recorded in the second CMS experiment.

Figure 26F graphically shows the effect and durability of a single administration of drug in week 3; sucrose intake was assessed 24 h later and then once weekly for 3 weeks post dose.

Figure 26G graphically shows the effect of base compound (1-10 mg/kg, p.o.) administered orally, compared to (*rac*)-ketamine (10 mg/kg, i.p.) or base compound (1.5 mg/kg, i.p.) on sucrose intake 24 h later.

All components of Figures 26A-26G show mean $\pm$ SEM ($n \geq 8/\text{group}$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus vehicle (control) or vehicle stressed as indicated. # $p < 0.05$ vs control animals receiving the same treatment.

Figure 27A graphically depicts the spontaneous locomotor activity of rats ($n=9/\text{group}$) dosed with vehicle, ketamine (3.2-32 mg/kg, s.c.), or base compound (3.2-32 mg/kg, s.c.) and mice ($n=10/\text{group}$) dosed with base compound (1-32 mg/kg, s.c.). Bar charts show total

locomotor activity over 0-30 min after dosing (as either distance travelled or beam breaks). Line graph shows the time course of rat locomotor activity with data presented as 5 min time bins, with rats dosed at time 0, and the given timepoint being the end of the 5 min time bin (i.e., 5 min = 0-5 min).

Figure 27B graphically depicts the effects of vehicle, ketamine, or base compound (1-32 mg/kg, s.c.) on latency to fall off the rotarod 5 min after dosing in rats (n=10/group) and mice (n=12/group).

Figure 27C graphically shows the effects of base compound (1-32 mg/kg, s.c.) compared to oxycodone (3 mg/kg, s.c.) on mouse conditioned place preference (n=10/group). Graph shows the change in amount of time spent on the drug paired side after place conditioning for each treatment.

Figure 27D graphically provides an overview of the plasma concentrations of base compound associated with the pharmacodynamic effects of the compound in rats. Black lines represent the plasma concentration of base compound at the minimum efficacious doses in the chronic mild stress paradigm and forced swim test, as indicated. Dashed grey lines indicate the plasma concentrations associated with a 50% reduction in latency to fall off the rotarod or a significant increase in spontaneous locomotor activity, as indicated. The solid grey line represents the minimum plasma concentration of base compound associated with decreases in EEG theta power and increases in EEG gamma power.

All components of Figure 27A-27D show mean $\pm$ SEM. Asterisks indicate significant differences compared to vehicle treated animals. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Figure 28 graphically shows the effects of base compound on EEG power in rats.

Figure 28A shows EEG spectrograms calculated for the time 30 minutes prior to injection (T = 0) through 180 minutes after injection of the indicated dose of base compound. Shade represents z-scored EEG power, where z-score values are referenced to 30 minutes prior to injection. Black arrows point to an increase of broadband gamma EEG power. White arrows point to a decrease in low-frequency EEG power.

Figure 28B shows average locomotor “activity” values in 30-minute time windows before and after injection of the indicated dose of base compound. The “activity” measure provided by the DSI recording system reflects the movement of the animal across the home cage.

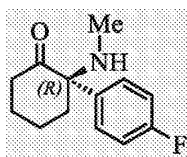
Figure 28C shows the average z-score normalized EEG spectra calculated as the average of the period from 0 to 60 minutes following injection of the indicated dose of base compound.

Figure 28D shows average values of z-score normalized EEG power calculated for 4 canonical EEG bands – delta (1-4 Hz), theta (5-12 Hz), beta (12-30 Hz), and gamma (30-80 Hz) over the period from 0 to 60 minutes following injection of the indicated dose of base compound. Asterisks indicate a significant difference compared to vehicle treated animals.

All data are the mean of n=8/group for Figure 28 and all error bars are SEM.

DETAILED DESCRIPTION

The present disclosure relates to a dosage regimen for treating psychiatric disorders and/or pain and/or the symptoms thereof in a subject comprising administering to said subject in need of treatment (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof, according to a prescribed schedule, as described herein. As a shorthand notation, the term “base compound” or “BASE COMPOUND” is used to denote (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one. The chemical structure of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is depicted below:



For clarity, in the context of the present disclosure, the chemical structure of a compound depicted with a specific stereochemical orientation at any particular chiral center, as defined by wedge and dash notation, is intended to represent the stereoisomer of said compound that is drawn in substantially pure form, or a mixture enriched in the stereoisomer that is drawn with the specified stereochemical orientation at the defined chiral center over the stereoisomer with the opposite orientation at said chiral center.

This disclosure also includes any salt of the compound depicted hereinabove, including any pharmaceutically acceptable salt, wherein a compound disclosed herein has a net charge (either positive or negative) and at least one counter ion (having a counter negative or positive charge) is added thereto to form said salt. The phrase "*pharmaceutically acceptable salt(s)*", as used herein, means those salts of compounds disclosed herein that are safe and effective for

pharmaceutical use in mammals and that possess the desired biological activity.

Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds disclosed herein. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds disclosed herein can form pharmaceutically acceptable salts with various amino acids. For a review on pharmaceutically acceptable salts see Berge et al., J Pharm Sci., 66(1), 1-19 (1977), incorporated herein by reference. In an embodiment, the pharmaceutically acceptable salt is the hydrochloride salt of the structure depicted hereinabove, i.e., (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one hydrochloride.

The term "substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof" denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 60% pure by weight, i.e., contains no more than 40% impurities, including no more than 40% by weight of the corresponding S isomer. In an embodiment, the term "substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof" denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 75% pure by weight. In an embodiment, the term "substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof" denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 80% pure by weight. In another embodiment, the term "substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof" denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 85% pure by weight. In a further embodiment, the term "substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof" denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 90% pure by weight. In a further embodiment, the term "substantially pure (R)-2-(4-

fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof” denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 95% pure by weight. In a further embodiment, the term “substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof” denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 97% pure by weight. In a further embodiment, the term “substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof” denotes that (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is at least 99% pure by weight. In the case of pharmaceutically acceptable salts of (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one, the foregoing purity percentages are calculated with respect to the base compound corrected for counterion mass (i.e., the percent by weight of salt counterion is not considered an impurity).

The terms “substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof” and “substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or pharmaceutically acceptable salts thereof” are synonymous and are used interchangeably.

As used herein, the term “SAD”, when referring to a trial or experiment, denotes Single Ascending Dose. On the other hand, “SAD”, when referring to a medical condition, denotes seasonal affective disorder.

In describing the methods, terms, such as “about” or approximately are used. The terms “about” or “approximately” as used herein mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part, on how the value is measured or determined, *i.e.*, the limitations of the measurement system, or on natural variance in the natural phenomenon to be quantified. For example, “about” can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, “about” can mean a range of up to 30%, a range of up to 20%, a range of up to 10%, a range of up to 5%, and/or a range of up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, *e.g.*, within 5-fold, or within 2-fold, of a value. Further, with respect to concentrations of a drug in plasma or related pharmacokinetic parameters, *e.g.*, C_{max} and AUC, “about” can mean within a range encompassing typical variability in such parameters

between different subjects for the drug in question. “About” and “approximately” are used interchangeably herein.

Throughout this disclosure, when a range of time intervals is referred to with respect to administration of the base compound or a pharmaceutically acceptable salt thereof, e.g., weekly to daily, it is to be understood that said range of administration intervals also encompasses all intermediate intervals in addition to the end points of the range, e.g., in the case of the range weekly to daily, includes daily, intervals of every other day, every 3 days, every 4 days, every 5 days, and every 6 days.

The terms “treating” and “treatment” refer to ameliorating, suppressing, eradicating, reducing the severity of, decreasing the frequency of, decreasing the incidence of, reducing the risk of, slowing the progression of damage caused by, delaying the onset of the condition, or improving the quality of life of a human patient or subject suffering from a condition.

The terms “effective amount” or “therapeutically effective amount” refer to an amount of a compound described herein, a pharmaceutical composition comprising the same, a medicament comprising the same, or another material comprising the same, which is effective to achieve a particular pharmacological and/or physiological effect including, but not limited to, reducing the frequency or severity of sadness or lethargy, depressed mood, anxious or sad feelings, diminished interest in all or nearly all activities, significant increased or decreased appetite leading to weight gain or weight loss, insomnia, irritability, fatigue, feelings of worthlessness, feelings of helplessness, inability to concentrate, and recurrent thoughts of death or suicide; or providing a desired pharmacologic and/or physiologic effect, for example, reducing, inhibiting, or reversing one or more of the underlying pathophysiological mechanisms underlying the neurological dysfunction, modulating dopamine levels or signaling, modulating serotonin levels or signaling, modulating norepinephrine levels or signaling, modulating glutamate or GABA levels or signaling, modulating synaptic connectivity or neurogenesis in certain brain regions, or a combination thereof. Thus, the term “therapeutically effective amount” or “effective amount” refers to that amount of the disclosed compound or composition comprising the same that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with the mood disorder or symptoms thereof, including improvement in the condition of the subject, including symptoms associated therewith, or delay or reduction in the progression of the condition.

The term “therapeutic index” used in reference to compound disclosed herein and associated therapeutic effects and side effects refers to the ratio of the dose of said compound required to induce a particular negative side effect to the dose of said compound required to induce the desired therapeutic effect.

The terms “administer,” “administration,” “administering,” or any grammatical variation thereof with respect to a subject or patient includes any route of introducing or delivering a disclosed compound thereto. Administration may be carried out by any suitable route, including oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation, via an implanted reservoir, parenteral (e.g., by subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraperitoneal, intrahepatic, intralesional, and intracranial injections or infusion techniques), and the like. Administration includes self-administration and the administration by another.

“Simultaneous administration” or “administered simultaneously,” as used herein means that the base compound or a pharmaceutically acceptable salt thereof and one or more additional antidepressants are administered at the same point in time, overlapping in time, or one following the other. In the latter case, the base compound or a pharmaceutically acceptable salt thereof and additional antidepressants are administered at times sufficiently close that the results observed are indistinguishable from those achieved when the base compound or a pharmaceutically acceptable salt thereof and antidepressants are administered at the same point in time.

“Concurrent administration,” “administration in combination,” and “concurrently” mean sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds “concurrently” or in “combination” means that the two or more compounds are administered closely enough in time that the presence of two or more compounds results in a biological effect distinct (e.g., greater than, less than, or different in type) from any of the compounds alone or a pharmaceutically acceptable salt thereof. The two or more compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in different formulations, for example, at the same point in time but at different anatomic sites or using

different routes of administration. In other words, the terms “concurrent administration,” “concurrently” and the like is broader than “simultaneous administration” or “administered simultaneously,” and includes “simultaneous administration” and “administered simultaneously.”

The term “area under the curve” (AUC) refers to the area under the plasma concentration versus time curve from time 0 to time t after the administration of one dose of the base compound or a pharmaceutically acceptable salt thereof but prior to the administration of any subsequent dose of the base compound or a pharmaceutically acceptable salt thereof. Throughout this disclosure, if no value of t is indicated with respect to an AUC, it is to be understood that the given AUC value refers to the time period of 0 to 24 h post administration. It is to be understood that AUC values listed throughout this disclosure refer to mean values in a typical human or animal population. Therefore, measured values for individual subjects may fall above or below an indicated value but this typical inter-subject variability is understood to be encompassed by the mean value indicated.

$C_{\max}$ refers to the maximum plasma concentration of base compound after the administration of one dose of the base compound or a pharmaceutically acceptable salt thereof but prior to the administration of any subsequent dose of the base compound or a pharmaceutically acceptable salt thereof. It is to be understood that $C_{\max}$ values listed throughout this disclosure refer to mean values in a typical human or animal population. Therefore, measured values for individual subjects may fall above or below an indicated value but this typical inter-subject variability is understood to be encompassed by the mean value indicated. In the case of base compound or a pharmaceutically acceptable salt thereof administered by the oral route, $C_{\max}$ typically occurs at about 1 h to about 2 h post dosing. In the case of base compound or a pharmaceutically acceptable salt thereof administered as an IV bolus or short IV infusion, $C_{\max}$ typically occurs at about the end of the injection or infusion. In the case of base compound or a pharmaceutically acceptable salt thereof administered by the IM route, $C_{\max}$ typically occurs at about 15 minutes to about 30 minutes post dosing. Accordingly, a measurement of plasma concentration in a subject should be performed at about the foregoing times relative to dosing in order to reflect the $C_{\max}$.

“Patient” or “subject” refers to humans. The human subject can be in any stage of development including adults, children, or infants. The human subject may be a biological male or female.

Unless indicated to the contrary, the terms “drug” and “medicament” are synonymous.

As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,” “having,” or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements, but may include other elements not expressly listed or inherent to such process, method, article, or apparatus.

As used herein, the phrase “consisting of” excludes any element, step, or ingredient not specifically specified in the present disclosure or claim. When the phrase “consists of” (or variations thereof) appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole.

As used herein, the transitional phrase “consisting essentially of” (and grammatical variants) is to be interpreted as encompassing the recited materials or steps and those that do not materially affect the basic and novel characteristic(s) of the subject matter of the present disclosure. The term “consisting essentially of” is a subset of “comprising” and may be used to replace the term “comprising,” but as used herein, it should not be interpreted as equivalent to “comprising.”

Also, “a” or “an” are employed to describe elements and components described herein. This is done merely for convenience and to give a general sense of the scope of the invention. This description should be read to include one or at least one. Moreover, the singular also includes the plural and *vice versa* unless it is obvious that it is meant otherwise.

Further, unless expressly stated to the contrary, “or” refers to an inclusive “or” and not to an exclusive “or.” For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

Moreover, the term “and/or” is synonymous with the term “or,” as used herein.

When a range or list of values is expressed, an embodiment includes the endpoint of the ranges and/or list and all the points therebetween. For example, a range of 6 to 9, includes the value 6 and 9 and all values therebetween. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the values range from about the two endpoints, where “about” is defined as herein described. All ranges are

inclusive and combinable. Further, reference to values stated in ranges includes each and every value within that range.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety, unless a particular passage is cited. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Unless indicated to the contrary, all percentages are by weight.

The compounds administered in the method claims may be present in the form of a pharmaceutical composition. These compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, and intradermal) administration or administration via an implant. The compositions may be prepared by any method well known in the art of pharmacy.

Such methods include the step of bringing in association compounds used in the present disclosure or combinations thereof with any auxiliary agent. The auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents, antioxidants, and wetting agents. Such auxiliary agents are suitably selected with respect to the intended form and route of administration and as consistent with conventional pharmaceutical practices.

Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragées or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

Tablets may contain the base compound or a pharmaceutically acceptable salt thereof and suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Gelatin capsules may contain the active ingredient compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid,

and the like. Similar diluents can be used to make compressed tablets. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. For instance, for oral administration in the dosage unit form of a tablet or capsule, the base compound or a pharmaceutically acceptable salt thereof can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

For oral administration in liquid dosage form, the oral drug component, the base compound or a pharmaceutically acceptable salt thereof, is combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

For parenteral administration, including intravenous and intramuscular injections, suitable compositions include aqueous and non-aqueous sterile solutions. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration, including those for intravenous and intramuscular injection, preferably contain a water-soluble salt of the base compound, suitable stabilizing agents, and if necessary, buffer substances, such as a phosphate buffer at a pH compatible with the pH of the plasma of the blood, for example, a pH ranging from about 5.0 to about 7.5, or salts to adjust the ionic strength, for

example, to obtain a solution isotonic with blood, for example, about 270 mOsm/ kg to about 300 mOsm/kg. For salt forms, a sterile formulation of a suitable soluble salt form of the composition herein can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% aqueous glucose solution. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions, including those for intravenous and intramuscular injection, can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. The compositions may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of sterile liquid carrier, for example water, prior to use. Parenteral forms, including those for intravenous and intramuscular injection, may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

For transdermal administration, e.g., gels, patches or sprays can be contemplated.

Compositions or formulations suitable for pulmonary or intranasal (i.e., to the nasal mucous membranes) administration include fine dusts or mists which may be generated by means of metered-dose pressurized aerosols, nebulizers, insufflators, or vaporizers, at room temperature or elevated temperature. The composition comprising the substantially pure base compound or a pharmaceutically acceptable salt thereof is placed in a medical device selected from the group consisting of an inhaler, a nebulizer, a nasal sprayer, an insufflator, and a vaporizer for administration to the subject. When administered by inhalation, a composition comprising the substantially pure base compound or a pharmaceutically acceptable salt thereof can be administered by pulmonary delivery system, that is, the active pharmaceutical ingredient (substantially pure base compound or a pharmaceutically acceptable salt thereof) is administered into the lung, or by a nasal delivery system, that is, the active pharmaceutical ingredient is administered to the nasal mucous membranes.

When the pulmonary delivery system is an inhaler system, in some embodiments, the inhaler system is a pressurized metered-dose inhaler, a dry powder inhaler, or a nebulizer. In some embodiments, the inhaler system is with a spacer.

In some embodiments, the pressurized metered dose inhaler includes a propellant, a co-solvent, a surfactant, a preservative, and/or an antioxidant. In some embodiments, the propellant

is selected from the group comprising fluorinated hydrocarbons such as trichloromonofluoromethane, dichloro-difluoromethane, dichloro-tetrafluoroethane, chloropentafluoroethane, monochloro-difluoroethane, difluoroethane, tetrafluoroethane, heptafluoropropane, and octafluorocyclobutane. In some embodiments, a co-solvent is present. In some embodiments, the co-solvent is selected from the group comprising purified water, ethanol, propylene glycol, glycerin, PEG400, PEG600, PEG800, and PEG1000. In some embodiments, a surfactant or lubricant is present. In some embodiments, the surfactant or lubricant is selected from the group comprising sorbitan trioleate, soya lecithin, lecithin, oleic acid, Polysorbate 80, magnesium stearate, and sodium lauryl sulfate. In some embodiments, preservatives or antioxidants are present. In some embodiments the preservatives or antioxidants are selected from the group comprising methylparaben, propylparaben, chlorobutanol, benzalkonium chloride, cetylpyridinium chloride, thymol, ascorbic acid, sodium bisulfite, sodium metabisulfite, sodium bisulfate, and EDTA. In some embodiments, the pH or tonicity is adjusted. In some embodiments, these adjustments are made using agents selected from the group comprising sodium oxide, ammonia, HCl, HBr, H₂SO₄, HNO₃, citric acid, ascorbic acid, CaCl₂, Na₂CO₃, K₂CO₃, CaCO₃, NaHCO₃, KHCO₃, NaCl, KCl, Na₃PO₄, Na₂HPO₄, NaH₂PO₄, K₃PO₄, K₂HPO₄, KH₂PO₄, NaOH, and KOH. In some embodiments, the dry powder inhaler includes a dispersal agent. In some embodiments, the dispersal agent or carrier particle is selected from the group comprising lactose, lactose monohydrate, lactose anhydrate, mannitol, and dextrose, in each case with a particle size of about 1 to about 100 μ m.

In some embodiments, if the inhaler is a nebulizer, it may include a co-solvent, a surfactant, a lubricant, a preservative, and/or an antioxidant. In some embodiments, a co-solvent is present. In some embodiments, the co-solvent is selected from the group comprising purified water, ethanol, propylene glycol, glycerin, PEG400, PEG600, PEG800, and PEG1000. In some embodiments, a surfactant or lubricant is present. In some embodiments, the surfactant or lubricant is selected from the group comprising sorbitan trioleate, soya lecithin, lecithin, oleic acid, Polysorbate 80, magnesium stearate, and sodium lauryl sulfate. In some embodiments, preservatives or antioxidants are present. In some embodiments the preservatives or antioxidants are selected from the group comprising methylparaben, propylparaben, chlorobutanol, benzalkonium chloride, cetylpyridinium chloride, thymol, ascorbic acid, sodium bisulfite, sodium metabisulfite, sodium bisulfate, and EDTA. In some embodiments, the pH or tonicity is

adjusted. In some embodiments, these adjustments are made using agents selected from the group comprising sodium oxide, ammonia, HCl, HBr, H₂SO₄, HNO₃, citric acid, ascorbic acid, CaCl₂, Na₂CO₃, K₂CO₃, CaCO₃, NaHCO₃, KHCO₃, NaCl, KCl, Na₃PO₄, Na₂HPO₄, NaH₂PO₄, K₃PO₄, K₂HPO₄, KH₂PO₄, NaOH, and KOH.

The substantially pure base compound or a pharmaceutically acceptable salt thereof used in the method of the present disclosure may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

The substantially pure base compound or a pharmaceutically acceptable salt thereof used in the method of the present disclosure may also be coupled to soluble polymers as targetable drug carriers or as prodrugs. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the substantially pure base compound or a pharmaceutically acceptable salt thereof may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and crosslinked or amphoteric block copolymers of hydrogels.

Pharmaceutical compositions herein may be provided with immediate release, delayed release, extended release, or modified release profiles. In some embodiments, pharmaceutical compositions with different drug release profiles may be combined to create a two-phase or three-phase release profile. For example, pharmaceutical compositions may be provided with an immediate release and an extended-release profile. In some embodiments, pharmaceutical compositions may be provided with an extended release and delayed release profile. Such composition may be provided as pulsatile formulations, multilayer tablets, or capsules containing tablets, beads, granules, and the like.

Pharmaceutical compositions herein may be provided with abuse deterrent features by techniques known in the art, for example, by making a tablet that is difficult to crush or to dissolve in water. The present disclosure further includes a pharmaceutical composition, as hereinafter

described, in combination with packaging material, including instructions for the use of the compositions for use as hereinafter described.

Although the substantially pure base compound or a pharmaceutically acceptable salt thereof may be administered by any means of administration, the amount administered may be described in terms of mg of the base compound or a pharmaceutically acceptable salt thereof. To maintain uniformity in the amounts administered when provided in mg across salt forms, the amounts do not take into account the identity of the pharmaceutically acceptable salt; instead, indicated doses in mg are solely based on the amount of the free base, (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one, so that equal amounts of moles of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one are administered regardless of the pharmaceutically acceptable salt selected. For example, the molecular weight of free base (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is 221.3 g/mole, while the formula weight of the hydrochloride salt of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is 257.7 g/mole. Accordingly, for example, 0.001 moles of the free base weighs 221.3 mg, while 0.001 moles of the hydrochloride salt of the free base weighs 257.7 mg. Therefore, with respect to this example, when it is stated that a listed dose of the hydrochloride salt is relative to the free base, it is to be understood that the dose listed is based on the amount of the free base present therein, which in this example, means a dose of 221.3 mg free base is equivalent to a dose of 257.7 mg hydrochloride salt, and the doses of both the free base and hydrochloride salt are listed as 221.3 mg. In other words, the amount of active ingredient is not dependent upon the identity of the pharmaceutically acceptable salt when the doses are expressed relative to the free base. Thus, when the dose level is described as “with respect to the free base”, “relative to the free base”, “relative to the base compound”, or with a similar term, it is understood that the amount of the pharmaceutically acceptable salt of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one administered is in terms of the equivalent amount of free base administered, so that, for example, 257.7 mg of the hydrochloride salt administered is equivalent to the administration of 221.3 mg of free base or active ingredient administered to the subject. Unless otherwise stated, all doses listed in a mass unit, e.g., mg, throughout the present disclosure should be understood to be relative to the base compound or free base of the drug in question, regardless of whether “relative to the base compound” or similar modifier is included before or after.

In describing additional compounds to “(R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof”, such as anti-depressants, when reciting the amounts present of these additional compounds, the phrase “defined free base form” denotes that the weight present is based on the free base form of the compound. It does not include any salt form or solvent associated therewith.

In the description below, the amounts provided for administration are based on the weight of a 70 kg person. However, the weight of person vary. For persons who weigh outside of the 65 to 80 kg range, the weight amounts provided, in an embodiment, is to be adjusted for the weight of the patient relative to a 70 kg person. For example, for a 105 kg patient, the amounts provided is to be adjusted by 1.5 times.

In embodiments, the psychiatric disorder is a depressive disorder. Some examples of depressive disorders include major depressive disorder, persistent depressive disorder, mood disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition. The depressive disorder may also be a treatment-resistant depressive disorder. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a depressive disorder, including any of those specifically pointed out above by any of the methods described herein.

In some embodiments, depression conditions include major depressive disorder and dysthymic disorder. In some embodiments, depression conditions develop under unique circumstances, including, but are not limited to, psychotic depression, postpartum depression, seasonal affective disorder (SAD), neuropsychiatric disorder, or depressions caused by other chronic medical conditions such as cancer, chronic pain, chemotherapy, chronic stress, post-traumatic stress disorders, and bipolar disorder (or manic-depressive disorder). In some embodiments, depression conditions that are expected to be treated according to this aspect of the present disclosure include, but are not limited to, major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, premenstrual syndrome, premenstrual dysphoric disorder, seasonal affective disorder (SAD), and depressions caused by other chronic medical conditions such as cancer, chronic pain, chemotherapy, chronic stress, post-traumatic stress disorder, obsessive-compulsive disorder, and bipolar disorder (or manic depressive

disorder). The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat any of the depressive disorders specifically pointed out above by any of the methods described herein.

Also provided herein are methods of treating refractory depression, *e.g.*, patients suffering from a depressive disorder that does not, and/or has not, responded to adequate courses of at least one, or at least two, other antidepressant compounds or therapeutics. For example, provided herein is a method of treating depression in a treatment-resistant patient, comprising a) optionally identifying the patient as treatment resistant and b) administering an effective dose of base compound. As used herein, the term "depressive disorder" encompasses refractory depression. In some embodiments, refractory depression occurs in patients suffering from depression who are resistant to standard pharmacological treatments, including tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), dual serotonin and norepinephrine reuptake inhibitors (SNRI), and triple reuptake inhibitors (inhibitors of the serotonin, norepinephrine, and dopamine transporters), and/or anxiolytic drugs, as well as non-pharmacological treatments such as psychotherapy, electroconvulsive therapy, vagus nerve stimulation, and/or transcranial magnetic stimulation. In some embodiments, a treatment-resistant patient may be identified as one who fails to experience alleviation of one or more symptoms of depression (*e.g.*, persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism), despite undergoing one or more standard pharmacological or non-pharmacological treatments. In certain embodiments, a treatment-resistant patient is one who fails to experience alleviation of one or more symptoms of depression despite undergoing treatment with two different antidepressant drugs. In other embodiments, a treatment-resistant patient is one who fails to experience alleviation of one or more symptoms of depression despite undergoing treatment with four different antidepressant drugs. In some embodiments, a treatment-resistant patient may also be identified as one who is unwilling or unable to tolerate the side effects of one or more standard pharmacological or non-pharmacological treatments. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a refractory or treatment-resistant depressive disorder, including any of those specifically pointed out above by any of the methods described herein.

In some embodiments, symptoms associated with depression include, but are not limited to, persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, and/or worthlessness, low energy, psychomotor retardation, delusions, restlessness, irritability, fatigue, loss of interest in pleasurable activities or hobbies, overeating, appetite loss, insomnia, hypersomnia, thoughts of suicide, or suicide attempts. In some embodiments, various symptoms associated with anxiety include fear, excessive worrying, panic, heart palpitations, shortness of breath, fatigue, nausea, and headaches among others. In addition, patients suffering from any form of depression often experience anxiety. The methods described in the present disclosure can be used to treat anxiety or any of the symptoms thereof utilizing the base compound or a pharmaceutically acceptable salt thereof described herein. In some embodiments, the presence, severity, frequency, and duration of symptoms of depression vary on a case-to-case basis. In other embodiments, the psychiatric disorder is a bipolar or related disorder. Some examples of bipolar and related disorders include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a bipolar or related disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a substance-related disorder. Substance use disorders typically involve abuse of psychoactive compounds, such as alcohol, caffeine, cannabis, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco, cocaine, amphetamine/methamphetamine. As used herein "substance" or "substances" are psychoactive compounds that can be addictive, such as alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. The method described herein may be used for treating or preventing a substance use craving, diminishing a substance use craving, and/or facilitating substance use cessation or withdrawal. In some embodiments, the method may be used to facilitate smoking cessation or cessation of opioid use. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a substance-related disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is an anxiety disorder. Some examples of anxiety disorders include separation anxiety disorder, selective mutism, mood disorder, specific

phobias, such as, but not limited to, acrophobia, aerophobia, aquaphobia, astraphobia, agoraphobia, claustrophobia, enochlophobia, hemophobia, zoophobia, glossophobia, iatrophobia, dentophobia, mysophobia (germophobia), and the like, social anxiety disorder (social phobia), panic disorder, panic attack, generalized anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat an anxiety disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is an obsessive-compulsive or related disorder, such as obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, substance/medication-induced obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat an obsessive-compulsive or related disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a trauma- or stressor-related disorders. Some examples of such psychiatric disorders include reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder, acute stress disorder, and adjustment disorders. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a trauma- or stressor-related disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a feeding and eating disorder. Some examples of such psychiatric disorders include anorexia nervosa, bulimia nervosa, binge-eating disorder, pica, rumination disorder, and avoidant/restrictive food intake disorder. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a feeding or eating disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a neurocognitive disorder. Some examples of neurocognitive disorders include delirium, major neurocognitive disorder, mild neurocognitive disorder, major or mild neurocognitive disorder due to Alzheimer's disease,

major or mild frontotemporal neurocognitive disorder, major or mild neurocognitive disorder with Lewy bodies, major or mild vascular neurocognitive disorder, major or mild neurocognitive disorder due to traumatic brain injury, substance/medication-induced major or mild neurocognitive disorder, major or mild neurocognitive disorder due to HIV infection, major or mild neurocognitive disorder due to prion disease, major or mild neurocognitive disorder due to Parkinson's disease, major or mild neurocognitive disorder due to Huntington's disease, major or mild neurocognitive disorder due to another medical condition, and major or mild neurocognitive disorder due to multiple etiologies. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a neurocognitive disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a neurodevelopmental disorder. Some examples of neurodevelopmental disorders include autism spectrum disorder, attention-deficit/hyperactivity disorder, stereotypic movement disorder, tic disorders, Tourette's disorder, persistent (chronic) motor or vocal tic disorder, and provisional tic disorder. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a neurodevelopmental disorder, including any of those specifically pointed out above by any of the methods described herein.

In some embodiments, a variety of other psychiatric or neurological conditions may be treated according to the methods of the present disclosure. In some embodiments, such psychiatric and neurological conditions include, but are not limited to, a learning disorder, autistic disorder (e.g., autism spectrum disorder), attention-deficit hyperactivity disorder, Tourette's syndrome, phobia, post-traumatic stress disorder, dementia, AIDS dementia, Alzheimer's disease, Parkinson's disease, spasticity, myoclonus, muscle spasm, bipolar disorder, a substance abuse disorder, urinary incontinence, and schizophrenia. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat these other psychiatric and neurological disorders, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is a personality disorder. The personality disorder may be within any of the known clusters, e.g., clusters A, B, or C. Some examples of personality disorders include paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, borderline personality disorder, antisocial personality disorder,

narcissistic personality disorder, histrionic personality disorder, avoidant personality disorder, obsessive-compulsive personality disorder, and dependent personality disorder. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a personality disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder may be associated with a sexual dysfunction. Some examples of such psychiatric disorders include delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, and substance/medication-induced sexual dysfunction. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat a sexual dysfunction disorder, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the psychiatric disorder is gender dysphoria. The base compound or a pharmaceutically acceptable salt thereof described in this disclosure may be administered to treat the gender dysphoria by any of the methods described herein.

In another aspect, the present disclosure is directed to treating pain afflicting the subject. Such pain syndromes may include, but are not limited to, chronic pain, neuropathic pain, chemotherapy induced neuropathy, or pain associated with headache disorders such as a migraine, cluster headache, or other headache disorders. In the method, the base compound or a pharmaceutically acceptable salt thereof described herein, typically in the form of a pharmaceutical composition, is used to treat the pain using any one of the methods described herein. These methods described herein provide an improvement (typically, a lessening of or a shortening of the duration of) in the pain symptoms. In an embodiment, the treatment with the base compound reduces the intake of opioid agonist analgesics (e.g., a decrease in the dose and/or frequency of their administration) that the patient is alternatively using to control their pain.

Pursuant to the present disclosure, there are two phases of treatment for treating psychiatric disorders. The first phase of treatment is the acute induction period of treatment. It commences from the first administration of the base compound or a pharmaceutically acceptable salt thereof to a subject suffering from a psychiatric disorder and concludes when

neuropsychiatric symptoms are in remission. At the conclusion of the acute induction period, qualitative neuropsychiatric symptoms indicative of depression, such as persistently sad mood, decreased interest in usually pleasurable activities, reduced appetite and weight loss or increased appetite and weight gain, feelings of hopelessness, fatigue, decreased or increased sleep, poor concentration and suicidal ideation/behavior, and the like are in remission and do not manifest itself. This can be observed by a medical professional, such as a doctor, or a nurse or medical technician in the psychiatric field. Remission of the neuropsychiatric symptoms can also be measured by a series of screening characteristics or symptoms exhibited by the subject, as evaluated by a health care professional and rating the characteristics or symptoms on a graduated scale, assigning points to various symptoms that would be manifested in a subject suffering from a mood disorder, with the less intense characteristics and/or symptoms assigned a lower value and the more intense characteristics or symptoms assigned a higher value, with the final score being the addition of the point value of each of the characteristics or symptoms assigned by the health care professional. For example, one such test is the Hamilton Depression Rating Scale, which asks the clinician to rate the subject based on an interview with the subject regarding the following symptoms: 1) depressed mood, 2) feelings of guilt, 3) suicidal thought or action, 4) insomnia initial, 5) insomnia middle, 6) insomnia late, 7) work and interests (assessing pleasure and functioning), 8) motor retardation, 9) motor agitation, 10) psychic anxiety, 11) somatic anxiety, 12) gastrointestinal somatic symptoms, 13) general somatic symptoms, 14) genital symptoms, 15) hypochondriasis, 16) weight loss, and 17) insight. A score of less than or equal to 7 on this scale is indicative of the remission of the neuropsychiatric symptoms. Another test is Montgomery-Asberg Depression Rating Scale, in which the clinician rates the subject on the following symptoms exhibited by a subject in a clinical interview: 1) apparent sadness; 2) reported sadness; 3) inner tension; 4) reduced sleep; 5) reduced appetite; 6) difficulty in concentration; 7) lassitude; 8) inability to feel (assessing pleasure and functioning); 9) pessimistic thoughts; 10) suicidal thoughts. The test is usually conducted by a health-care professional, in which the subject is asked questions in the categories enumerated above, and the answers are rated on a scale. A score of less than or equal to 10 on this scale is indicative of the remission of the neuropsychiatric symptoms.

This acute induction phase in an embodiment lasts usually for a period of less than 6 months after the first dose of the base compound or a pharmaceutically acceptable salt thereof is

administered to the subject suffering from a psychiatric disorder, and in another embodiment, up to about four months after the first dose of the base compound or a pharmaceutically acceptable salt thereof is administered to the subject suffering from a psychiatric disorder. In an embodiment, it lasts from about 4 to about 16 weeks, in another embodiment from about 4 to about 8 weeks and in another embodiment, from about 4 to about 6 weeks after administration of the first dose of the base compound or a pharmaceutically acceptable salt thereof to the subject suffering from a psychiatric disorder, provided there is adherence to the schedule described herein. However, there is no specific set time-period, as the length of this phase is dependent upon the progress of the subject, so in some cases, it may be shorter than the times described herein, and in other cases, it may be longer than the times described herein.

At the conclusion of the acute induction phase of treatment, the second phase of treatment may commence, identified herein as the maintenance treatment phase, in which the subject being treated for a psychiatric disorder is periodically screened to determine if the clinical symptoms, i.e., neuropsychiatric symptoms, remain in remission or sufficiently improved, and these symptoms are screened for a sufficient period of time to determine if the neuropsychiatric symptoms remain in remission. The length of the maintenance treatment phase is determined by the psychiatrist or other medical professional that is treating the subject. In an embodiment, it lasts for about 8 weeks to about 52 weeks, and in another embodiment, from about 8 weeks to about 26 weeks from the commencement of the maintenance treatment phase, but it can be longer or shorter, dependent upon the subject's condition, as determined by a medical professional, such as a psychiatrist. Towards the end of the maintenance treatment phase, the medical professional, such as a psychiatrist, will evaluate the subject one more time to ensure that the psychiatric disorder suffered by the patient remains in remission or otherwise sufficiently improved. Once the medical professional, such as the psychiatrist, determines that the psychiatric disorder is in remission for a sufficient time, the subject no longer is administered the base compound or a pharmaceutically acceptable salt thereof, and the maintenance treatment phase is concluded. If, however, the medical professional observes a worsening of the condition during the maintenance phase of treatment, the dosage or frequency of dosing of the base compound or a pharmaceutically acceptable salt thereof may be increased, as determined by the medical professional.

Although the base compound or a pharmaceutically acceptable salt thereof may be administered by any means of administrations, the amount administered may be described in terms of the concentration of base compound achieved in the plasma of the subject. In an embodiment, blood is drawn from the subject, and plasma is obtained from the blood by techniques known in the art. For example, plasma is obtained from blood that has been mixed with an anticoagulant in the collection tube and has, therefore, not clotted. This mixed blood may then be centrifuged, yielding plasma. The concentration of base compound in the plasma thus obtained is then measured by techniques known to one of ordinary skill in the art, for example, liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the like.

The dosing regimen describes a method of treating a psychiatric disorder. In the acute induction phase of treatment, the dosing regimen described herein is therapeutically effective to treat a subject suffering from a psychiatric disorder to put into remission or substantially improve the neuropsychiatric symptoms associated with the psychiatric disorder. The dosing regimen described herein is therapeutically effective to maintain the neuropsychiatric symptoms associated with the psychiatric disorder in remission or substantially improved and minimize the risk of the subject having a relapse of the psychiatric disorder. However, due to typical inter-subject variability in psychiatric disorders, it is to be understood that not all subjects will adequately respond to treatment with base compound.

With respect to treating pain, the dosing regimen is one that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application as well as the frequency of the dose and the duration of the treatment will vary from patient to patient, but also with the route of administration, the nature of the condition being treated, the age and general health of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage regimen ultimately being at the discretion of the attendant physician, in an embodiment, there are also two phases of treatment, the acute induction phase of treatment, and the maintenance phase of treatment. Although the lengths of time and the dosing regimen administered to the patient of the two phases of treatment with respect to treating pain may overlap with the lengths of time and the dosing regimens for treating psychiatric disorder, the outward manifestation signs for the commencement and termination of each phase may be different. With respect to treating pain symptoms, the first dosage in the

acute induction phase of treatment commences when the patient is treated for pain, i.e., when the medical personnel, such as a physician treating the pain administers the first dose of the base compound or pharmaceutically acceptable salts to the patient. The dosing schedule in the acute induction phase for treating pain is the same with respect to treating psychiatric disorders, but the patient suffering from pain symptoms may not need to be screened, as described hereinabove, as the patient who suffers from the psychiatric disorder. The acute induction phase of treatment when treating pain terminates when the patient no longer feels pain ("hereinafter referred to as the pain being in remission"). At this point, the maintenance phase of treatment commences. In this embodiment, the maintenance phase of treatment has the same dosing regimen as the maintenance phase for the treatment of psychiatric disorders. However, the maintenance phase of treatment for treating pain, in this embodiment, terminates when the physician concludes that the pain has not returned for a sufficient time and that it is unlikely that the pain symptoms suffered by the patient will return. At this point, the physician will dismiss the patient. Unless the pain originally suffered by the patients reoccurs, the patient may not need any further treatment. If, again, the pain returns to the patient, then the physician will again treat the patient.

In an embodiment, the present disclosure relates to a method of treating a psychiatric disorder and/or pain in a subject in need thereof comprising administering to said subject a base compound or a pharmaceutically acceptable salt thereof in one or more doses during an acute induction phase in an amount sufficient to achieve in said subject from each administration of the base compound or a pharmaceutically acceptable salt thereof after each dose an AUC ranging from about 390 to about 3,600 h·ng/mL, wherein the base compound is substantially pure (R)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one. The frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. In an embodiment, the acute induction phase concludes with the commencement of a maintenance treatment phase that commences immediately after the conclusion of the acute induction period when neuropsychiatric symptoms from the psychiatric disorder are in remission or when the patient no longer suffers from the pain. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject at treatment interval ranging from every other week to three days a week for a period of about four to about six weeks during the acute induction period. In another embodiment, the base

compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve an AUC ranging from about 390 to about 2,100 h·ng/mL during the acute induction period. In a further embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve an AUC ranging from about 550 to about 1,800 h·ng/mL during the acute induction period. In an embodiment, the AUC is measured after the administration of a dose of the base compound or a pharmaceutically acceptable salt thereof, such as from about 0 to about 24 hours after its administration. In an embodiment, these values of the AUC and of the C_{max} are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

At the conclusion of the acute induction phase, the maintenance treatment phase commences, wherein the objective is to maintain the remission or improvement of the neuropsychiatric and/or pain symptoms. The base compound or a pharmaceutically acceptable salt thereof is administered to the subject in an amount sufficient to achieve in said subject from each administration of the base compound or a pharmaceutically acceptable salt thereof after each dose an AUC ranging from about 390 to about 2,100 h·ng/mL. The frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. For example, to achieve this level, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to every other week basis for a period of at least 8 weeks or until the conclusion of the maintenance treatment phase. In an embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 1,800 h·ng/mL on a weekly to every other week basis. In another embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 230 h·ng/mL to about 970 h·ng/mL on a weekly to daily basis to a subject in need thereof for a period of at least eight weeks during the maintenance treatment. In another embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to

about 760 h·ng/mL on a weekly to daily basis to a subject in need thereof during a maintenance treatment phase. In an embodiment, these values of the AUC are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

In another embodiment, the present disclosure relates to a method of treating a psychiatric disorder and/or pain in a subject in need of such treatment comprising administering the base compound or a pharmaceutically acceptable salt thereof to the subject in need of treatment during the acute induction phase in an amount sufficient to achieve a C_{max} in plasma ranging from about 72 ng/mL to about 540 ng/mL at treatment intervals ranging from every other week to three days a week. The dosage and the frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve a C_{max} in the plasma of the subject ranging from about 72 ng/mL to about 330 ng/mL during the acute induction period. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve a C_{max} in the plasma of the subject ranging from about 110 ng/mL to about 280 ng/mL during the acute induction period. Typically, the C_{max} is measured after the administration of a dose of the base compound or a pharmaceutically acceptable salt thereof, such as from about 1 to about 3 hours after its administration for an oral dose, or immediately after injection for an IV bolus, or immediately on conclusion of the infusion for an IV infusion, or about 15 to about 30 minutes after administration for an IM injection. In an embodiment, these values of the C_{max} are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

At the conclusion of the acute induction phase, the maintenance treatment phase commences, wherein the objective is to maintain the remission or improvement of the neuropsychiatric and/or pain symptoms. The base compound or a pharmaceutically acceptable salt thereof is administered to the subject in an amount sufficient to achieve in said subject after each dose a C_{max} ranging from about 72 ng/mL to about 330 ng/mL. The frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. To achieve this level, in an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to every other week basis for a

period of at least 8 weeks, or in an embodiment up to 52 weeks, or until the conclusion of the maintenance treatment phase. In an embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 280 ng/mL on a weekly to every other week basis. In another embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase is in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 39 ng/mL to about 150 ng/mL on a weekly to daily basis to a subject in need thereof for a period of at least eight weeks during the maintenance treatment. In another embodiment, the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase is in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 130 ng/mL on a weekly to daily basis to a subject in need thereof during a maintenance treatment phase. In an embodiment, these values of C_{max} are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person. For each of the C_{max} values given hereinabove, the C_{max} is measured about 1 to about 3 hours after administration of the base compound or a pharmaceutically acceptable salt thereof for an oral dose, or immediately after injection for an IV bolus, or immediately on conclusion of the infusion for an IV infusion, or about 15 to about 30 minutes after administration for an IM injection.

In another embodiment, the present disclosure relates to a method of treating a patient afflicted with a psychiatric disorder and/or pain comprising administering orally to a patient in need thereof the base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment at a dosage ranging from about 40 mg to about 360 mg relative to the base compound at treatment intervals ranging from every other week to three days a week. The frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered orally at a dosage range of about 40 to about 180 mg relative to the base compound during the acute induction phase of treatment. In a further embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered orally at a dosage range of about 60 to about 140 mg relative to the base compound during the acute induction phase of treatment, and in a further embodiment, from about 140 mg

to about 220 mg. In an embodiment, these dosage amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

At the conclusion of the acute induction phase, the maintenance treatment phase commences, wherein the objective is to maintain the remission or improvement of the neuropsychiatric and/or pain symptoms. The base compound or a pharmaceutically acceptable salt thereof is administered to the subject orally in an amount ranging from about 40 to about 180 mg and in another embodiment, from about 140 mg to about 220 mg, all of these dosage amounts being relative to the base compound on a weekly to every other week basis to the patient in need thereof for a period of at least 8 weeks, and in an embodiment up to 52 weeks, during a maintenance treatment phase that commences immediately after the conclusion of the acute induction period. The frequency of the dosage is determined by one of ordinary skill in the art, such as the psychiatrist or other doctor in the psychiatry field. In an embodiment the dose level of the base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 360 mg and in another embodiment, from about 40 to about 140 mg, and in a further embodiment, from about 140 mg to about 220 mg, with all of these dosage amount being relative to the base compound on a weekly to every other week basis. In a further embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject suffering from a psychiatric disorder ranging from about 20 to about 100 mg relative to the base compound on a weekly to daily basis during the maintenance phase. In a further embodiment, the dose level of the base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 80 mg relative to the base compound on a weekly to daily basis during the maintenance treatment phase. In an embodiment, if administered orally, the base compound or a pharmaceutically acceptable salt thereof is administered as a single unit dose. In an embodiment, these amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

In an embodiment, the base compound or a pharmaceutically acceptable salt thereof during the acute induction phase or during the maintenance treatment phase or both phases for a psychiatric disorder or pain is administered concurrently with an antidepressant. The antidepressant may be administered simultaneously with or concurrently with the base compound or a pharmaceutically acceptable salt thereof, as defined hereinabove.

In addition, the base compound or a pharmaceutically acceptable salt thereof may be administered by one route and the antidepressant may be administered by the same or different route to the subject. For example, the base compound or a pharmaceutically acceptable salt thereof may be administered orally and the antidepressant may also be administered orally or may be administered by a different route, such as by, for example, intravenously, or by inhalation or intramuscularly. In addition, in an embodiment, the antidepressant and the base compound or a pharmaceutically acceptable salt thereof may be mixed together prior to the administration to the subject.

In an embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof blocks the serotonin transporter. In another embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is a selective serotonin reuptake inhibitor. In an embodiment, the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine. In a further embodiment, the antidepressant drug to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is a serotonin-norepinephrine reuptake inhibitor. In an embodiment, the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.

In another embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is a tricyclic or tetracyclic antidepressant. In a further embodiment, the tricyclic or tetracyclic antidepressant is imipramine, desipramine, amitriptyline, nortriptyline, amoxapine, clomipramine, dibenzepin, dosulepin, doxepin, lofepramine, maprotiline, norclomipramine, opipramol, protriptyline, trimipramine, mitrazapine, mianserin, or setiptiline.

In another embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is bupropion.

In another embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is a monoamine oxidase inhibitor (MAOI). In a further embodiment, the MAOI is isocarboxazid, hydracarbazine, phenelzine, tranylcypromine, bifemelane, methylthionium chloride, moclobemide, pirlindole, rasagiline, selegiline, or safinamide.

In another embodiment, the antidepressant to be used simultaneously or concurrently with the base compound or a pharmaceutically acceptable salt thereof is gepirone.

In additional embodiments, treatment with the base compound or a pharmaceutically acceptable salt thereof, for example, as a maintenance treatment phase, commences after an acute induction treatment with esketamine, arketamine, or racemic ketamine or combination thereof. As indicated hereinabove, the antidepressant may be administered by a different mode than the base compound or a pharmaceutically acceptable salt thereof. For example, the base compound or a pharmaceutically acceptable salt thereof may be administered orally, while esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the acute induction phase of treatment. For example, in an embodiment, esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.

In an embodiment, the present disclosure relates to a method of treating a patient having a psychiatric disorder or pain comprising administering the base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to a patient in need thereof on a daily basis, wherein the base compound or a pharmaceutically acceptable salt thereof is administered at a dosage level ranging from about 20 mg to about 100 mg relative to the base compound per day or in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 230 to about 970 h·ng/mL or a C_{max} ranging from about 39 ng/mL to about 150 ng/mL. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered orally. In another embodiment, the daily dose of the base compound or a pharmaceutically acceptable salt thereof is administered as a single unit dose. In another embodiment, the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is administered as a single unit dose. In a further embodiment, the daily dose of the base compound or a pharmaceutically acceptable salt thereof and the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor are administered together as a single unit dose in a single pharmaceutical composition. In an embodiment, the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, vortioxetine, duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran. In an embodiment, fluoxetine is administered at

a daily dose ranging from about 10 to about 80 mg, paroxetine is administered at a daily dose ranging from about 10 to about 60 mg, citalopram is administered at a daily dose ranging from about 10 to about 40 mg, escitalopram is administered at a daily dose ranging from about 5 to about 20 mg, fluvoxamine is administered at a daily dose ranging from about 25 to about 300 mg, sertraline is administered at a daily dose ranging from about 50 to about 200 mg, vortioxetine is administered at a daily dose ranging from about 5 to about 20 mg, duloxetine is administered at a daily dose ranging from about 30 to about 120 mg, venlafaxine is administered at a daily dose ranging from about 37.5 to about 375 mg, desvenlafaxine is administered at a daily dose ranging from about 25 to about 200 mg, milnacipran is administered at a daily dose ranging from about 12.5 to about 200 mg, and levomilnacipran is administered at a daily dose ranging from about 20 to about 120 mg. In an embodiment, the foregoing amounts are relative to the free base of the indicated compound. In an embodiment, these amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

The present disclosure further relates to a method of treating a subject having pain comprising administering orally to a patient in need thereof the base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment at a dosage ranging from about 40 mg to about 360 mg relative to the base compound or at an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 3,600 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 540 ng/mL at treatment intervals ranging from every other week to three days a week for a period of about four to about six weeks. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered at a dosage range of about 40 to about 180 mg relative to the base compound or in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 2,100 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 330 ng/mL during the acute induction phase of treatment. In a further embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered at a dosage range of about 60 to about 140 mg relative to the base compound or in amount sufficient to achieve in the plasma of the subject an AUC ranging from about 550 h·ng/mL to about 1,800 h·ng/mL or a C_{max} ranging about 110 ng/mL to about 280 ng/mL during the acute induction phase of treatment. In an embodiment, these amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

In an embodiment, the method additionally comprises administering the base compound or a pharmaceutically acceptable salt thereof in an amount ranging from about 40 to about 180 mg relative to the base compound or an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 2,100 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 330 ng/mL on a weekly to every other week basis to the patient in need thereof for a period of at least 8 weeks during the maintenance treatment phase. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject during the maintenance treatment phase in an amount ranging from about 40 to about 140 mg relative to the base compound or in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 1,800 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 280 ng/mL on a weekly to every other week basis. Further, in an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 20 to about 100 mg relative to the base compound or an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 230 h·ng/mL to about 970 h·ng/mL or a C_{max} ranging from about 39 ng/mL to about 150 ng/mL on a weekly to daily basis to a patient in need thereof for a period of at least eight weeks during the maintenance treatment phase. Further, in another embodiment the base compound or a pharmaceutically acceptable salt thereof is administered to the patient in an amount during the maintenance treatment phase ranging from about 40 to about 80 mg relative to the base compound or in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 760 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 130 ng/mL on a weekly to daily basis. In an embodiment, these amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person.

In an embodiment, the pain is chronic pain or neuropathic pain. In another embodiment, the pain is chemotherapy induced neuropathy. In a further embodiment, the treatment results in a decreased intake of opioids by the patient.

In an embodiment, the present disclosure relates to a method of treating a patient having pain comprising administering the base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to a patient in need thereof on a daily basis, wherein the base compound or a pharmaceutically acceptable salt thereof is administered at a dosage level in an amount ranging

from about 20 mg to about 100 mg relative to the base compound or in an amount per day in an amount sufficient to achieve in the plasma an AUC ranging from about 230 h·ng/mL to about 970 h·ng/mL or a C_{max} ranging from about 39 ng/mL to about 150 ng/mL on a weekly to daily basis to a patient in need thereof for a period of at least eight weeks during the maintenance treatment phase. Further, in another embodiment the base compound or a pharmaceutically acceptable salt thereof is administered to the patient in an amount during the maintenance treatment phase ranging from about 40 to about 80 mg relative to the base compound or in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 760 h·ng/mL or a C_{max} ranging from about 72 ng/mL to about 130 ng/mL on a weekly to daily basis. In an embodiment, these amounts are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person. In an embodiment, the daily dose of base compound or a pharmaceutically acceptable salt thereof is administered as a single unit dose.

In an embodiment, the present disclosure relates to a dosing kit comprising unit doses of a first pharmaceutical composition comprising base compound or a pharmaceutically acceptable salt thereof and a first pharmaceutical carrier therefor and unit doses of a second pharmaceutical composition comprising a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor and a second pharmaceutical carrier therefor and instructions for administering the first pharmaceutical composition and the second pharmaceutical composition to a patient suffering from a psychiatric disorder or pain.

In a further embodiment, the present disclosure is directed to a pharmaceutical composition in solid dosage form comprising a first component of about 20 to about 100 mg of the base compound or a pharmaceutically acceptable salt thereof relative to the base compound and a second component that is one of the following: about 10 to about 80 mg of fluoxetine, about 10 to about 60 mg of paroxetine, about 10 to about 40 mg of citalopram, about 5 to about 20 mg of escitalopram, about 25 to about 300 mg of fluvoxamine, about 50 to about 200 mg of sertraline, about 5 to about 20 mg of vortioxetine, about 30 to about 120 mg of duloxetine, about 37.5 to about 375 mg of venlafaxine, about 25 to about 200 mg of desvenlafaxine, about 12.5 to about 200 mg of milnacipran, or about 20 to about 120 mg of levomilnacipran, along with a pharmaceutical carrier therefor. In an embodiment, the foregoing amounts are relative to the free base of the indicated compound. In a further embodiment, the pharmaceutical composition comprises a first component comprising about 20 to about 140 mg of the base compound or a

pharmaceutically acceptable salt thereof relative to the base compound and a second component comprising one or more of the following: about 10 to about 80 mg of fluoxetine, about 10 to about 60 mg of paroxetine, about 10 to about 40 mg of citalopram, about 5 to about 20 mg of escitalopram, about 25 to about 300 mg of fluvoxamine, about 50 to about 200 mg of sertraline, or about 5 to about 20 mg of vortioxetine, along with a pharmaceutical carrier therefor. In an embodiment, the foregoing amounts are relative to the free base of the indicated compound. In another embodiment, the pharmaceutical composition comprises a mixture of two or more components, wherein the first component comprises about 20 to about 100 mg of the base compound or a pharmaceutically acceptable salt thereof relative to the base compound and the remaining component(s) comprises at least one of the following: about 30 to about 120 mg of duloxetine, about 37.5 to about 375 mg of venlafaxine, about 25 to about 200 mg of desvenlafaxine, about 12.5 to about 200 mg of milnacipran, or about 20 to about 120 mg of levomilnacipran, along with a pharmaceutical carrier therefor. In an embodiment, the foregoing amounts are relative to the free base of the indicated compound.

In another embodiment, the base compound or a pharmaceutically acceptable salt thereof may be administered as an IV bolus or short infusion of, for example, less than or equal to about 30 minutes in one embodiment, and in another embodiment, less than or equal to about 15 minutes, for a time and dosage effective to treat the psychiatric disorder or pain. In an embodiment, in the acute induction phase of treatment, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 13 to about 120 mg relative to the base compound, and in another embodiment, in an amount to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 13 to about 60 mg relative to the base compound or in another embodiment, in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL. In a further embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 20 to about 47 mg relative to the base compound or in another embodiment, in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from

about 110 ng/mL to about 280 ng/mL. The base compound is administered to the subject in treatment intervals ranging from every other week to three days a week until symptoms from the psychiatric disorder or pain are in remission or sufficiently improved. In an embodiment, the acute induction phase of treatment lasts for about 4 to about 26 weeks, and in another embodiment for about 4 to about 12 weeks, and in another embodiment for about 4 to about 6 weeks, and in another embodiment for about 2 to about 4 weeks.

At the conclusion of the acute induction phase, the maintenance treatment phase optionally commences, wherein the objective is to maintain the remission or improvement of the neuropsychiatric or pain symptoms. The base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes in amount ranging from about 13 mg to about 60 mg relative to the base compound or in another embodiment, in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to every other week basis for a period of at least 8 weeks, or in another embodiment up to 52 weeks, or until the conclusion of the maintenance treatment phase. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes to the patient during the maintenance treatment phase in an amount ranging from about 13 mg to about 47 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 280 ng/mL.

In another embodiment, in a different dosage regimen for the maintenance treatment phase, the base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 7 mg to about 33 mg relative to the base compound or in another embodiment, in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 39 ng/mL to about 150 ng/mL. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to daily basis for a period of at least 8 weeks and in an embodiment, up to 52 weeks, or until the conclusion of the maintenance treatment phase. In another embodiment,

the base compound or a pharmaceutically acceptable salt thereof is administered as an IV bolus or short infusion in less than or equal to about 15 minutes to the patient during the maintenance treatment phase in an amount ranging from about 13 mg to about 27 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 130 ng/mL.

In an embodiment, the listed doses of base compound or a pharmaceutically acceptable salt thereof to be administered as an IV bolus or short infusion in less than or equal to about 15 minutes and corresponding $C_{\max}$ values are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person. By using an IV bolus or short IV infusion, compared to oral administration at the same dose, a higher $C_{\max}$ is achieved at a faster rate and a higher $C_{\max}/AUC$ ratio is achieved.

In another embodiment, the base compound or a pharmaceutically acceptable salt thereof may be administered intramuscularly (IM) at a dosage amount effective to treat the psychiatric disorder or pain. In an embodiment, it is administered in one dosage. In an embodiment, in the acute induction phase of treatment, the subject suffering from a psychiatric disorder or pain is administered the base compound or a pharmaceutically acceptable salt thereof IM. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 20 to about 180 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 540 ng/mL. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 20 to about 90 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 330 ng/mL during the acute induction phase of treatment. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 30 to about 70 mg relative to the base compound, and in another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 110 ng/mL to about 280 ng/mL. The base compound or a pharmaceutically acceptable salt thereof is administered to the subject in treatment intervals ranging from every other week to three days a week until the psychiatric disorder or pain are in remission or sufficiently improved. In an embodiment, the

acute induction phase of treatment lasts for about 4 to about 26 weeks, and in another embodiment for about 4 to about 12 weeks, and in another embodiment for about 4 to about 6 weeks, and in another embodiment for about 2 to about 4 weeks.

At the conclusion of the acute induction phase, the maintenance treatment phase optionally commences, wherein the objective is to maintain the remission or improvement of the neuropsychiatric or pain symptoms. The base compound or a pharmaceutically acceptable salt thereof is administered to the subject IM in an amount ranging from about 20 to about 90 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 330 ng/mL. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to every other week basis for a period of at least 8 weeks or in an embodiment, up to 52 weeks, or until the conclusion of the maintenance treatment phase. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered IM to the patient during the maintenance treatment phase in an amount ranging from about 20 to about 70 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 280 ng/mL.

In another embodiment, in a different dosage regimen for the maintenance treatment phase, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject IM in an amount ranging from about 10 to about 50 mg relative to the base compound and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 39 ng/mL to about 150 ng/mL. In another embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered in the above-indicated amount during the maintenance treatment phase to the subject on a weekly to daily basis for a period of at least 8 weeks, or in an embodiment, up to 52 weeks, or until the conclusion of the maintenance treatment phase. In an embodiment, the base compound or a pharmaceutically acceptable salt thereof is administered to the patient IM during the maintenance treatment phase in an amount ranging from about 20 to about 40 mg relative to the base compound, and in another embodiment, in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 130 ng/mL.

In an embodiment, the listed doses of base compound or a pharmaceutically acceptable salt thereof to be administered by IM injection and the corresponding values of $C_{\max}$ are for an approximately 65 to approximately 80 kg person, e.g., about 70 kg person. By using an IM injection, compared to oral administration at the same dose, a higher $C_{\max}$ is achieved at a faster rate and a higher $C_{\max}/AUC$ ratio is achieved.

The following examples further illustrate the subject matter of the present disclosure.

EXAMPLES

A. Examples with Human Subjects

1. EXAMPLES WITH SINGLE ASCENDING DOSE

The examples that follow are part of a SAD (Single Ascending Dose) trial on 6 groups of healthy adult volunteers, wherein each group consisted of eight people. Six members of each group each received single oral doses of base compound, either 20 mg, 60 mg, 100 mg, 140 mg, 220 mg, or 360 mg throughout the trial, while two members of each group received single oral doses of placebo, either 20 mg, 60 mg, 100 mg, 140 mg, 220 mg, or 360 mg throughout the trial. In these studies, the placebo administered was all the same. There were some MAD (Multiple Ascending Dose) studies, in which there were 2 groups of 12 where 9 participants of each group received a single oral dose (140 mg or 220 mg) of base compound, where 4 doses were administered every other day for seven days, and 3 participants of each group received multiple oral doses of placebo when the nine participants in these groups received multiple doses (140 mg or 220 mg) of base compound over seven days. In some cases, there were 12 crossover studies where 100 mg of base compound or placebo was orally administered, where the participant was either fed or fasted for a prescribed period of time. The various pharmacodynamic measures are outlined in FIG. 17.

EXAMPLE 1 Human Pharmacokinetic

The following example describes a double-blind, placebo-controlled human trial to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of single doses of base compound administered orally. The study was conducted on human subjects ranging in age from

18 to 50 years with a mean age of 25.2 years, a mean body mass of 71.1 kg, and a mean body mass index (BMI) of 22.7 kg/m², ranging from 19 to 31 kg/m². There were a total of 48 subjects tested, half of which were female and 44 of which were white. They were divided into 6 groups of 8 subjects, wherein 2 subjects in each group received placebo and the other 6 subjects in each group received a single oral dose of base compound at the following dose levels: 20 mg, 60 mg, 100 mg, 140 mg, 220 mg, or 360 mg. The doses indicated are on the basis of free base compound and corrected for salt counterion mass.

Blood was drawn from each subject at multiple time points post dose, viz., 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours and 30 hours after its administration, processed to plasma by standard methods, and analyzed for base compound using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Figure 1A shows the plasma concentration of base compound over time as a linear measurement and Figure 1B shows a semi-log measurement. The semi-log measurement is traditionally shown as dose-proportional increases, such as observed in Figure 1B, and demonstrate parallel lines between the different drug doses. The results shown in Figures 1A and 1B were obtained from the single ascending dose (SAD) trial of the Phase 1 protocol of base compound administered orally in contrast to typical intravenous infusion with the NMDA antagonist ketamine or intranasal administration of the NMDA antagonist esketamine (S-ketamine). With respect to the administration of base compound, from the graphs, it was noted that there was an increased density during the initial few hours of base with respect to the plasma concentration affecting the pharmacokinetic parameters (especially the peak concentration (C_{max}) and area under the curve 0-24 h (AUC_{0-24h}) and half-life of the drug ($t_{1/2}$).

The values of area under the plasma concentration versus time curve from time 0 to 24 hours post dose (AUC_{0-24}) and maximum plasma concentration (C_{max}) for each cohort receiving base compound are provided in Table 1 below.

Table 1. Human Pharmacokinetic Parameters of Base Compound in Plasma

Base Compound Dose (mg)	n	Mean AUC ₀₋₂₄ (h*ng/mL)	AUC ₀₋₂₄ CV%	Maximum Individual AUC ₀₋₂₄ (h*ng/mL)	Mean C _{max} (ng/mL)	C _{max} CV%	Maximum Individual C _{max} (ng/mL)	Mean t _{1/2} (h)	Median t _{max} (h)
20	6	227	20.2	273	39.17	14.5	47.7	4.37	1
60	6	554	14.3	676	105.0	12.7	122	4.41	1.5
100	6	966	40.2	1598	153.5	20.0	205	4.56	1.5
140	6	1762	23.3	2218	276.7	16.1	353	4.63	2
220	6	2428	27.1	3558	381.8	13.3	434	3.95	2.5
360	6	3587	48.2	6588	540.8	46.7	980	3.77	1.5

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration versus time curve from time 0 to 24 hours; C_{max} = maximum plasma concentration; CV% = coefficient of variation; t_{1/2} = half-life; t_{max} = time of maximum concentration.

As shown in Table 1, the coefficient of variation (CV%) for the AUC₀₋₂₄ was under 27.1% in 4 of the 6 groups and was 40.2% and 48.2% for the 100 and 360 mg groups, respectively. The CV% for the C_{max} was ≤20% for 5 of the 6 groups and was 46.7% for the 360 mg group. The half-life (t_{1/2}) was 4.37 to 4.63 hours for the 20 to 140 mg groups while being slightly less (3.95 and 3.77 hours) for the 220 and 360 mg groups. The median time to reach maximum concentration (t_{max}) values ranged from 1 to 2.5 hours across groups.

Regarding safety, there were no deaths, or serious or severe treatment emergent adverse events (TEAE) in any of the groups. A dose-dependent increase in TEAEs occurred through the 220 mg dose; with most TEAEs categorized as mild.

EXAMPLE 2 Human Body Sway Measurements

The body sway measurement provides an objective assessment of postural stability and ataxia by measuring body movements in a single plane.

Methods. The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the human subjects as described in Example 1 and Figure 17. At 1 hour, 3 hours, 8 hours and 24 hours after administration of the base compound, body sway was measured with a pot string meter (celesco) based on the Wright ataxiometer. With a string attached to the waist, all body movements over a period of 2 minutes were integrated and expressed as mm sway. Subjects were instructed to wear a pair of comfortable, low-heeled shoes on each session. Before starting a measurement, subjects were asked to stand still and comfortably, with their feet approximately 10 cm apart and their hands in a relaxed position alongside the body and eyes closed. Subjects were not allowed to talk during the measurement.

Body sway was recorded in all subjects according to the following methods, with the results summarized in Figure 2.

Results. Body sway measurements over time following administration of different dose levels of base compound are presented in Figure 2. Up to doses of 100 mg, body sway induced by the base compound did not exceed pre-dose values. At 140 mg and 220 mg, minimal increases at 1.5 h and 3.5 hours post drug administration were noted. At the high dose of 360 mg, a large increase in body sway was observed at these two time points post drug administration but had returned to near baseline by 8 h post dose. Collectively, these findings suggest that doses of base compound of 220 mg or lower induce minimal to no ataxic side effects and may be the most suitable doses for therapeutic use.

EXAMPLE 3 Human Dissociative Effects

Dissociative effects of channel blocking NMDA receptor antagonists were noted during the development of these drugs as general anesthetics in the 1960s when subjects would experience derealization, depersonalization, and amnesia when coming out of frank anesthesia. The most widely used scale to measure dissociative symptoms is the Clinician-Administered Dissociative States Scale (CADSS), which includes dissociative effects (derealization, depersonalization, and amnesia) using the Clinician Administered Dissociation Symptom Scale. This 28 item scale contains both subjective and objective items that are scored (0 to 4 for each item) by an experienced clinician. The CADSS developers identified a total CADSS score of greater than 4 at any timepoint to be abnormal. Dissociation was quantified in all subjects using the CADSS, with the mean CADSS total score results summarized in Figure 3.

Methods. The 23-item CADSS scale sums together the three sub-scales of derealization, depersonalization, and amnesia to arrive at the Total CADSS score. The clinician asks 23 questions such as “Do things seem to be unreal to you, as if in a dream?” and scores the response using anchors ranging from 0 (not at all) to an item score of 4 (extreme, e.g., I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream). While this scale consisting of 23 items was originally developed to measure dissociative states in patients with post-traumatic stress disorder (PTSD) and other dissociative disorders, it has been universally adopted to understand dose (exposure)-dependent dissociative effects of NMDA receptor antagonists. The TEAEs reported by at least one participant in the base compound dose level of

the SAD trial from the protocol is based on spontaneous reports to a psychiatric physician or any other clinical staff. The verbatim report from the trial participant is matched to the MedRA hierarchy of adverse events. MedRA is the acronym for the Medical Dictionary for Regulatory Activities that is updated on a regular basis and is accepted by all regulatory authorities for the scoring of adverse events during clinical trials of medications or medical devices. Adverse events (AEs) are recorded from the time of admission to the clinical unit for a trial such as the current one through discharge from the clinical unit and through generally 30 days after administration of the drug. Treatment-emergent AEs (TEAEs) are AEs reported by the participant after administration of a trial treatment, in this case, for example, base compound or placebo. As discussed above, the spontaneous verbatim report is matched to the Preferred Term from the MedRA hierarchy which most accurately describes the event. Each preferred term is listed under broader System Organ Class (SOC) terms such as Psychiatric Disorders or Nervous System Disorders which comprised a majority of TEAEs for the SAD, MAD and Food studies of the Phase 1 protocol. An adjudication meeting was held prior to data base lock to ascertain that the verbatim listing was matched to the best Preferred Term and SOC category. Thus, slow response to stimuli could be either a subjective report by the participant to an observer or it could be an objective observation by an observer. TEAEs could also be clinically significant laboratory (hematology or chemistry) reports or clinically abnormal vital signs observed by the clinical staff

In the Single Ascending Dose (SAD) trial described in Example 1 and Figure 17, dissociative effects were assessed by an experienced clinician from the reports of healthy male and female volunteers using the CADSS at about 37 min, 2 hours, 3 hours 44 minutes, 6 hours, and 30 hours following administration of placebo and base compound doses of 20-360 mg (20, 60, 100, 140, 220 and 360 mg; 6 participants on active drug at each given dose level).

Results. All participants had baseline CADSS total scores of 0, indicating no pre-dose dissociation. At 37 minutes post-dose, no participant in the 20 to 100 mg base compound dose groups had a CADSS total score greater than 4, a criterion used to indicate a clinically significant increase in dissociation.

The break-down of the various specific assessments for the different groups are depicted in Figures 4 and 5.

For the 140 mg dose group, 1 out of 6 participants had a CADSS total score of >4 at 37 minutes post-dose. For the 220 and 360 mg doses, 4 of 6 participants had a CADSS total score of

>4, indicating that most participants in these groups experienced some dissociation. This rate of CADSS-defined dissociation for these highest 2 dose levels is similar to that reported for esketamine (range of 60% to 84% (Spravato Package Insert)).

Mean CADSS scores by timepoint and treatment group are shown in Figure 3.

Similar to past observations with ketamine (Fava M et al., *Mol Psychiatry*, 2020, 25: 1592-1603. doi: 1038/s41380-018-0256-5), there was a base compound dose-dependent increase in mean CADSS scores at about 30 minutes post dose where mean CADSS total scores for the 220 and 360 mg dose groups were 7.0 (range of 1 to 14) and 19.2 (range of 0 to 43), respectively. In comparison, patients in a Phase 3 study of esketamine nasal spray with an antidepressant displayed an approximate 7-point change from baseline at approximately 40 minutes post esketamine (See, Wajs, et al., *J Clin Psychiatry*, 81(3), 12891 (2020); <https://pubmed.ncbi.nlm.nih.gov/32316080/>). For all base compound dose groups, mean CADSS total scores decreased at the 2 h and 3 h 44 min post-dose timepoints. At 2 h post-dose, 1 out of 6 participants in each of the 100, 140, and 220 mg dose groups had a CADSS total score of >4, with scores of 10, 5, and 9, respectively, and 3 participants in the 360 mg group had a CADSS total score >4, with scores of 22, 26, and 29. The mean CADSS total score for the 360 mg group was 10.0 (range of 0 to 29) at the 2 h post-dose timepoint. At 3 h 44 min post-dose, no participants in the 20 to 220 mg groups had a CADSS total score >4 and only 2 participants in the 360 mg group had CADSS total scores of >4, with scores of 12 and 15. At 6 hours post-dose, no participant had a CADSS total score of >4, with all participants having CADSS total scores of 0 except for 2 participants in the 360 mg group who had non-zero CADSS total scores of 1 and 3. At 30 hours post dose, all participants had CADSS total scores of 0. Collectively, these findings suggest that doses of base compound lower than 220 mg induce reduced dissociative side effects compared to ketamine and esketamine at typical antidepressant doses and therefore, may be the most suitable doses for therapeutic use.

Figure 7 shows the dose-dependent and time-dependent effects of base compound at increasing dissociation in the SAD trial. As the graph shows, there are minimal dissociative effects of base compound over the expected therapeutic dose range of 60-140 mg.

Figure 6 provides a graphical depiction of the percentage of human subjects who were orally administered base compound exhibiting CADSS greater than 4 at any time following base compound administration. CADSS scores greater than 4 are considered a clinically significant

endpoint. This figure shows dose-dependent effects of base compound at increasing dissociative effects (derealization, depersonalization, and amnesia) using the Clinician Administered Dissociation Symptom Scale. This figure shows the aggregated incidence of base compound (20-360 mg) at inducing a CADSS score > 4 at any time point where the results of the SAD, MAD and food effect studies from the Phase 1 protocol have been combined. The SAD trial examined doses of 20, 60, 100, 140, 220 and 360 mg while the MAD trial examined doses of 140 and 220 mg. The food effect trial examined a dose of 100 mg base compound in a crossover fashion under both fed and fasted states. The SAD and MAD studies were all conducted in the fasting condition. Of note, the incidence of abnormal dissociative scores as determined by the CADSS instrument was none to minimal (26.7) over the expected therapeutic dose range of 60-140 mg. In contrast, the esketamine package insert for MDD and the Spravato Package Insert of esketamine notes that the incidence of dissociative effects is approximately 60-84% for therapeutic doses (56 and 84 mg intranasal esketamine).

EXAMPLE 4 Human EEG

Resting-state electroencephalography (EEG) is very sensitive to central actions of pharmacological substances. For this reason, pharmaco-EEG (pEEG) has become an established method to assess drug effects on central nervous system (CNS) functioning. The measurement and analysis of EEG activity in pharmacological research generally comprises a number of electrodes to obtain an impression of 'overall' cerebral EEG activity. The time-domain recordings are transformed into the frequency domain and changes in EEG power in certain frequency bands are then quantified. The frequency bands of interest include the delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ) bands.

In the Phase 1 clinical trial described in Example 1, EEG activity was recorded in all subjects according to the following methods, with the results summarized in Figure 7A, 7B, 7C, and 7D.

Methods. For the resting-state EEG setup, the TMSi EEG recording equipment was used. 21 electrodes were embedded in an EEG cap according to the international 10-20 system. The scalp electrode impedance was kept below 5k Ω . The ground electrode was placed at AFz EEG location. All signals were sampled at a sampling rate of 1024 Hz and are filtered prior to

storage using a first order recursive high-pass filter with a cut-off frequency at 0.1 Hz. Digital markers were recorded by the amplifier indicating the start and end of each eye state. Subjects were seated in a comfortable position and were looking towards the wall. Subjects were instructed not to stare, to limit their head and eye-movements, and to suppress eye-blinks. Each recording employed alternating periods with eyes opened (Figure 8A and Figure 8B) and closed (Figure 8C and Figure 8D) with a duration of 64-seconds per period. This is repeated 5 times, resulting in 10 minutes of usable EEG. Between eyes opened and closed sessions, subjects were given some time to get adjusted to the 'new' lightning conditions. This is especially important when transitioning from closed to opened eyes. Subjects were informed to close or open their eyes based on custom scripts that also sent trigger information to the EEG recording device.

Analysis of the EEG recordings was performed automatically after the measurement using custom scripts written in Matlab by Mathworks. EEG recordings were high-pass filtered at 0.5 Hz to remove DC offset. Notch filter at 50 Hz was applied to remove line noise. Bad channels were identified as channels with low correlation with their neighboring channels. Identified bad channels were then interpolated as an average of their neighboring channels. All EEG signals were re-reference by subtracting the average EEG signal obtained from all EEG electrodes. Noisy epochs in signals were detected as epochs that crossed variance estimated from baseline recording using predefined threshold and were excluded from further analysis. EEG signals were separately normalized by dividing signals by their root-mean-square (RMS) value obtained from the baseline recording. EEG signal power was computed by convolving EEG signal with a group of log-spaced complex Morlet wavelets in the frequency range of 1-100 Hz and scaling factor $f_0/s_f = 8$ followed by squaring the result. Power values were separately averaged for eyes open and eyes closed conditions across consecutive timepoints. Power values were further averaged across canonical EEG bands including delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-25 Hz), slow gamma (GammaS, 30-50 Hz), and fast gamma (GammaF, 65-95 Hz) to obtain band-specific spectral averages. Finally, EEG band-specific power values were averaged across all electrodes to obtain single value of EEG band-specific power value for each subject, time point, EEG band and state (eyes open or eyes closed).

The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the human subjects as described in Example 1 and Figure 17. The EEG measurements using the method described hereinabove were taken 2 hours before

administration, 1 hour before administration, 1 hour after administration, 3 hours after administration and 8 hours after administration of base compound or placebo.

Results. The EEG results at different dose levels in the eyes open state are presented in Figures 8A, 8B, 8C, and 8D. Figure 8A depicts the EEG results when the eyes are open, which are graphically depicted in Figure 8B, while Figure 8C depicts the results when the eyes are closed, which are graphically depicted in Figure 8D. The base compound induced dose-dependent effects across several frequency bands, with the most prominent effects seen in the alpha (decreased power) and gamma (increased power) frequency bands. Interestingly, effects on alpha power were apparent at doses as low as 60 mg, while dissociative effects as quantified by the CADSS (see Example 3) and ataxia as quantified by body sway (see Example 2) were absent at this dose. At intermediate doses from 100 to 220 mg, effects on alpha power were even stronger and some changes in gamma power were observed, while dissociative effects and ataxia remained limited. Strong dissociative and ataxic effects were only observed at the high dose of 360 mg, where dramatic increases in gamma power were also seen on EEG. Overall, these findings, in combination with those of Examples 2 and 3, demonstrate that the base compound can be dosed at levels sufficient to modulate brain activity while inducing limited dissociative and ataxic side effects. Additional examples are provided to support the efficacy of the compounds of the present disclosure for treating psychiatric diseases.

EXAMPLE 5 Real Time Intensity Scale For Various Doses of Base Compound

The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the subjects as described in Example 1 and Figure 17. The subjects answered questions which were specifically designed to monitor the trajectory of psychotomimetic drugs like NMDA receptor antagonists or psychedelic 5-HT_{2A} receptor agonists after the administration of the drugs, and subjects' reported effects on Bodily Intensity, Visual Intensity, and Emotional-Metacognitive intensity are monitored on a 10 point scale (0=not at all; 10=extremely) that are recorded by a clinician so that that subject only has to verbally report the drug's intensity of effects at that time. The Real Time Intensity score is recorded by a clinician from the verbal report of the subject; the subject does not have to read the question or make a motor response on paper or electronic device to record their answer. Thus, the fidelity of the measurement is not as affected by sensory/motor impairment at higher doses of

the base compound. The Real Time Intensity Total Score is simply a mean of the scores on the Bodily, Visual, and Emotional-Metacognitive intensity score. In the SAD trial, these measurements were recorded at 15 and 30 min, and 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose. The results are graphically depicted in Figure 9.

As shown by the graph, oral administration of base compound increased the patient reported Real Time Intensity Scale for Total Score using healthy male and female subjects described in Example 1 and Figure 17 in the single ascending dose (SAD) trial. The base compound increased the Total Score in a dose-dependent manner. However, relatively modest effects were observed for doses of 100 mg or less.

EXAMPLE 6 5D-ASC Score After Administration of Various Doses of Base Compound

Figure 10 shows dose-related increases on the major 5 dimensions of the 5-Dimensional Altered States of Consciousness (5D-ASC). This scale consists of 94 questions that are designed to quantify alterations of consciousness whether those effects are induced by environmental perturbations (e.g., sleep deprivation) or drugs such as NMDA receptor antagonists or psychedelic 5-HT_{2A} receptor agonists. These questions measure the 5D-ASC and is typically provided at a prescribed period of following the resolution of drug effects. In the case of base compound of the SAD trial described herein, the 5D-ASC were measured approximately 8 hours following administration of the drug. The 5 major dimensions of this instrument are anxious ego dissolution, auditory alterations, oceanic boundlessness, reduction of vigilance and visionary restructuralization. Of note, dimensions such as anxious ego dissolution and oceanic boundlessness are especially related to dissociative effects of NMDA receptor antagonists that led to them being described as dissociative anesthetics as very high doses led to anesthesia while lower doses led to dissociative effects as drug concentrations rose or as drug concentrations decreased while patients anesthetic effects wore off. The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the subjects as described in Example 1. The subjects in each group were evaluated at approximately 8 hours following administration of the drug. The results are depicted in Figure 10.

EXAMPLE 7 VAS Alertness

Another dissociative effect from the administration of base compound at the various dosages was measured. It is the Bond and Lader VAS Alertness factor. This test was given to each subject in each of the groups, including the groups to which placebo were administered. This test is self-administered and evaluates 16 dimensions of mood: Alert-Drowsy, Calm-Excited, Strong-Feeble, Muzzy-Clear headed, Well Coordinated-Clumsy, Lethargic-Energetic, Contented-Discontented, Troubled-Tranquil, Mentally Slow-Quick Witted, Tense-Relaxed, Attentive-Dreamy, Incompetent-Proficient, Happy-Sad, Antagonistic-Friendly, Interested-Bored, and Withdrawn-Social. Each of the subjects in each group is required to indicate by marking on a 100 mm line the extent that the above-listed dimension of mood is appropriate at the time of the measurement, which, in this trial, is 2 hours before administration of the base compound, at the time of the administration of the base compound, 2 hours after administration of the base compound, 3 hours after administration of the base compound, 4 hours after administration of the base compound, 6 hours after administration of the base compound, 8 hours after administration of the base compound, and 24 hours after administration of the base compound. From the individual responses, the values on the VAS alertness, consisting of alertness, contentment and calmness, is determined by a trained professional in the psychiatric field, such as a trained clinician, trained technician, trained doctor, and the like. The mean of the results is determined for each subject in each of the groups. The group administered the placebo also participated in this test for comparative purposes. The results are depicted in Figure 16.

The results show that the base compound increases sedation of the subject relative to that of the subject to which placebo was administered.

EXAMPLE 8 Effect of Oral Administration of Base Compound on SPV CFB

The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the subjects as described in Example 1 and Figure 17 and its effect on saccadic movement and saccadic peak velocity ("SPV") and the change from baseline ("CFB") was measured. A saccade is a rapid, conjugate, eye movement that shifts the center of gaze from one part of the visual field to another. Saccades are mainly used for orienting gaze towards an object of interest. Saccades may be horizontal, vertical, or oblique. Saccades are rapid, ballistic movements of the eye that abruptly changes the point of eye fixation. For example, saccadic

movement ranges in amplitude from the small movements made while reading, for example, to the much larger movements made while gazing around a room.

The effect of saccadic peak velocity is depicted in Figure 11. This figure depicts the change from baseline of the saccadic peak velocity at the various oral dosages over time. The saccadic peak velocity was measured 1 hour before administration, at the time of administration, 1 hour after administration, 3 hours after administration, 8 hours after administration and 24 hours after administration of the base compound or placebo. This measurement was effected by techniques known in the art.

As shown by the data, there was none to modest decreases from 60-140 mg of base compound when orally administered. The 360 mg dose shows the greatest deviation from baseline, and is comparable to slightly higher exposures relative to therapeutic esketamine exposure which is administered intravenously.

EXAMPLE 9 Effect of oral administration of Base Compound on Systolic Blood Pressure

The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the subjects as described in Example 1 and Figure 17 and the electrocardiogram was taken of the human subject 24 hours prior to oral administration of the base compound, 2 hours prior to oral administration of the base compound, at the administration of the base compound, 2 hours after administration of the base compound, 6 hours after administration of the base compound, 8 hours after administration of the base compound and 24 hours after administration of the base compound.

Figure 12 shows dose-dependent and time-dependent effects of base compound at increasing systolic blood pressure (SBP) from baseline values (-24 h and -2 h prior to drug administration) in the SAD trial protocol. Triplicate vital sign measurements (SBP, diastolic blood pressure, pulse, temperature, respiration rate) were obtained after 5 min rest in the supine position. Figure 13 shows generally dose-related increases in blood pressure 30 min after base compound was orally administered. Of note is that increases in SBP in the lower end of the expected therapeutic dose range (60-140 mg) was generally improved compared to increases in SBP with respect to esketamine nasal administration. Due to the number of measures included in the SAD trial, the vital signs were only singleton measurements, rather than triplicate measures which would decrease variability.

EXAMPLE 10 Effect of Base Compound on QTcF and Heart Rate

The base compound was orally administered at dosages of 20 mg, 60 mg, 100 mg, 140 mg, 220 mg or 360 mg to the subjects as described in Example 1 and the electrocardiogram was taken of the human subject 24 hours prior to oral administration of the base compound, 2 hours prior to oral administration of the base compound, at the administration of the base compound, 2 hours after administration of the base compound, 6 hours after administration of the base compound, 8 hours after administration of the base compound and 24 hours after administration of the base compound. The effect on QT interval on an electrocardiogram was measured. The QT interval is a measurement that is made on an electrocardiogram which is used to evaluate the electrical properties of the heart. It is determined from the beginning of the Q wave to the end of the T wave and it approximates the time that it takes from the start of the cardiac ventricles to contract until they relax. If the QT interval is abnormally long or short in a subject, the subject has an increased risk of abnormal heart rhythms and sudden cardiac arrest.

Figures 15 and 14, respectively show dose-dependent and time-dependent effects, respectively, of base compound at increasing heart rate (beats per minute, bpm) and increasing QTcF (QT interval of the 12 lead ECG corrected for heart rate by the Fredericia's formula) in the SAD trial of the Phase 1 protocol. Baseline 12 lead electrocardiograms (ECGs) were obtained at -24 and -2 h prior to drug administration. Single 12-lead ECGs were obtained at 30 min, 2, 6 and 24 h following drug administration to measure ECG parameters of heart rate, PR interval, QRS interval, and QTcF. Of note, there were not clinically important increases in QTcF over the expected base compound therapeutic dose range of 60-140 mg. Modest increases in heart rate were noted over this therapeutic dose range, unlike the clear increase in heart rate at a high dose of 360 mg. More specifically, as shown by Figure 14, QTcF was increased by 13.7 ms after administration of 360 mg of base compound as compared to placebo, while QTcF was increased by 4.7 ms after administration of 140 mg of base compound as compared to placebo (singleton ECGs). Figure 15 shows that the heart rate was increased by 14.3 beats per minute after administration of 360 mg of base compound as compared to placebo, while the administration of 140 mg of base compound decreased the heart rate by 1.2 beats per minute as compared to placebo.

2. EXAMPLES WITH MULTIPLE ASCENDING DOSES

The following examples relate to MAD (Multiple Ascending Dose) studies, in which there were 2 groups of 12 healthy adult volunteers, which were mostly male [70.8%] and white [70.8%]. Nine participants of each group received a single oral dose (140 mg or 220 mg) of base compound at one time, where 4 doses were administered every other day for seven days, and 3 participants of each group received multiple oral doses of placebo when the nine participants in these groups received multiple doses (140 mg or 220 mg) of base compound. The doses indicated are on the basis of free base compound and corrected for salt counterion mass. Unless indicated to the contrary, these are the subjects in the MAD studies.

EXAMPLE 11 Human Pharmacokinetics Results

Blood was drawn from each subject in the MAD trial at multiple time points post dose on days 1 and 7 of the MAD trial, viz., 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours and 96 hours after administration of base compound to the subject, processed to plasma by standard methods, and analyzed for base compound using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Figure 18A shows the plasma concentration of base compound over time on the first day of administration as a linear measurement, and Figure 18B shows a semi-log measurement of the data in Figure 18A. On the seventh day, the plasma concentration of base compound over time was measured and recorded. Figure 18C shows the plasma concentration of base compound over time on the seventh day of administration as a linear measurement and Figure 18D shows a semi-log measurement of the data in Figure 18C. The semi-log measurement is traditionally shown as dose-proportional increases, such as observed in Figures 18B and 18D, and demonstrate parallel lines between the different drug doses. With respect to the administration of base compound from the graphs, it was noted that there was an increased density during the initial few hours of the administration of base compound with respect to the plasma concentration. The data shows that there was no evidence of accumulation with every other day dosing over the seven days,

EXAMPLE 12 Human EEG

Resting-state electroencephalography (EEG) is very sensitive to central actions of pharmacological substances. For this reason, pharmaco-EEG (pEEG) has become an established method to assess drug effects on central nervous system (CNS) functioning. The measurement and analysis of EEG activity in pharmacological research generally comprises a number of

electrodes to obtain an impression of 'overall' cerebral EEG activity. The time-domain recordings are transformed into the frequency domain and changes in EEG power in certain frequency bands are then quantified. The frequency bands of interest include the delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ) bands.

In the Phase 1 clinical trial described in Example 12, EEG activity was recorded in all subjects in the MAD trial on the first day and on the seventh day according to the following methods, with the results summarized in Figure 19A, 19B, 19C, and 19D.

Methods. For the resting-state EEG setup, the TMSi EEG recording equipment was used. 21 electrodes were embedded in an EEG cap according to the international 10-20 system. The scalp electrode impedance was kept below 5k Ω . The ground electrode was placed at AFz EEG location. All signals were sampled at a sampling rate of 1024 Hz and are filtered prior to storage using a first order recursive high-pass filter with a cut-off frequency at 0.1 Hz. Digital markers were recorded by the amplifier indicating the start and end of each eye state.

As described above, subjects received base compound of 140 mg and 220 mg on days 1, 3, 5 and 7. The EEG were measured only on days 1 and 7. Subjects were seated in a comfortable position and were looking towards the wall. Subjects were instructed not to stare, to limit their head and eye-movements, and to suppress eye-blinks. Each recording employed alternating periods with eyes opened on the first day and seventh day (Figure 19A and Figure 19B, respectively) and closed on the first day and seventh day (Figure 19C and Figure 19D, respectively) with a duration of 64-seconds per period. In FIGS. 19A-19D, the number besides placebo (PBO) and active (ACT) indicates the number of subjects. This is repeated 5 times, resulting in 10 minutes of usable EEG. Between eyes opened and closed sessions, subjects were given some time to get adjusted to the 'new' lighting conditions. This is especially important when transitioning from closed to opened eyes. Subjects were informed to close or open their eyes based on custom scripts that also sent trigger information to the EEG recording device.

Analysis of the EEG recordings was performed automatically after the measurement using custom scripts written in Matlab by Mathworks. EEG recordings were high-pass filtered at 0.5 Hz to remove DC offset. Notch filter at 50 Hz was applied to remove line noise. Bad channels were identified as channels with low correlation with their neighboring channels. Identified bad channels were then interpolated as an average of their neighboring channels. All EEG signals were re-reference by subtracting the average EEG signal obtained from all EEG

electrodes. Noisy epochs in signals were detected as epochs that crossed variance estimated from baseline recording using predefined threshold and were excluded from further analysis. EEG signals were separately normalized by dividing signals by their root-mean-square (RMS) value obtained from the baseline recording. EEG signal power was computed by convolving EEG signal with a group of log-spaced complex Morlet wavelets in the frequency range of 1-100 Hz and scaling factor $f_0/s_f = 8$ followed by squaring the result. Power values were separately averaged for eyes open and eyes closed conditions across consecutive timepoints. Power values were further averaged across canonical EEG bands including alpha (8-13 Hz) and fast gamma (GammaF, 65-95 Hz) to obtain band-specific spectral averages. Finally, EEG band-specific power values were averaged across all electrodes to obtain single value of EEG band-specific power value for each subject, time point, EEG band and state (eyes open or eyes closed).

The base compound was orally administered at dosages of 140 mg or 220 mg to the human subjects. The EEG measurements using the method described hereinabove were taken 2 hours before administration, 1 hour before administration, 1 hour after administration, 3 hours after administration and 8 hours after administration of base compound or placebo.

Results. The EEG results at different dose levels in the eyes open state are presented in Figures 19A, 19B, 19C, and 19D. FIGS 19A and 19B depict the EEG results when the eyes are open on Days 1 and 7 at oral doses of 140 mg and 220 mg, respectively, which are graphically depicted in FIGs. 20A and 20B, while FIGS. 19C and 19D depict the results when the eyes are closed, which are graphically depicted in FIGS. 20C and 20D. The data from day 1 in the MAD trial replicate the suppression of alpha activity and enhancement of gamma activity observed in SAD trials. Overall, these findings demonstrate that the base compound can be dosed at 140 and 220 mg, which are levels sufficient to modulate brain activity, while not exhibiting tachyphylaxis or sensitization during the seven-day trial.

EXAMPLE 13 Human Dissociative Effects

Using the methodology of Example 3, dissociative effects were assessed by an experienced clinician from the reports of the human subject in the MAD trial using the CADSS at about 37 minutes, 2 hours, 3 hours 44 minutes, 6 hours, and 30 hours following administration of placebo and base compound doses of 140 mg and 220 mg on day 1, day 3, day 5, and day 7. The results are tabulated in FIG. 21, in which responses regarding many complaints (events) were measured.

In particular, the complaints of gastrointestinal disorders, general disorders, nervous system disorders, and psychiatric disorders were tabulated. As shown by the data, there were no SAEs (severe adverse events) or TEAEs (severe treatment emergent adverse effects) were observed, which results are consistent with the results from the SAD trial.

Figure 22 provides a graphical depiction of the percentage of human subjects in the MAD trial who were orally administered base compound and exhibited CADSS greater than 4 at any time following base compound administration of 140 mg and 220 mg on day 1, day 3, day 5 and day 7. This figure depicts the dose-dependent effects of base compound at increasing dissociative effects (derealization, depersonalization, and amnesia) using the Clinician Administered Dissociation Symptom Scale. The procedure used is described in Example 3 hereinabove, the contents of which are incorporated by reference, and the CADSS values are the mean of the values obtained from each group of subjects on day 1, day 3, day 5 and day 7 of the trial. As indicated when discussing Example 3, CADSS scores greater than 4 are considered a clinically significant endpoint. This figure shows the aggregated incidence of base compound (at 140 mg and 220 mg) at inducing a CADSS score > 4 on day 1, day 3, day 5, and day 7 of the trial.

The data for day 1 replicates the data for day 1 of the SAD trial with respect to the increased incidence in CADSS total scores greater than 4 that were observed when 140 and 220 mg of base compound were administered to the subjects. There was no evidence of tachyphylaxis from the administration of 140 mg of base compound, and little, if any evidence of tachyphylaxis from the administration of 140 mg of base compound. In addition, there was no evidence of sensitization during the trial from day 1 to day 7.

Figure 23A and Figure 23B graphically depicts the real time intensity on a scale from 0 to 10 from the administration of 140 mg and 220 mg of base compound to the human subject in the MAD trial following the procedure of Example 5 on days 1 and 7, respectively. As shown by the data, the base compounds increased the subjects reported real time Intensity total score from oral administration of base compound at 140 mg and 220 mg, respectively. The data for day 1 increasing the total Intensity scores replicates the data observed in the SAD trial. In addition, there is no evidence for tachyphylaxis or sensitization observed during the course of the 7-day trial.

Another dissociative effect from the administration of base compound at 140 mg and 220 mg subject was measured. It is the Bond and Lader VAS Alertness factor. This test was given to

each subject in the MAD trial who was administered the 140 mg and 220 mg base compound on day 1, day 3, day 5 and day 7 of the trial. The data is obtained on day 1 and day 7 of the MAD trial. This test is self-administered and evaluates 16 dimensions of mood: Alert-Drowsy, Calm-Excited, Strong-Feeble, Muzzy-Clear headed, Well Coordinated-Clumsy, Lethargic-Energetic, Contented-Discontented, Troubled-Tranquil, Mentally Slow-Quick Witted, Tense-Relaxed, Attentive-Dreamy, Incompetent-Proficient, Happy-Sad, Antagonistic-Friendly, Interested-Bored, Withdrawn-Social. Each of the subjects in each group is required to indicate by marking on a 100 mm line the extent that the above-listed dimension of mood is appropriate at the time of the measurement, which is 1 hour before administration of the base compound, at the time of the administration of the base compound, 1 hour after administration of the base compound, 2 hours after administration of the base compound, 3 hours after administration of the base compound, 4 hours after administration of the base compound, 6 hours after administration of the base compound, 8 hours after administration of the base compound, and 24 hours after administration of the base compound. From the individual responses, the values on the VAS alertness, consisting of alertness, contentment and calmness, is determined by a trained professional in the psychiatric field, such as a trained psychiatric clinician, trained psychiatric technician, trained psychiatric doctor, and the like. A mean of the results is determined for each subject in each of the groups. The group administered the placebo also participated in this test for comparative purposes. The results are depicted in Figures 24A and 24B.

The data for day 1 replicates the decrease in VAS alertness observed in the SAD trial for the subjects administered base compound at 140 mg and 120 mg. There was no evidence for sensitization from day 1 to day 7 for the subjects who were administered the base compound at 140 and 220 mg doses.

EXAMPLE 14 Effect of oral administration of Base Compound on Systolic Blood Pressure

The base compound was orally administered at dosages 140 mg and 220 mg to the subjects in the MAD trial on days 1, 3, 5, and 7 of the MAD trials, and the electrocardiogram was taken of each of the subjects in each group on days 1 and 7 at 24 hours prior to oral administration of the base compound, 2 hours prior to oral administration of the base compound, at the administration of the base compound, 2 hours after administration of the base compound, 6 hours after administration of the base compound, 8 hours after administration of the base

compound and 24 hours after administration of the base compound. A placebo was administered to each subject in the placebo groups and the electrocardiogram was taken of each subject in the placebo group according to the above schedule.

Figures 25A and 25B show dose-dependent and time-dependent effects of base compound at 140 mg and 220 mg at increasing systolic blood pressure (SBP) from baseline values (-24 h and -2 h prior to drug administration) in the MAD trial. Triplicate vital sign measurements (SBP, diastolic blood pressure, pulse, temperature, respiration rate) were obtained after 5 min rest in the supine position. The mean values for each subject at each time interval is determined and plotted on the graph in Figures 25A and 25B. The data in the MAD trial replicates the increase in systolic blood pressure observed in the SAD trial for 140 and 220 mg dosages. There is no evidence for sensitization for any of the subjects in the groups to which 140 mg and 220 mg of base compound were administered during the 7-day trial.

CONCLUSIONS FROM THE MAD TRIAL

The base compound increases in a dose-proportional manner without evidence for accumulation (4 doses/7days).

The base compound replicates dose-proportional EEG changes with no evidence for tachyphylaxis or sensitization.

The base compound replicates dose-proportional increase in dissociative effects without evidence for sensitization.

The base compound replicates dose-proportional increases in sedative effects without evidence for sensitization.

The base compound replicates dose-proportional increases in systolic blood pressure without evidence of either tachyphylaxis or desensitization.

B. Examples with Non-Human Subjects

EXAMPLE 15 Forced Swim Test

Animals. Male Sprague-Dawley rats, aged 8-10 weeks, were used in the experiments. Animals were housed in groups of 2 under controlled temperature ($22 \pm 3^{\circ}\text{C}$) and relative humidity (30-70%) conditions, with 12-hour light/dark cycles, and with *ad libitum* food and water. All efforts were made to minimize suffering.

Drugs and Drug Administration. The hydrochloride salt of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one, in a saline vehicle, and the positive control desipramine were administered subcutaneously (s.c.), with doses calculated based on the freebase. All compounds were administered at a volume of 5 mL/kg. Test compounds and vehicle were administered 0.5 h after the start of the training swim (Swim 1), which was 23.5 h before the test swim (Swim 2). Desipramine was administered 3 times, at 23.5 h, 5 h, and 0.5 h before the test swim (Swim 2), each time at a dose of 20 mg/kg.

Forced Swim Test (FST). Animals were randomized based on body weight to ensure that inter-group variations were minimal and did not exceed $\pm 20\%$ of the mean body weight across the groups. Group size was $n = 10$ per treatment. Rats were handled for about 2 min daily for the 5 days prior to the beginning of the experimental procedure. On the first day of the experiment (i.e., Day 0), post randomization, training swim sessions (Swim 1) were conducted between 12:00 and 18:00 h with all animals by placing rats in individual glass cylinders (46 cm tall x 20 cm in diameter) containing 23 – 25 °C water 30 cm deep for 15 minutes. At the conclusion of Swim 1, animals were dried with paper towels, placed in heated drying cages for 15 minutes, and then returned to their home cages. Animals were then administered the appropriate drug or vehicle treatment(s), as described above. For clarity, a compound administration time of 23.5 h before Swim 2 means 0.5 h after the start of Swim 1 and 0.25 h after the completion of Swim 1 (i.e., immediately after return to the home cage). On Day 1 (i.e., 24 h after start of Swim 1), animals performed the test swim (Swim 2) for a period of 5 min but otherwise under the same conditions as Swim 1. During all swim sessions, the water was changed between each animal.

Behavioral scoring was conducted by observers who were blind to the treatment groups. Animals were continuously observed during Swim 2 and the total time spent engaging in the following behaviors was recorded: immobile, swimming, and climbing. A rat was judged to be immobile when it remained floating in the water without struggling and made only those movements necessary to keep its head above water. A rat was judged to be swimming when it made active swimming motions, more than necessary to merely maintain its head above water (e.g., moving around in the cylinder). A rat was judged to be climbing when it made active movements with its forepaws in and out of the water, usually directed against the walls.

Statistical Analysis. Data points are presented as the mean $\pm$ standard error of the mean (SEM). Analysis was performed using GraphPad Prism 9 or 10. Comparisons between groups were

performed using the one-way analysis of variance (ANOVA), followed by Dunnett's test for comparisons to vehicle.

The results are depicted in Figure 26A. It shows the effect of acute administration of base compound (1-32 mg/kg, s.c.) on immobility time in naïve rats tested in the FST 24h after dosing ($n \geq 10/\text{group}$). A one-way ANOVA revealed a significant main effect of treatment ($F(5, 104) = 30.19, p < 0.0001$). Asterisks indicate a significant difference from the vehicle treated group using Dunnett's post-hoc test. The active comparator, desipramine (20 mg/kg, s.c.), dosed 3 times (23.5, 4 and 0.5 h) prior to testing also decreased immobility time. These results show that the base compound produced dose-dependent reductions in immobility time in the FST 23.5 hours post dose. All doses significantly reduced immobility time (as determined in independent PK experiments, the lowest interpolated C_{max} exposure associated with a significant reduction in immobility time was 114 ng/mL), with the lowest dose achieving maximal efficacy being 3.2 mg/kg.

In the following examples, unless otherwise specified, all experiments used adult male C57BL6/J mice housed 2-5/cage, or adult male Sprague-Dawley rats housed 2/cage. All animals had *ad libitum* access to food and water and were maintained in a light and temperature-controlled vivarium. All studies with live animals were approved by the ethics committee at the institution where they took place and conform to the standards set forth in the NIH Guide for Care and Use of Laboratory Animals.

EXAMPLE 16 Chronic Mild Stress (CMS)

A CMS trial was carried out in male Wistar-Han rats as described in articles by Papp in Eur. J. Pharmacol., 1996, 1996; Papp in Curr. Protoc. Pharmacol., 2012, 57; Wilner et al. in Neurosci Biobehav Rev. 1992, 16, 525-534; Papp et al., J Psychopharmacol, 2020; 34, 1418-1430 and Papp et al. Curr Protoc. 2023, 3 the contents for conducting this protocol being incorporated by reference. Figure 26B depicts an overview of the experimental schedule for CMS studies. Blue arrows represent weekly sucrose drinking tests (Tuesdays). Green arrows show when animals received weekly treatments (Mondays). The black arrow shows the timing for the EPM (Wednesday), and the grey arrow for the NOR test (Thursday). For each treatment group $n=8$ rats were exposed to CMS stressors, and $n=8$ rats were unstressed controls. A second CMS study was conducted to evaluate efficacy of the base compound after oral dosing and the duration of

efficacy following a single dose in male Wistar-Kyoto rats (Charles River, Sulzfeld, Germany). Animals in both studies were single housed prior to the onset of stress. The EPM and NOR tests were not performed in the second study.

Figure 26C shows the effect of base compound (0.75-9 mg/kg, i.p.) and (*rac*)-ketamine (10 mg/kg, i.p.) on sucrose intake. Weeks 1 and 2 show the effect of CMS on sucrose intake prior to the initiation of drug treatment. During weeks 3-7, animals were administered base compound, (*rac*)-ketamine (as a positive control), or vehicle 24 h prior to measuring sucrose intake. During weeks 8-10, drug treatment was terminated while the CMS paradigm continued to test the durability of the antidepressant-like effect. A Mixed Model GLM with repeated measures was conducted on the data collected during weeks 3-10 (treatment duration and washout) from stressed animals, which revealed a significant main effect of Trial ($F(7, 306.9) = 10.508, p < 0.0001$), and a significant effect of Treatment ($F(5, 70.2) = 8.31, p < 0.0001$). Post-hoc testing with Šidák's multiple comparisons revealed that only the group treated with 0.75 mg/kg of base compound failed to differentiate from vehicle ($F(1, 71.1) = 2.2499, p = 0.13$) indicating a minimum efficacious dose of base compound of 1.5 mg/kg (i.p.).

Rats exposed to CMS showed a robust anhedonic phenotype evidenced by a reduction in sucrose intake compared to control rats in weeks 1 and 2 of stress exposure; this reduction was maintained throughout the study in the vehicle group (Figure 26C). In the first week of base compound testing (week 3 of stress), administration of ketamine (10 mg/kg, i.p.) or base compound (3 or 9 mg/kg, i.p.) reversed the deficit in sucrose intake in stressed rats measured 24 h after dosing. The two highest doses of base compound (15 and 20 mg/kg, i.p.) caused substantial behavioral disruption in non-stressed animals, so animals from those two dose levels were re-randomized and assigned to receive either 0.75 or 1.5 mg/kg for the remaining trials. In weeks 4-7, ketamine and base compound (1.5-9 mg/kg) reversed the effects of CMS on sucrose intake while the lowest dose of base compound (0.75 mg/kg) was not effective. For weeks 8-10, stress continued but dosing ceased. The increase in sucrose intake caused by ketamine and base compound was maintained in weeks 8-9, largely returning to stressed vehicle levels by week 10, indicating that the anti-anhedonic effects of both compounds were durable through 15 days after the final dose. The rapid and durable effects of (*rac*)-ketamine in CMS appear to model the well-documented rapid acting efficacy of (*rac*)-ketamine in patients with depression.

Figure 26D shows the percent time spent in the open arms in the Elevated Plus Maze (EPM), which was conducted 48 h after initial treatment. Open bars show data from unstressed control rats, while filled bars are rats exposed to CMS. A two-way ANOVA revealed a significant main effect of Treatment ($F(5, 84) = 5.591, p = 0.0002$), a significant main effect of Stress ($F(1, 84) = 9.126, p = 0.0033$) and a significant interaction ($F(5, 84) = 2.568, p = 0.0327$). Post-hoc testing with Šidák's multiple comparisons test revealed significant differences between stressed and unstressed groups treated with vehicle ($p = 0.0040$) and 0.75 mg/kg of base compound ($p = 0.0315$) indicating these groups showed an increase in anxiety due to exposure to CMS. In rats dosed with base compound at ≥ 1.5 mg/kg (i.p.) or ketamine (10 mg/kg i.p.) anxiety levels were not different in control vs stressed rats indicating that drug treatment had reduced CMS-induced anxiety.

Figure 26E shows the results from the Novel Object Recognition task (NOR). The NOR was conducted 72 h after the initial compound administration. Open bars show data from unstressed control rats, while filled bars are rats exposed to CMS. A two-way ANOVA revealed a significant main effect of Treatment ($F(5, 84) = 2.988, p = 0.0157$), a significant main effect of Stress ($F(1, 84) = 9.464, p = 0.0028$) but no significant interaction ($F(5, 84) = 1.834, p = 0.1150$). In rats dosed with base compound at ≥ 1.5 mg/kg (i.p.) or ketamine (10 mg/kg, i.p.) recognition indices were not different in control vs stressed rats indicating that drug treatment had reduced CMS-induced impairment of recognition memory.

Base compound was effective at reversing CMS-induced anhedonia, anxiety and cognitive impairment. At the minimal efficacious dose (MED) of base compound (1.5 mg/kg, i.p.) the peak plasma concentration was measured to be 92 ng/mL.

In an additional experiment, the durability of a single administration of (*rac*)-ketamine or base compound (1.5 or 9 mg/kg, i.p.), and the efficacy 24 h after a single oral administration of base compound (1, 3.2, 10 mg/kg, p.o.), were assessed. Figures 26F and 26G show the effects of (*rac*)-ketamine or base compound on sucrose intake in WKY rats ($n=8/\text{group}$). Figure 26F shows the effect of a single administration of drug in week 3; sucrose intake was assessed 24 h later and then once weekly for a total of 3 weeks post-dose. A two-way ANOVA revealed a significant main effect of group ($F(4,35) = 12.34, p < 0.0001$), time ($F(2.456, 85.94) = 12.34, p < 0.0001$), and a significant interaction ($F(12, 105) = 4.334, p < 0.0001$). Post hoc testing with Dunnett's test showed that only stressed vehicle animals were significantly different from unstressed

vehicle animals in week 3 ($p = 0.006$) and week 4 ($p = 0.0004$). By week 5, all stressed animals were significantly different from unstressed vehicle animals (p 's < 0.001). The ability of a single dose of either base compound or (*rac*)-ketamine to restore sucrose intake was maintained for 14 days, with sucrose intake returning to stressed baseline levels 21 days after dosing (Figure 26F).

Figure 26G shows the effect of base compound (1-10 mg/kg, p.o.) administered orally, compared to (*rac*)-ketamine (10 mg/kg, i.p.) or base compound (1.5 mg/kg, i.p.) on sucrose intake 24 h later. A one-way ANOVA revealed a significant main effect of treatment ($F(6, 49) = 10.58, p < 0.0001$). Asterisks indicate a significant difference from the vehicle + stress group using Dunnett's post-hoc testing. When administered orally, base compound produced dose-dependent increases in sucrose intake, with 10 mg/kg restoring sucrose intake to unstressed levels 24 h after dosing (Figure 26G). At the oral MED of base compound (10 mg/kg), the peak plasma concentration was measured to be 257 ng/mL.

As shown, in the first CMS, the base compound showed similar robust, rapid-acting, and durable antidepressant-like effects to ketamine. The base compound was effective at reversing the detrimental effects of stress on sucrose intake, anxiety, and memory with once weekly dosing. The base compound is expected to also produce a rapid, robust antidepressant response in humans with intermittent dosing.

EXAMPLE 17 Studies of Motor Effects

The effects of base compound (3.2-32 mg/kg, s.c.) on motor function were compared to those of (*rac*)-ketamine (3.2-32 mg/kg, s.c.) in rats. Spontaneous locomotor activity (sLMA) was monitored for 30 min pre-dose and 60 min post-dose. Motor coordination was assessed 5 min after dosing using an accelerating rotarod. Plasma samples were collected from satellite rats to determine concentrations of base compound or (*rac*)-ketamine 30 or 18 min after dosing, respectively. Base compound (1-32 mg/kg, s.c.) was also assessed in mice in both sLMA and the rotarod.

(a) Spontaneous Locomotor Activity (sLMA)

The effects of base compound (3.2-32 mg/kg, s.c.) on sLMA in rats were compared to (*rac*)-ketamine (3.2-32 mg/kg, s.c.). Figure 27A top left depicts the spontaneous locomotor activity of rats ($n=9/\text{group}$) dosed with vehicle, ketamine (3.2-32 mg/kg, s.c.) or base compound (3.2-32 mg/kg, s.c.; left) and in mice ($n=10/\text{group}$) dosed with base compound (1-32 mg/kg, s.c.;

right). Bar charts show total distance traveled over 0-30 min after dosing. Line graph of Figure 27A (top right) shows the time course of rat locomotor activity with data presented as 5 min bins, with rats dosed at time 0, and the given timepoint being the end of the 5 min bin (i.e., 5 min = 0-5 min). A one-way ANOVA revealed a significant main effect of treatment on the total distance traveled in the rats ($F(6, 56) = 20.13, p < 0.0001$). Dunnett's post-hoc test showed significant differences between vehicle and ketamine at 10 mg/kg ($p = 0.0001$), and at 32 mg/kg ($p < 0.0001$), and between vehicle and base compound at 32 mg/kg ($p < 0.0001$). In mice there was no significant effect of base compound on spontaneous locomotor activity ($F(4, 45) = 2.042, p = 0.1046$) (Figure 27A (bottom)).

Both base compound and (*rac*)-ketamine produced dose-dependent effects on rat sLMA with (*rac*)-ketamine producing robust increases at doses ≥ 10 mg/kg, and base compound increasing activity only at 32 mg/kg (Figure 27A; left). The exposure after base compound (32 mg/kg, s.c.) in satellite animals was 3,018 ng/mL, which was ~30-fold higher than the exposure at the MED in CMS, indicating a large separation between efficacious plasma exposures and those associated with motor side effects (Figure 27A).

(b) Rotarod

The ataxic effects of base compound (3.2-32 mg/kg, s.c.) and (*rac*)-ketamine 3.2-32 mg/kg, s.c.) were explored in rats using the rotarod. Ketamine decreased the latency to fall off the rotarod at all doses tested, while base compound produced decreases only at 10 and 32 mg/kg (Figure 27B; left). The dose of base compound resulting in a 50% reduction in latency to fall (ED_{50}) was 17.4 mg/kg, whereas for (*rac*)-ketamine it was 3.4 mg/kg.

Ataxic effects were also assessed in mice. Like in rats, the base compound did not produce ataxia at 1 or 3.2 mg/kg and had only a minor effect on the latency to fall at 10 mg/kg (Figure 27B; right). The ED_{50} ataxic dose of base compound in mice was 37.4 mg/kg, s.c..

In the locomotor and rotarod assays, rats were less affected after administration of base compound compared to ketamine. Importantly, the motor impairment seen in these assays following base compound occurred at doses/exposures far higher than those that were efficacious in CMS. For base compound, 1.5 mg/kg (i.p.) was fully efficacious in CMS and no impairment in rotarod performance was seen at 3.2 mg/kg (s.c.), and only mild effects at 10 mg/kg ($ED_{50} = 17.4$ mg/kg, s.c.). Using plasma concentrations to compare across studies which used different

routes of administration (ROA), the peak plasma concentration of base compound associated with the calculated ED₅₀ for latency to fall off the rotarod was interpolated as 1,876 ng/mL. This is ~20-fold higher than the C_{max} measured after administration of base compound at 1.5 mg/kg (i.p.; 92 ng/mL), the MED in CMS, indicating a large separation between antidepressant-like efficacy and motor side effects (Figure 27D).

EXAMPLE 18 Conditioned Place Preference (CPP)

The effects of base compound (1-32 mg/kg; s.c.) on CPP were compared to oxycodone (3 mg/kg; s.c.) in mice.

Figure 27C shows the effects of base compound (1-32 mg/kg, s.c.) compared to oxycodone (3 mg/kg, s.c.) on mouse conditioned place preference (n=10/group). Graph shows the change in time spent on the drug paired side after place conditioning. While the one-way ANOVA revealed a significant main effect of treatment ($F(5, 54) = 5.091, p = 0.0007$), Dunnett's post-hoc test showed that only the group treated with oxycodone was significantly different from vehicle ($p = 0.0065$).

Base compound did not induce a CPP in mice at 1-32 mg/kg, s.c., while the animals treated with oxycodone (3 mg/kg, s.c.) as a positive control showed an increased time spent on the drug-paired side (Figure 27C).

EXAMPLE 19 Rat EEG Studies

The effects of base compound (1-10 mg/kg, s.c.) on EEG were measured using a within-subjects design in a cohort of 8 freely moving rats implanted with 2 cortical electrodes connected to a DSI transmitter as described in an article by Kantor et al., *Behav. Brain Res.* 2023: 449:114473, the contents related to the protocol incorporated by reference.

Effects of base compound (1-10 mg/kg, s.c.) on the amplitude of cortical EEG oscillations were assessed for 30 min prior to and 180 min post-injection (Figure 28).

Base compound produced a dose-dependent reduction in power in both theta (5-12 Hz) and beta (12-25 Hz) bands, while increasing power in the gamma (30-80 Hz) band (Figures 28A and 28C). These effects were not confounded by changes in activity levels (Figure 28B). The effect on gamma was most pronounced in the 10 mg/kg group and peaked between 50-70 Hz. The effects lasted ~40 min in the 1 mg/kg group, ~90 min in the 3.2 mg/kg group, and ~120 min

in the 10 mg/kg group (Figure 28A). Base compound had dose-dependent effects on delta (1-4 Hz; one-way ANOVA $F(3, 31) = 1.03$, $p = 0.4$), theta (5-12 Hz; one-way ANOVA $F(3,31) = 4.63$, $p = 0.009$, Tukey's HSD test: Vehicle > 3.2 mg/kg and 10 mg/kg), beta (12-30 Hz; one-way ANOVA $F(3, 31) = 3.59$, $p = 0.026$, Tukey's HSD test: Vehicle > 10 mg/kg) and gamma (30-80 Hz; one-way ANOVA $F(3, 31) = 32.5$, $p < 0.0001$, Tukey's HSD test: Vehicle < 3.2 mg/kg < 10 mg/kg; Figure 28D). The MED for decreasing theta and increasing gamma power was 3.2 mg/kg, which, based on subcutaneous rat PK, was associated with a peak plasma concentration of 342 ng/mL.

The EEG is a quantitative translational biomarker of target engagement. Ketamine reduces power in low frequency bands and increases power in the gamma band both preclinically and clinically. The reduction of low frequency activity and increase in gamma seen in the EEG experiment with base compound demonstrate clear target engagement, consistent with NMDAR blockade. A dose of 3.2 mg/kg (s.c.), which achieves similar exposure to the minimum efficacious dose in CMS (1.5 mg/kg, i.p.), was sufficient to affect this biomarker of NMDAR blockade, which demonstrates this dose of base compound is producing significant engagement of NMDAR *in vivo*.

Figure 27D provides an overview of the plasma concentrations of base compound associated with the pharmacodynamic effects of the drug. Green lines represent the plasma concentration of base compound at the minimum efficacious doses in the chronic mild stress paradigm and forced swim test, as indicated. Red lines indicate the plasma concentrations associated with a 50% reduction in latency to fall off the rotarod or a significant increase in spontaneous locomotor activity, as indicated. The blue line represents the minimum plasma concentration of base compound associated with decreases in EEG theta power and increases in gamma power in rats.

Based on these results, the data show that the base compound exhibits antidepressant activity in test animals predictive of the effect of the base compound in humans.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. Therefore, it is to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

WHAT IS CLAIMED IS:

1. A method of treating a patient having a psychiatric disorder comprising administering orally to a patient in need thereof a base compound or a pharmaceutically acceptable salt thereof at a dose ranging from about 40 to about 360 mg relative to the base compound at each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.
2. The method according to claim 1 wherein base compound or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 40 to about 180 mg.
3. The method according to claim 1 wherein base compound or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 60 to about 140 mg.
4. The method according to any one of claims 1-3 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant.
5. The method according to any one of claims 1-4 wherein the antidepressant blocks the serotonin transporter.
6. The method according to claim 5 wherein the antidepressant is a selective serotonin reuptake inhibitor.
7. The method according to claim 6 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.
8. The method according to claim 5 wherein the antidepressant drug is a serotonin-norepinephrine reuptake inhibitor.
9. The method according to claim 8 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.
10. The method according to any one of claims 1-9 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof orally in an amount ranging from about 40 to about 180 mg relative to the base compound at each administration at treatment intervals ranging from weekly to every other week to the patient in need thereof during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

11. The method according to claim 10 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 140 mg.
12. The method according to any one of claims 1-9 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof in an amount ranging from about 20 to about 100 mg relative to the base compound at each administration at treatment intervals ranging from weekly to daily to the patient in need thereof during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.
13. The method according to claim 12 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 80 mg.
14. The method according to any one of claims 10-13 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant during the maintenance phase.
15. The method according to claim 14 wherein the antidepressant is a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.
16. The method according to any one of claims 10-15 wherein the maintenance treatment phase follows an induction treatment involving the administration of esketamine, arketamine, or racemic ketamine.
17. The method according to claim 16 wherein the esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the induction treatment.
18. The method according to claim 17 wherein esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.
19. A method of treating a patient having a psychiatric disorder comprising administering to a patient in need thereof a base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 3,600 h·ng/mL subsequent to each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL subsequent to each administration at treatment

intervals ranging from every other week to three days a week, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

20. The method according to claim 19 wherein base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 2,100 h·ng/mL or in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 330 ng/mL.

21. The method according to claim 19 wherein base compound or a pharmaceutically acceptable salt thereof is administered in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 550 h·ng/mL to about 1800 h·ng/mL or in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 110 ng/mL to about 280 ng/mL.

22. The method according to any one of claims 19-21 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant.

23. The method according to claim 22 wherein the antidepressant blocks the serotonin transporter.

24. The method according to claim 23 wherein the antidepressant is a selective serotonin reuptake inhibitor.

25. The method according to claim 24 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.

26. The method according to claim 23 wherein the antidepressant drug is a serotonin-norepinephrine reuptake inhibitor.

27. The method according to claim 26 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.

28. The method according to any one of claims 19-27 additionally comprising administering to the subject in need of treatment substantially pure base compound or a pharmaceutically acceptable salt thereof in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 2,100 h·ng/mL subsequent to each administration or an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72 ng/mL to about 330 ng/mL subsequent to each administration at treatment intervals ranging from

weekly to every other week during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

29. The method according to claim 28 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the subject in need of treatment is an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 1,800 h·ng/mL or an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 280 ng/mL during the maintenance treatment phase.

30. The method according to any one of claims 19-27 additionally comprising administering to the subject in need of treatment substantially pure base compound or a pharmaceutically acceptable salt thereof in an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 230 h·ng/mL to about 970 h·ng/mL subsequent to each administration or an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 39 ng/mL to about 150 ng/mL subsequent to each administration at treatment intervals ranging from weekly to daily during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

31. The method according to claim 30 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the subject in need of treatment is an amount sufficient to achieve in the plasma of the subject an AUC ranging from about 390 h·ng/mL to about 760 h·ng/mL or an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 130 ng/mL during the maintenance treatment phase.

32. The method according to any one of claims 28-31 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant during the maintenance phase.

33. The method according to claim 32 wherein the antidepressant is a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.

34. The method according to any one of claims 28-33 wherein the maintenance treatment phase follows an induction treatment involving the administration of esketamine, arketamine, or racemic ketamine.

35. The method according to claim 34 wherein the esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the induction treatment.

36. The method according to claim 35 wherein esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.
37. The method according to any one of claims 1-36 wherein the psychiatric disorder is major depressive disorder.
38. The method according to any one of claims 1-36 wherein the psychiatric disorder is treatment-resistant depression.
39. The method according to any one of claims 1-36 wherein the psychiatric disorder is a neuropsychiatric disorder.
40. The method according to any one of claims 1-36 wherein the psychiatric disorder is an anxiety disorder, bipolar depressive disorder, post-partum depression, obsessive-compulsive disorder, post-traumatic stress disorder, or a substance use disorder.
41. The method according to any one of claims 1-36 wherein the psychiatric disorder is an anxiety disorder selected from generalized anxiety disorder, panic disorder, and social anxiety disorder.
42. The method according to any one of claims 1-36 wherein the psychiatric disorder is a substance use disorder selected from alcohol use disorder, opioid use disorder, amphetamine/methamphetamine use disorder, cocaine use disorder, tobacco/nicotine use disorder, and cannabinoid use disorder.
43. A method of treating a patient having a psychiatric disorder comprising administering a base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to the patient in need thereof on a daily basis, wherein base compound or a pharmaceutically acceptable salt thereof is administered orally at a dose level ranging from about 20 to about 100 mg per day relative to the base compound, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.
44. The method according to claim 43 wherein the daily dose of base compound or a pharmaceutically acceptable salt thereof is administered as a single unit dose.
45. The method according to claim 43 wherein the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, vortioxetine, duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.

46. The method according to claim 45 wherein fluoxetine is administered at a daily dose ranging from about 10 to about 80 mg, paroxetine is administered at a daily dose ranging from about 10 to about 60 mg, citalopram is administered at a daily dose ranging from about 10 to about 40 mg, escitalopram is administered at a daily dose ranging from about 5 to about 20 mg, fluvoxamine is administered at a daily dose ranging from about 25 to about 300 mg, sertraline is administered at a daily dose ranging from about 50 to about 200 mg, vortioxetine is administered at a daily dose ranging from about 5 to about 20 mg, duloxetine is administered at a daily dose ranging from about 30 to about 120 mg, venlafaxine is administered at a daily dose ranging from about 37.5 to about 375 mg, desvenlafaxine is administered at a daily dose ranging from about 25 to about 200 mg, milnacipran is administered at a daily dose ranging from about 12.5 to about 200 mg, and levomilnacipran is administered at a daily dose ranging from about 20 to about 120 mg, wherein all dose levels are relative to the free base form.
47. The method according to any one of claims 43-46 wherein the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is administered as a single unit dose.
48. The method according to any one of claims 43-47 wherein the daily dose of base compound or a pharmaceutically acceptable salt thereof and the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor are administered together as a single unit dose in a single pharmaceutical composition.
49. The method according to any one of claims 43-48 wherein the psychiatric disorder is major depressive disorder.
50. The method according to any one of claims 43-48 wherein the psychiatric disorder is treatment-resistant depression.
51. The method according to any one of claims 43-48 wherein the psychiatric disorder is a neuropsychiatric disorder.
52. The method according to any one of claims 43-48 wherein the psychiatric disorder is an anxiety disorder, bipolar depressive disorder, post-partum depression, obsessive-compulsive disorder, post-traumatic stress disorder, or a substance use disorder.
53. The method according to claim 52 wherein the psychiatric disorder is an anxiety disorder selected from generalized anxiety disorder, panic disorder, and social anxiety disorder.

54. The method according to claim 52 wherein the psychiatric disorder is a substance use disorder selected from alcohol use disorder, opioid use disorder, amphetamine/methamphetamine use disorder, cocaine use disorder, tobacco/nicotine use disorder, and cannabinoid use disorder.
55. The method according to any one of claims 1-54 wherein the mean weight of the patient ranges from about 65 kg to about 80 kg.
56. A method of treating a patient having pain comprising administering orally to the patient in need thereof a base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment at a dose ranging from about 40 to about 360 mg relative to the base compound at each administration at treatment intervals ranging from every other week to three days a week, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.
57. The method according to claim 56 wherein base compound or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 40 to about 180 mg .
58. The method according to claim 56 wherein base compound or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 60 to about 140 mg.
59. The method according to any one of claims 56-58 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.
60. The method according to claim 59 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.
61. The method according to claim 59 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.
62. The method according to any one of claims 56-61 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof orally in an amount ranging from about 40 to about 180 mg relative to the base compound at each administration at treatment intervals ranging from weekly to every other week to the patient in need thereof during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.
63. The method according to claim 62 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 140 mg.

64. The method according to any one of claims 56-61 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof orally in an amount ranging from about 20 to about 100 mg relative to the base compound at each administration at treatment intervals ranging from weekly to daily to the patient in need thereof during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

65. The method according to claim 64 wherein the dose level of base compound or a pharmaceutically acceptable salt thereof administered to the patient during the maintenance treatment phase ranges from about 40 to about 80 mg.

66. The method according to any one of claims 62-65 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor during the maintenance phase.

67. The method according to any one of claims 62-66 wherein the maintenance treatment follows an induction treatment involving the administration of esketamine, arketamine, or racemic ketamine.

68. The method according to claim 67 wherein the esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the induction treatment.

69. The method according to claim 68 wherein esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.

70. The method according to any one of claims 56-69 wherein the pain is chronic pain.

71. The method according to any one of claims 56-69 wherein the pain is neuropathic pain.

72. The method according to any one of claims 56-69 wherein the pain is chemotherapy induced neuropathy.

73. The method according to any one of claims 56-72 wherein the treatment results in a decreased intake of opioids by the patient.

74. A method of treating a patient having pain comprising administering a base compound or a pharmaceutically acceptable salt thereof concurrently with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor to a patient in need thereof orally on a daily basis, wherein base compound or a pharmaceutically acceptable salt thereof is administered

at a dose level ranging from about 20 to about 100 mg relative to the base compound per day, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

75. The method according to claim 74 wherein the daily dose of base compound or a pharmaceutically acceptable salt thereof is administered as a single unit dose.

76. The method according to claim 74 or 75 wherein the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, vortioxetine, duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.

77. The method according to claim 76 wherein fluoxetine is administered at a daily dose ranging from about 10 to about 80 mg, paroxetine is administered at a daily dose ranging from about 10 to about 60 mg, citalopram is administered at a daily dose ranging from about 10 to about 40 mg, escitalopram is administered at a daily dose ranging from about 5 to about 20 mg, fluvoxamine is administered at a daily dose ranging from about 25 to about 300 mg, sertraline is administered at a daily dose ranging from about 50 to about 200 mg, vortioxetine is administered at a daily dose ranging from about 5 to about 20 mg, duloxetine is administered at a daily dose ranging from about 30 to about 120 mg, venlafaxine is administered at a daily dose ranging from about 37.5 to about 375 mg, desvenlafaxine is administered at a daily dose ranging from about 25 to about 200 mg, milnacipran is administered at a daily dose ranging from about 12.5 to about 200 mg, and levomilnacipran is administered at a daily dose ranging from about 20 to about 120 mg, wherein all dose levels are relative to the free base form.

78. The method according to any one of claims 74-77 wherein the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor is administered as a single unit dose.

79. The method according to any one of claims 74-78 wherein the daily dose of base compound or a pharmaceutically acceptable salt thereof and the daily dose of the selective serotonin reuptake inhibitor or the serotonin-norepinephrine reuptake inhibitor are administered together as a single unit dose in a single pharmaceutical composition.

80. The method according to any one of claims 74-79 wherein the pain is chronic pain.

81. The method according to any one of claims 74-79 wherein the pain is neuropathic pain.

82. The method according to any one of claims 74-79 wherein the pain is chemotherapy induced neuropathy.
83. The method according to any one of claims 74-82 wherein the treatment results in a decreased intake of opioids by the patient.
84. A dosing kit comprising unit doses of a first pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a first pharmaceutical carrier therefor and unit doses of a second pharmaceutical composition comprising a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor and a second pharmaceutical carrier therefor and instructions for administering the first pharmaceutical composition and the second pharmaceutical composition to a patient suffering from a psychiatric disorder or pain, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.
85. A pharmaceutical composition comprising a first component of about 20 to about 100 mg of a base compound or a pharmaceutically acceptable salt thereof relative to the base compound and a second component that is one of the following: about 10 to about 80 mg of fluoxetine, about 10 to about 60 mg of paroxetine, about 10 to about 40 mg of citalopram, about 5 to about 20 mg of escitalopram, about 25 to about 300 mg of fluvoxamine, about 50 to about 200 mg of sertraline, about 5 to about 20 mg of vortioxetine, about 30 to about 120 mg of duloxetine, about 37.5 to about 375 mg of venlafaxine, about 25 to about 200 mg of desvenlafaxine, about 12.5 to about 200 mg of milnacipran, or about 20 to about 120 mg of levomilnacipran, along with a pharmaceutical carrier therefor, wherein all dose levels are relative to the free base form, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.
86. The pharmaceutical composition of claim 85 wherein the first component is about 20 to about 100 mg of base compound or a pharmaceutically acceptable salt thereof and the second component is one of the following: about 10 to about 80 mg of fluoxetine, about 10 to about 60 mg of paroxetine, about 10 to about 40 mg of citalopram, about 5 to about 20 mg of escitalopram, about 25 to about 300 mg of fluvoxamine, about 50 to about 200 mg of sertraline, or about 5 to about 20 mg of vortioxetine.
87. The pharmaceutical composition of claim 85 wherein the first component is about 20 to about 100 mg of base compound or a pharmaceutically acceptable salt thereof or a

pharmaceutically acceptable salt thereof and the second component is one of the following:
about 30 to about 120 mg of duloxetine, about 37.5 to about 375 mg of venlafaxine, about 25 to about 200 mg of desvenlafaxine, about 12.5 to about 200 mg of milnacipran, or about 20 to about 120 mg of levomilnacipran.

88. A method for treating a psychiatric disorder or pain in a subject comprising administering a base compound or a pharmaceutically acceptable salt thereof as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 13 to about 120 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 540 ng/mL subsequent to each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

89. The method according to claim 88 wherein the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 13 to about 60 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL.

90. The method according to claim 88 wherein the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 20 to about 47 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 110 ng/mL to about 280 ng/mL.

91. The method according to any one of claims 88-90 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 13 to about 60 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL subsequent to each administration at treatment intervals ranging from weekly to every other week during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

92. The method according to claim 91 wherein the base compound or a pharmaceutically acceptable salt thereof is administered to the patient during the maintenance treatment phase in

an amount ranging from about 13 to about 47 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 280 ng/mL.

93. The method according to any one of claims 88-90 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof as an IV bolus or short infusion in less than or equal to about 15 minutes in an amount ranging from about 7 to about 33 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 39 ng/mL to about 150 ng/mL subsequent to each administration at treatment intervals ranging from weekly to daily during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

94. The method according to claim 93 wherein the base compound or a pharmaceutically acceptable salt thereof is administered to the patient during the maintenance treatment phase in an amount ranging from about 13 to about 27 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 130 ng/mL.

95. The method according to any one of claims 88-94 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant.

96. The method according to claim 95 wherein the antidepressant blocks the serotonin transporter.

97. The method according to claim 96 wherein the antidepressant is a selective serotonin reuptake inhibitor.

98. The method according to claim 97 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.

99. The method according to claim 96 wherein the antidepressant drug is a serotonin-norepinephrine reuptake inhibitor.

100. The method according to claim 99 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.

101. The method according to any one of claims 91-94 wherein the maintenance treatment follows an induction treatment involving the administration of esketamine, arketamine, or racemic ketamine.

102. The method according to claim 101 wherein the esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the induction treatment.
103. The method according to claim 102 wherein esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.
104. The method according to any one of claims 88-103 wherein the disorder is major depressive disorder.
105. The method according to any one of claims 88-103 wherein the disorder is treatment-resistant depression.
106. The method according to any one of claims 88-103 wherein the disorder is a neuropsychiatric disorder.
107. The method according to any one of claims 88-103 wherein the disorder is an anxiety disorder, bipolar depressive disorder, post-partum depression, obsessive-compulsive disorder, post-traumatic stress disorder, or a substance use disorder.
108. The method according to any one of claims 88-103 wherein the disorder is an anxiety disorder selected from generalized anxiety disorder, panic disorder, and social anxiety disorder.
109. The method according to any one of claims 88-103 wherein the disorder is a substance use disorder selected from alcohol use disorder, opioid use disorder, amphetamine/methamphetamine use disorder, cocaine use disorder, tobacco/nicotine use disorder, and cannabinoid use disorder.
110. The method according to any one of claims 88-103 wherein the disorder is chronic pain.
111. The method according to any one of claims 88-103 wherein the disorder is neuropathic pain.
112. The method according to any one of claims 88-103 wherein the disorder is chemotherapy induced neuropathy.
113. The method according to any one of claims 88-103 wherein the treatment results in a decreased intake of opioids by the patient.
114. A method for treating a psychiatric disorder or pain in a subject comprising administering a base compound or a pharmaceutically acceptable salt thereof as an IM injection in an amount ranging from about 20 to about 180 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a $C_{\max}$ ranging from about 72

ng/mL to about 540 ng/mL subsequent to each administration at treatment intervals ranging from every other week to three days a week during an acute induction phase of treatment, wherein the base compound is substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one.

115. The method according to claim 114 wherein the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 20 to about 90 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL.

116. The method according to claim 114 wherein the base compound or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 30 to about 70 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 110 ng/mL to about 280 ng/mL.

117. The method according to any one of claims 114-116 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof as an IM injection in an amount ranging from about 20 to about 90 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 330 ng/mL subsequent to each administration at treatment intervals ranging from weekly to every other week during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

118. The method according to claim 117 wherein the base compound or a pharmaceutically acceptable salt thereof is administered to the patient during the maintenance treatment phase in an amount ranging from about 20 to about 70 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 280 ng/mL.

119. The method according to any one of claims 114-116 additionally comprising administering substantially pure base compound or a pharmaceutically acceptable salt thereof as an IM injection in an amount ranging from about 10 to about 50 mg relative to the base compound at each administration or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 39 ng/mL to about 150 ng/mL subsequent to each administration at treatment intervals ranging from weekly to daily during a maintenance treatment phase that commences immediately after the conclusion of the acute induction phase.

120. The method according to claim 119 wherein the base compound or a pharmaceutically acceptable salt thereof is administered to the patient during the maintenance treatment phase in an amount ranging from about 20 to about 40 mg or in an amount sufficient to achieve in the plasma of the subject a C_{max} ranging from about 72 ng/mL to about 130 ng/mL.
121. The method according to any one of claims 114-120 wherein base compound or a pharmaceutically acceptable salt thereof is administered concurrently with an antidepressant.
122. The method according to claim 121 wherein the antidepressant blocks the serotonin transporter.
123. The method according to claim 122 wherein the antidepressant is a selective serotonin reuptake inhibitor.
124. The method according to claim 123 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.
125. The method according to claim 122 wherein the antidepressant drug is a serotonin-norepinephrine reuptake inhibitor.
126. The method according to claim 125 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.
127. The method according to any one of claims 117-120 wherein the maintenance treatment follows an induction treatment involving the administration of esketamine, arketamine, or racemic ketamine.
128. The method according to claim 127 wherein the esketamine, arketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously, sublingually, or orally during the induction treatment.
129. The method according to claim 128 wherein esketamine is administered intranasally, arketamine is administered subcutaneously, and racemic ketamine is administered intravenously.
130. The method according to any one of claims 114-129 wherein the disorder is major depressive disorder.
131. The method according to any one of claims 114-129 wherein the disorder is treatment-resistant depression.
132. The method according to any one of claims 114-129 wherein the disorder is a neuropsychiatric disorder.

133. The method according to any one of claims 114-129 wherein the disorder is an anxiety disorder, bipolar depressive disorder, post-partum depression, obsessive-compulsive disorder, post-traumatic stress disorder, or a substance use disorder.
134. The method according to any one of claims 114-129 wherein the disorder is an anxiety disorder selected from generalized anxiety disorder, panic disorder, and social anxiety disorder.
135. The method according to any one of claims 114-129 wherein the disorder is a substance use disorder selected from alcohol use disorder, opioid use disorder, amphetamine/methamphetamine use disorder, cocaine use disorder, tobacco/nicotine use disorder, and cannabinoid use disorder.
136. The method according to any one of claims 114-129 wherein the disorder is chronic pain.
137. The method according to any one of claims 114-129 wherein the disorder is neuropathic pain.
138. The method according to any one of claims 114-129 wherein the disorder is chemotherapy induced neuropathy.
139. The method according to any one of claims 114-129 wherein the treatment results in a decreased intake of opioids by the patient.
140. The method according to any one of claims 1-83 and 88-139 wherein the base compound is administered in the form of a pharmaceutical composition comprising the base compound and a pharmaceutically acceptable carrier.