

A TREATMENT FOR PATIENTS WITH MOOD DISORDERS USING *N*-ETHYL-2-(5-FLUORO-1*H*-INDOL-3-YL)-*N*-METHYLETHAN-1-AMINE OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

FIELD OF THE DISCLOSURE

The present disclosure relates to dosing regimens of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof for effectively treating mood disorders in a subject in need thereof.

BACKGROUND OF THE DISCLOSURE

Depression is a common psychological problem and refers to a mental state of low mood and aversion to activity. Various symptoms associated with depression include persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, and/or worthlessness, low energy, restlessness, irritability, fatigue, loss of interest in pleasurable activities or hobbies, excessive sleeping, overeating, appetite loss, insomnia, thoughts of suicide, and suicide attempts. The presence, severity, frequency, and duration of the above-mentioned symptoms vary on a case-by-case basis.

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 (SSRIs). This high prevalence of treatment-resistant depression (TRD) makes clear the need for new, more efficacious pharmacotherapies for depression that will target new mechanisms and/or patient populations.

Tryptamines are monoamine alkaloids that contain an indole ring and are structurally similar to the amino acid tryptophan, from which the name derives. There are a significant number of tryptamine compounds that include naturally occurring compounds and chemical derivatives with similar structure that may be ring unsubstituted or ring substituted. Many tryptamines are agonists of the serotonin 2A (5-HT_{2A}) receptor and/or modulators of other serotonin receptors and are known to be psychoactive and, in many cases, cause prolonged hallucinations. The most well-known tryptamines are psychedelic compounds, including compounds derived from entheogenic fungi (psilocybin and psilocin), *N,N*-dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), bufotenin, and ibogaine. These compounds are known to have significant effects on thought,

perception, and behavior. However, these compounds are currently classified as Schedule I drugs under the Controlled Substances Act due to their alleged high abuse potential, no accepted medical use, and lack of established safety. Moreover, tryptamines are metabolized by a number of pathways, in some cases including monoamine oxidase, limiting the oral bioavailability of some compounds and resulting in very short durations of action. Conversely, other tryptamines have very long durations of action, which makes them challenging to use in a guided therapy setting, where supervised sessions of many hours in duration are costly for patients and inconvenient for healthcare providers.

The present disclosure relates to a specific tryptamine and a pharmaceutically acceptable salt, which are useful for treating mood disorders in humans and more specifically, to the dosage regimen for treating the same.

SUMMARY OF THE DISCLOSURE

The present disclosure relates, in part, to a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose administered is in an amount relative to the base compound ranging from about 8 mg to about 16 mg IV or inhaled or about 8 mg to about 24 mg IM, wherein the optional second dose administered is in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, wherein the optional successive periodic doses are administered each time in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.

In another embodiment, the present disclosure relates to a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt

thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose is administered in an amount effective to achieve subsequent to its administration a first C_{max} of base compound in plasma of the subject ranging from about 16 ng/mL to about 44 ng/mL, wherein the optional second dose is administered in an amount effective to achieve subsequent to its administration a second C_{max} of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL, wherein the optional successive periodic doses are administered in an amount effective to achieve subsequent to each administration a C_{max} of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.

In another embodiment, the present disclosure relates to a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose is administered in an amount effective to achieve subsequent to its administration a first area under the curve of base compound concentration in the plasma versus time of the subject (AUC) ranging from about 18 h·ng/mL to about 48 h·ng/mL, wherein the optional second dose is administered in an amount effective to achieve subsequent to its administration a second AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL, wherein the optional successive periodic doses are administered in an amount effective to achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.

In another embodiment, the present disclosure relates to any of the foregoing methods of treating a mood disorder or pain in a subject in need of such treatment additionally comprising administering to the subject substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof in an amount relative to the free base form of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one of about 40 mg to about 360 mg PO or about 13 mg to about 120 mg IV or about 20 mg to about 180 mg IM, within about 3 h of the administration to the subject of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.

In another embodiment, the present disclosure relates to any of the foregoing methods of treating a mood disorder or pain in a subject in need of such treatment additionally comprising administering to the subject racemic ketamine, S-ketamine, or R-ketamine or a pharmaceutically acceptable salt thereof in an amount relative to the free base form of racemic ketamine, S-ketamine, or R-ketamine of about 10 mg to about 100 mg IV, IM, or IN in the case of racemic ketamine and S-ketamine, or about 20 mg to about 200 mg IV, IM, or IN in the case of R-ketamine, within about 3 h of the administration to the subject of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.

In another embodiment, the present disclosure relates to any of the foregoing methods of treating a mood disorder or pain in a subject in need of such treatment wherein an antidepressant is administered concurrently or simultaneously with the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment or during a maintenance treatment phase that immediately follows the acute induction phase of treatment or during both the acute induction phase of treatment and the maintenance treatment phase.

In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.

In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof and substantially pure (*R*)-2-

(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof.

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.

FIG. 1 graphically shows the effect of administration of the indicated doses of base compound or placebo by *IV* administration on each dimension and total score of the 5-Dimensional Altered States of Consciousness Scale (5D-ASC). Data points represent the mean percentage of maximal effect $\pm$ standard error of the mean for each dimension or total score for groups of 6 (each dose of base compound) or 12 (placebo) subjects.

FIG. 2 graphically shows the effect of administration of the indicated doses of base compound or placebo on each dimension and total score of the Mystical Experience Questionnaire-30 (MEQ-30). Data points represent the mean percentage of maximal effect $\pm$ standard error of the mean for each sub-factor or total score for groups of 6 (each dose of base compound) or 12 (placebo) subjects.

FIG. 3 graphically shows the effect of *IV* administration of the indicated doses of base compound or placebo on the “do you feel a drug effect right now?” item of the Drug Effects Questionnaire (DEQ) over time after administration. Data points represent the mean percentage of maximal effect $\pm$ standard error of the mean at each time point for groups of 6 (each dose of base compound) or 12 (placebo) subjects.

FIG. 4 graphically shows the effect of *IV* administration of base compound at the indicated doses on pEEG signals relative to baseline at 20 minutes after dosing 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. Separate scales were used for lower EEG bands (Delta, Theta, and Alpha) and higher EEG bands (Beta, GammaS and GammaF). Single arrow marks substantial decrease in Theta EEG power starting at the 1 mg dose. Double arrow marks substantial increase in Fast Gamma EEG power starting at the 10 mg dose. Data are from Eyes Closed condition. Data were averaged across subjects at each dose level after removing placebo subjects.

FIG. 5 graphically shows the effect of administration of base compound on the combined head twitch response (HTR) and wet dog shake (WDS) behaviors observed in the 20 min immediately after dosing at dose levels of 0.032-10 mg/kg (SC). Data are mean $\pm$ standard error of the mean and are collected from n=6 rats/group. The maximum effect of the standard 5-HT_{2A} receptor agonist hallucinogen 2,5-dimethoxy-4-propylamphetamine (DOPR; 0.32 mg/kg, SC) is indicated by the horizontal dotted line.

FIG. 6 shows graphically the effect of acute administration of base compound (0.1-3.2 mg/kg, SC) on immobility time as compared to desipramine (20 mg/kg, SC, t.i.d.) in naive rats tested in the FST 24 h after dosing (n=10/group). Asterisks indicate a significant difference from the vehicle-treated group using Dunnett's post-hoc test.

FIG. 7A depicts an overview of the experimental schedule for the chronic mild stress (CMS) study paradigm in Wistar Kyoto rats. Short arrows (with ☉) represent weekly sucrose drinking tests (Tuesdays). Long arrows (with 🏠) show when animals received weekly drug treatments (Mondays). The black arrow labelled with EPM shows the timing for the EPM (Wednesday, Week 5), and the grey arrow labelled with NOR shows the timing for the NOR test (Thursday, Week 5). For each treatment group n=8 rats were exposed to CMS stressors and n=8 rats were unstressed controls. Rats were single housed prior to the onset of stress.

FIG. 7B graphically shows the effect of base compound (0.3 or 1 mg/kg, SC) and (*rac*)-ketamine (10 mg/kg, IP) on sucrose intake over the course of the study.

FIG. 7C graphically shows the percent time spent in the open arms of the EPM, which was conducted 48 h after the third drug treatment. Open bars show data from unstressed control rats, while filled bars show data from rats exposed to CMS for each treatment group. * indicates $P < 0.05$ vs Control Vehicle group; # indicates $P < 0.05$ vs Control group within same treatment.

FIG. 7D graphically shows the results from the NOR task. The NOR task was conducted 72 h after the third drug treatment. Open bars show data from unstressed control rats, while filled bars show data from rats exposed to CMS for each treatment group.

* indicates $P < 0.05$ vs Control Vehicle group; # indicates $P < 0.05$ vs Control group within same treatment.

FIG. 8A shows EEG spectrograms calculated for the time 30 minutes prior to injection (T = 0) through 180 minutes after injection of the indicated dose (SC) of base compound or vehicle.

Shade represents z-scored EEG power, where z-score values are referenced to 30 minutes prior to injection. White arrows point to a decrease in low-frequency EEG power.

FIG. 8B shows values of theta (5-12 Hz) EEG power relative to vehicle. Power was averaged over the period from 0 to 120 minutes following injection of the indicated dose (SC) of base compound. Asterisks indicate a significant difference compared to vehicle and 1 indicates no change relative to vehicle. All data are the mean of $n=8$ /group and all error bars are SEM.

FIG. 9 depicts graphically the ability of base compound to occupy 5-HT_{2A} receptors in the rat cortex in vivo. This relationship was derived from data collected in rats dosed with base compound (0.32-3.2 mg/kg, SC) followed by the radiolabeled 5-HT_{2A} receptor agonist tracer [³H]Cimbi-36. FIG. 9A shows binding potential data measured at various plasma concentrations, and FIG. 9B is the modeled occupancy-dose relationship used to calculate the ED₅₀ dose of 0.32 mg/kg (SC).

FIG. 10 depicts graphically the relationship between plasma concentration of base compound and specific pharmacodynamic effects in rats, as well as proposed translation of those findings to humans. Base compound achieved 50% 5-HT_{2A} receptor occupancy (IVRO) at a plasma concentration of 13.2 ng/mL. The peak head twitch and wet dog shake behavioral response (HTR & WDS) occurred at a plasma level of 41.3 ng/mL, indicated by an unfilled diamond in the HTR & WDS row. Significant changes in rat EEG power spectrum occurred at plasma levels of base compound from 41.3-104.0 ng/mL. Antidepressant-like effects of base compound were seen in the chronic mild stress paradigm (CMS) at plasma concentrations of 12.4-41.3 ng/mL. Peak plasma concentrations after 10-min IV infusion of base compound in healthy humans at the indicated doses are overlaid as indicated by vertical dotted lines.

FIG. 11 depicts mean ($\pm$ SEM) concentration-time profiles comparing administration of the base compound at 10 mg either by a 10-min IV infusion with each timepoint averaged from 6 subjects or by IM injection with each timepoint averaged from 7-9 subjects.

FIG. 12 graphically compares the effects of administration of a 10 mg dose of the base compound by the IM and IV routes on each dimension and total score of the 5-Dimensional Altered States of Consciousness Scale (5D-ASC) reported retrospectively by participants. Each bar represents the mean percentage of maximal effect $\pm$ standard error of the mean for each dimension or total score averaged from 9 subjects for IM dosing of the base compound, 3 subjects for IM placebo, and 6 subjects for IV dosing. Placebo data are not visible, as all values

were zero. Abbreviations are: OB – Oceanic Boundlessness, DED – Dread of Ego Dissolution, VRes – Visual Restructuring, AA – Auditory Alterations, VRed – Reduction of Vigilance.

FIG. 13 graphically shows the effect of administration of a 10 mg dose of the base compound by *IM* and *IV* administration and placebo by *IM* administration on each dimension and total score of the Mystical Experience Questionnaire-30 (MEQ-30) reported retrospectively by participants. Each bar represents the mean percentage of maximal effect $\pm$ standard error of the mean for each dimension or total score averaged from 8 subjects for *IM* dosing, 6 subjects for *IV* dosing of the base compound, and 3 subjects for *IM* placebo. Placebo data are not visible, as all values were zero.

FIG. 14A graphically compares the effects of administration of a 10 mg dose of the base compound by the *IM* or *IV* routes and placebo (*IM*) reported by participants on the Visual Intensity subscale of the Real Time Intensity (RTI) assessment. Each point represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 9 participants from the *IM* base compound group, 6 subjects from the *IV* base compound group, and 3 subjects from the *IM* placebo group.

FIG. 14B graphically compares the effects of administration of a 10 mg dose of the base compound by the *IM* or *IV* routes and placebo (*IM*) reported by participants on the Bodily Intensity subscale of the Real Time Intensity (RTI) assessment. Each point represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 9 participants from the *IM* base compound group, 6 subjects from the *IV* base compound group, and 3 subjects from the *IM* placebo group.

FIG. 14C graphically compares the effects of administration of a 10 mg dose of the base compound by the *IM* or *IV* routes and placebo (*IM*) reported by participants on the Emotional / Metacognitive Intensity subscale of the Real Time Intensity (RTI) assessment. Each point represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 9 participants from the *IM* base compound group, 6 subjects from the *IV* base compound group, and 3 subjects from the *IM* placebo group.

FIG. 14D graphically compares the effects of administration of a 10 mg dose of the base compound by the *IM* or *IV* routes and placebo (*IM*) reported by participants on the Total Intensity subscale of the Real Time Intensity (RTI) assessment. The total intensity represents an average of the intensity values from the 3 subscales shown in FIGS. 15A-C. Each point represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 9 participants from the *IM* base compound group, 6 subjects from the *IV* base compound group, and 3 subjects from the *IM* placebo group.

FIG. 15A graphically compares the effects of administration of ascending dose levels of the base compound reported by participants in separate cohorts on the Visual Intensity subscale of the Real Time Intensity (RTI) assessment. All doses were administered as a 10 min *IV* infusion beginning at Timepoint '0'. Each point for the 0.34 mg group represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 4 participants. Each point for the 1.0, 3,3, 10, 15, and 20 mg cohorts represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 6 participants. Placebo values are not shown on the graph, as all were very close to '0'.

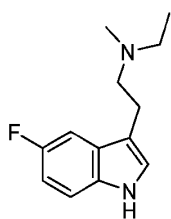
FIG. 15B graphically compares the effects of administration of ascending dose levels of the base compound reported by participants in separate cohorts on the Bodily Intensity subscale of the Real Time Intensity (RTI) assessment. All doses were administered as a 10 min *IV* infusion beginning at Timepoint '0'. Each point for the 0.34 mg group represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 4 participants. Each point for the 1.0, 3,3, 10, 15, and 20 mg cohorts represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 6 participants. Placebo values are not shown on the graph, as all were very close to '0'.

FIG. 15C graphically compares the effects of administration of ascending dose levels of the base compound reported by participants in separate cohorts on the Emotional/Metacognitive subscale of the Real Time Intensity (RTI) assessment. All doses were administered as a 10 min *IV* infusion beginning at Timepoint '0'. Each point for the 0.34 mg group represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 4 participants. Each point for the 1.0, 3,3, 10, 15, and 20 mg cohorts represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 6 participants. Placebo values are not shown on the graph, as all were very close to '0'.

FIG. 15D graphically compares the effects of administration of ascending dose levels of the base compound reported by participants in separate cohorts on the Total Intensity subscale of the Real Time Intensity (RTI) assessment. All doses were administered as a 10 min *IV* infusion beginning at Timepoint '0'. Each point for the 0.34 mg group represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 4 participants. Each point for the 1.0, 3,3, 10, 15, and 20 mg cohorts represents the mean ($\pm$ SEM) intensity on a scale of 0 to 10 for 6 participants. A total of 12 placebo participants were pooled from all 6 cohorts (2 per cohort). Placebo values are not easily visible on the graph, as all were very close to '0'.

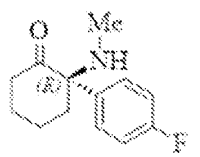
DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure relates to dosing levels and regimens for treating mood disorders and/or the symptoms thereof in a subject comprising administering to said subject in need of treatment a pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor, according to a prescribed schedule, as described herein. The structure of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is depicted below:



As a shorthand notation, the term “base compound” is used to denote *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine in its free base form without any salt counterion.

In some embodiments, the present disclosure also relates to methods of treating mood disorders involving the administration of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one concurrently or simultaneously or in combination with *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine. 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 compounds depicted hereinabove, including any pharmaceutically acceptable salt, wherein a compound disclosed herein has a net charge (either positive or negative) and at least one counterion (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, especially humans, and possess the desired biological activity. A pharmaceutically acceptable salt 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, malate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds disclosed herein can form a pharmaceutically acceptable salt with various amino acids. For a review on a pharmaceutically acceptable salt see Berge, et al., J. Pharm Sci., 66, 1-19 (1977), incorporated herein by reference. In an embodiment, the pharmaceutically acceptable salt is the hydrochloride or fumarate salt of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine, i.e., *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine hydrochloride or *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine fumarate. In an embodiment, the pharmaceutically acceptable salt is the hydrochloride salt of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one, i.e., (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one hydrochloride.

The term "substantially pure" with respect to a compound or a pharmaceutically acceptable salt thereof disclosed herein, e.g., "substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof", denotes that the compound or a pharmaceutically acceptable salt thereof, e.g., *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof, is at least 60% pure by weight, i.e., contains no more than 40% impurities. In embodiments, the term "substantially pure" denotes that the compound or a pharmaceutically acceptable salt thereof is at least 75%, 80%, 85%, 90%, 95%, 97%, or 99% pure by weight. In an embodiment, the term "substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof" denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine

or a pharmaceutically acceptable salt thereof is at least 75% pure by weight. In an embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 80% pure by weight. In another embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 85% pure by weight. In a further embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 90% pure by weight. In a further embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 95% pure by weight. In a further embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 97% pure by weight. In a further embodiment, the term “substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof” denotes that *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is at least 99% pure by weight. In the case of a pharmaceutically acceptable salt of a disclosed compound, the foregoing purity percentages are calculated with respect to the free base of the compound corrected for counterion mass (i.e., the percent by weight of salt counterion is not considered an impurity).

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 a compound or a pharmaceutically acceptable salt thereof disclosed herein, *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, intervals of every other day, every 3 days, every 4 days, every 5 days, and every 6 days are also encompassed.

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 or a pharmaceutically acceptable salt thereof 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 terms “therapeutically effective amount” or “effective amount” also refer to

that amount of the disclosed compound or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a 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 any compound or pharmaceutically acceptable salt thereof disclosed herein and associated therapeutic effects and side effects refers to the ratio of the dose of said compound or pharmaceutically acceptable salt thereof required to induce a particular negative side effect to the dose of said compound or pharmaceutically acceptable salt thereof 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 the pharmaceutical composition comprising a disclosed compound or a pharmaceutically acceptable salt thereof 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,” or like term, as used herein means that the base compound or a pharmaceutically acceptable salt thereof and one or more additional active compounds, including but not limited to 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 active compounds 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 additional active compounds are administered at the same point in time.

“Concurrent administration,” “administration in combination,” and “concurrently” or like term, 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. 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.

The term “area under the curve” (AUC) refers to the area under the plasma concentration of base compound versus time curve from time 0 to time t after the administration of one dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof but prior to the administration of any subsequent dose of the pharmaceutical composition comprising substantially pure 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 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 pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof but prior to the administration of any subsequent dose of the pharmaceutical composition of the substantially pure 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 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. In the case of

base compound or a pharmaceutically acceptable salt thereof administered by inhalation, $C_{\max}$ typically occurs at the end of the inhalation process. 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 true $C_{\max}$.

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

Unless indicated to the contrary, the terms “drugs” 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 values 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 the subject matter of this disclosure 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.

Various abbreviations are used throughout the specification. For example, IM is intramuscularly, IV is intravenously, PO is orally, NMDAR is *N*-methyl-D-aspartate receptor, and 5-HT_{2A} is serotonin 2A.

The compounds administered in the method claims are present in the form of a pharmaceutical composition. These compositions include those suitable for oral, rectal, nasal, inhalation, topical (including transdermal, buccal and sublingual), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, and intradermal) administration or administration via an implant. In an embodiment, the pharmaceutical composition comprising a base compound comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is administered intravenously,

intramuscularly, by inhalation, intranasally, subcutaneously, or orally. In another embodiment, it is administered intravenously, intramuscularly, or by inhalation.

The pharmaceutical compositions may be prepared by any method well known in the art of pharmacy.

Such methods include the step of bringing in association compounds, including the base compound or a pharmaceutically acceptable salt thereof 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, e.g., substantially pure base compound or a pharmaceutically acceptable salt thereof 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 substantially pure 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 (e.g., substantially pure base compound or a pharmaceutically acceptable salt thereof) 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 substantially pure 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 substantially pure 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 active ingredient, e.g., substantially pure base compound or a pharmaceutically acceptable salt thereof, suitable stabilizing agents, and if necessary, buffer substances, such as a phosphate buffer at a pH compatible with the pH of the plasma or 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 250 mOsm/kg to about 325 mOsm/kg, or 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) conditions 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 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, PEGS00, 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, tromethamine, 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 1-100 μ m. In some embodiments, the nebulizer 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, PEGS00, 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, tromethamine, 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 substantially pure base compound or a pharmaceutically acceptable salt thereof 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, polyhydroxyethylaspartamidephenol, 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, polycyanoacylates, and crosslinked or amphipathic 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, etc.

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.

In embodiments, the mood disorder is a depressive disorder. Some examples of depressive disorders include major depressive disorder, persistent depressive disorder, psychiatric disorders, 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 substantially pure

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 not limited to, psychotic depression, postpartum depression, seasonal affective disorder (SAD), and depressions caused by 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). 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 chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress, post-traumatic stress disorder, obsessive-compulsive disorder, and bipolar disorder (or manic depressive disorder).

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 (SNRIs), and triple reuptake inhibitors (TRIs; 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 treatment. The substantially pure 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, excessive sleeping, 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 substantially pure base compound or a pharmaceutically acceptable salt thereof described herein. In some embodiments, presence, severity, frequency, and duration of symptoms of depression vary on a case-to-case basis.

In other embodiments, the mood 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 mood 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 mood disorder is an anxiety disorder. Some examples of anxiety disorders include separation anxiety disorder, selective mutism, psychiatric 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 mood 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 mood disorder is a trauma- or stressor-related disorders. Some examples of such mood 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 mood disorder is a feeding and eating disorder. Some examples of such mood 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 mood 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 mood 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 mood and neurological conditions may be treated according to the methods of the present disclosure. In some embodiments, such mood 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 other mood and neurological disorders, including any of those specifically pointed out above by any of the methods described herein.

In other embodiments, the mood 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 mood disorder may be associated with a sexual dysfunction. Some examples of such mood 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 mood 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. The pain may be associated with a mood disorder afflicting the subject or occur without the presence of a mood disorder. In an embodiment, the pain is a migraine, cluster headache, or other headache disorder.

In the method, the base compound or a pharmaceutically acceptable salt thereof described herein, typically in the form of a pharmaceutical composition, are used to treat this symptom 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) one or more symptoms of the headache disorder or prevent a recurrence of one or more symptoms of the headache disorder. In another embodiment, the pain is chronic pain. In another embodiment, the pain is neuropathic pain. In another embodiment, the pain is chemotherapy induced neuropathy. In another embodiment, the treatment with the base compound or a pharmaceutically acceptable salt thereof 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 the patient's pain.

Although the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof may be administered to the subject by any means of administration, the amount administered may be described in terms of mg of the base compound. To maintain consistency 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; indicated doses in mg are solely based on the amount of the free base, *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine, so that equal amounts of moles of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine are administered, regardless of the pharmaceutically acceptable salt selected. For example, the molecular weight of free base *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is 220.29 g/mole, while the formula weight of the hydrochloride salt of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is 256.75 g/mole. Accordingly, for example, 0.001 moles of the free base weighs 220.29 mg, while 0.001 moles of the hydrochloride salt of the free base weighs 256.75 g/mole. 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 220.29 mg free base is equivalent to a dose of 256.75 mg hydrochloride salt, and the doses of both the free base and hydrochloride salt are listed as 220.29 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 *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine administered is in terms of the equivalent amount of free base administered, so that, for example, 256.75 mg of the hydrochloride salt administered is equivalent to the administration of 220.29 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.

Although the 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 the concentration of base compound achieved in the plasma of the subject. In an embodiment, the plasma from the subject is obtained by techniques known to one of ordinary skill in the art. 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 pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof of the present disclosure may be administered to the subject in need of such treatment in dosages that will provide optimal therapeutic efficacy. It will be appreciated that the dose required for use in any particular subject or application, as well as the frequency of dosing 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, such as the psychiatrist.

In accordance with the present disclosure, the subject suffering from a mood disorder is administered a first dose of a pharmaceutical composition comprising a substantially pure base compound or a pharmaceutically acceptable salt thereof in the dosage amount described herein. Subsequent thereto, within at most a week thereafter, the medical professional, such as a

psychiatrist, treating the subject determines whether neuropsychiatric symptoms associated with the mood disorder are in remission. This can be effected by observation or conducting the screening tests described hereinbelow. If the medical professional determines that the neuropsychiatric symptoms are in remission, in an embodiment, the medical professional discharges the subject; however in another embodiment, the medical professional periodically determines whether the neuropsychiatric symptoms are in remission. The time intervals after the discharge of the subject for periodic testing of whether the neuropsychiatric symptoms are in remission is determined by the medical professional taking into account various factors, including without limitation, the type of mood disorder that the subject has, the severity of the mood disorder, the age and health condition 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. If the neuropsychiatric symptoms remain in remission after this subsequent determination, the medical professional will continue to monitor the subject periodically to ascertain whether the neuropsychiatric symptoms remain in remission.

If, however, the subject's condition worsens and the neuropsychiatric symptom are no longer in remission, the subject begins treatment once again and is administered a first dose of the pharmaceutical composition comprising a substantially pure base compound or a pharmaceutically acceptable salt thereof, as described hereinbelow in the acute induction phase of treatment.

In another embodiment, after the first dosage of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a determination that the neuropsychiatric symptoms are in remission, the medical professional may continue to administer additional pharmaceutical compositions comprising a substantially pure base compound or its pharmaceutically acceptable salt thereof in accordance with the maintenance phase of treatment, as described hereinbelow.

In another embodiment, if after the subject is administered the first dosage of the pharmaceutical composition comprising a substantially pure base compound or a pharmaceutically acceptable salt thereof, the medical professional will continue to administer a second dosage of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof as the subject enters the acute induction of treatment, as discussed hereinbelow followed by the optional maintenance phase of treatment,

described below. The optional second dose is administered to the patient within about two weeks after the administration of the first dose. If additional doses are administered, the base compound or a pharmaceutically acceptable salt thereof is administered to the patient about every other week or about monthly or about every other month after the administration of the second dose thereof.

In an embodiment, the subject being treated concludes the acute induction of treatment when the neuropsychiatric symptoms are in remission. At this stage, the medical professional may discharge the patient and periodically determine whether the neuropsychiatric symptoms are in remission, as described hereinabove.

In a further embodiment, after the acute induction phase of treatment, the medical professional may immediately place the subject into the maintenance treatment phase, which commences immediately after the conclusion of the acute induction phase of treatment, as described hereinbelow.

In an embodiment, the subject may experience two phases of treatment for treating mood 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 mood 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 psychiatric, 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, including a medical professional, such as a psychiatrist, 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 or health care professional 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 or medical professional rates the subject on the following symptoms exhibited by a subject in a clinical interview: 1) apparent sadness, 2) reported sadness; 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.

In an embodiment, if the neuropsychiatric symptoms are substantially improved to indicate to the medical professional that the patient can enter the maintenance phase of treatment, then the acute induction phase of treatment ends. In this case, there needs to be a significant reduction of the neuropsychiatric symptoms experienced by the patient for the patient to begin the maintenance phase of treatment so that it becomes apparent to the medical professional that the patient is ready to begin the maintenance phase of treatment., such as a lowering of the scores of the various tests described hereinabove or in the examples below. In addition, there is an observable manifestation in the behavior of the patient to the medical professional to justify the patient entering the next phase of treatment.

This acute induction phase in an embodiment lasts usually for a period of less than six months, and, in another embodiment, about 6 weeks or less, after the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject suffering from a mood disorder, and in another embodiment, up to about four months after the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt

thereof is administered to the subject suffering from a mood 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 pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof to the subject suffering from a mood 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 commences, identified herein as the maintenance treatment phase, in which the subject being treated for a mood disorder is periodically screened to determine if the clinical symptoms, i.e., neuropsychiatric symptoms, remain in remission, and these symptoms are screened for a sufficient period of time to determine if the 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, during the maintenance phase of treatment, the base compound or a pharmaceutically acceptable salt thereof is administered to the subject about two to about every four weeks. In another embodiment, it is administered every week to about every two weeks. Periodically, the subject is subjected to a screening exam, as described hereinabove, for a prescribed period of time, depending upon the severity of the mood disorder. At the end of the prescribed period, the psychiatrist or other medical professional will conduct a screening exam, and if, in the determination of the psychiatrist or if the subject matches or improves upon the score on a recognized screening test, such as the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale, and the like, and if the medical professional determines that the risk of a relapse is minimized or unlikely, the maintenance phase of treatment is concluded and the subject is no longer administered the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof. In an embodiment, the maintenance phase of treatment 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. If, however, the medical professional observes a worsening of the condition during the maintenance treatment

phase, the dosage or frequency of dosing of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof may be increased, as determined by the medical professional, and continued administration of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt is continued until it is determined by the medical professional that the risk of a relapse is minimized or unlikely, such as by using the results of the screening tests described hereinabove.

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 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 patient 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, when the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered intramuscularly, the administration thereof to the subject occurs in seconds. In an embodiment, the composition is a sterile liquid composition and the administration to the subject occurs in 30 seconds or less, and in another embodiment, in 15 seconds or less, and in another embodiment, in 10 seconds or less. The patient will respond to treatment as long as an effective C_{max} of the base compound or a pharmaceutically acceptable salt is achieved in the plasma of the patient.

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

In an embodiment, the present disclosure relates to a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose of the pharmaceutical composition and an optional second dose of the pharmaceutical composition and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or pharmaceutically acceptable salt thereof and a

pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose of the pharmaceutical composition administered is in an amount relative to the base compound ranging from about 8 mg to about 16 mg IV or inhaled or about 8 mg to about 24 mg IM, wherein the optional second dose of the pharmaceutical composition administered is in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, wherein the optional successive periodic doses of the pharmaceutical composition are administered each time in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine. In an embodiment, the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in an amount relative to the base compound ranging from about 10 mg to about 12 mg IV or inhaled or in an amount relative to the base compound ranging from about 10 mg to about 15 mg IM. In another embodiment, the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in an amount relative to the base compound ranging from about 14 mg to about 16 mg IV or inhaled or in an amount relative to the base compound ranging from about 14 mg to about 24 mg IM.

In an embodiment, the optional second dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in an amount relative to the base compound ranging from about 10 mg to about 12 mg IV or inhaled or about 10 mg to about 15 mg IM. In another embodiment, the optional second dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in an amount relative to the base compound ranging from about 14 mg to about 18 mg IV or inhaled or about 14 mg to about 27 mg IM. In another embodiment, the optional second dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in an amount relative to the base compound ranging from about 14 mg to about 16 mg IV or inhaled or about 14 mg to about 24 mg IM. In another embodiment, the optional second dose of the pharmaceutical composition is administered within about 3 weeks of the first

dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof. In another embodiment, the optional second dose of the pharmaceutical composition is administered within about 2 weeks of the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof. In another embodiment, the optional second dose of the pharmaceutical composition is administered three to seven days after the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof.

After the initial administration of the first dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a second dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof during the acute induction phase of treatment, further doses of pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof are optionally administered; if administered, they may be administered in successive periodic doses. The amount of each optional periodic dose as well as the interval between doses is determined by the psychiatrist, as described hereinabove. In an embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in successive periodic doses during the acute induction phase of treatment in an amount relative to the base compound ranging from about 12 mg to about 18 mg IV or inhaled or about 12 mg to about 27 mg IM. In another embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in successive periodic doses during the acute induction phase of treatment in an amount relative to the base compound ranging from about 10 mg to about 16 mg IV or inhaled or about 10 mg to about 24 mg IM. In another embodiment, the successive periodic doses of the acute induction phase of treatment are administered at intervals ranging from about every two weeks to every two months commencing after the administration of the second dose to the subject. In another embodiment, only the first dose of base compound is administered. In another embodiment, only the first and second doses of base compound are administered. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six months

from the administration of the first dose. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six weeks from the administration of the first dose. In an embodiment, when the acute induction phase of treatment is concluded and when the neuropsychiatric symptoms are in remission or substantially improved, the maintenance phase of treatment commences.

In an embodiment, additional pharmaceutical composition(s) comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor is administered in periodic successive doses in an amount relative to the base compound ranging from about 3 mg to about 20 mg IV or inhaled or about 3 mg to about 30 mg IM, over a maintenance phase of treatment. In an embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about every two weeks to about every twelve weeks, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount relative to the base compound ranging from about 12 mg to about 18 mg IV or inhaled or about 12 mg to about 27 mg IM. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about every two weeks to about six months, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount relative to the base compound ranging from about 10 mg to about 16 mg IV or inhaled or about 10 mg to about 24 mg IM. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about every week to about every two weeks during the maintenance phase of treatment in an amount relative to the base compound ranging from about 3 mg to about 10 mg IV or inhaled or about 3 mg to about 15 mg IM. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount relative to the base compound ranging from about 3 mg to about 10 mg IV or inhaled or about 3 mg to about 15 mg IM. In another embodiment, a dose of the pharmaceutical composition comprising substantially

pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount relative to the base compound ranging from about 3 mg to about 7 mg IV or inhaled or about 3 mg to about 10 mg IM. In an embodiment, all doses of the pharmaceutical composition are administered IV. In a further embodiment, each IV dose of the pharmaceutical composition is administered in about 15 minutes or less. In another embodiment, all doses of the pharmaceutical composition are administered by inhalation. In an embodiment, all doses of the pharmaceutical compositions are administered IM. In an embodiment, one or more of the optional steps are performed. In an embodiment, all of the optional steps are performed.

In an embodiment, the present disclosure relates to a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof during an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose is administered in an amount effective to achieve subsequent to its administration a first $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL, wherein the optional second dose of the pharmaceutical composition is administered in an amount effective to achieve subsequent to its administration a second $C_{\max}$ of base compound in plasma of the subject ranging from about 26 ng/mL to about 44 ng/mL, wherein the optional successive periodic doses of the pharmaceutical composition are administered in an amount effective to achieve subsequent to each administration a $C_{\max}$ of base compound in plasma of the subject ranging from about 22 ng/mL to about 44 ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine. In an embodiment, the first dose is administered in an amount effective to achieve subsequent to its administration a first $C_{\max}$ of base compound in plasma of the subject ranging from about 16 ng/mL to about 44 ng/mL, the optional second dose of the pharmaceutical composition is administered in an amount effective to achieve subsequent to its administration a second $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about

44 ng/mL, and the optional successive periodic doses of the pharmaceutical composition are administered in an amount effective to achieve subsequent to each administration a $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL. In an embodiment, the first $C_{\max}$ with respect to the base compound achieved in the plasma of the subject ranges from about 22 ng/mL to about 26 ng/mL. In another embodiment, the first $C_{\max}$ of the base compound in plasma of the subject ranges from about 36 ng/mL to about 44 ng/mL. In another embodiment, the first $C_{\max}$ with respect to the base compound achieved in the plasma of the subject ranges from about 18 ng/mL to about 26 ng/mL. In another embodiment, the first $C_{\max}$ with respect to the base compound achieved in the plasma of the subject ranges from about 30 ng/mL to about 44 ng/mL. In a further embodiment, the second $C_{\max}$ of the base compound achieved in plasma of the subject ranges from about 36 ng/mL to about 44 ng/mL. In a further embodiment, the second $C_{\max}$ of the base compound achieved in plasma of the subject ranges from about 18 ng/mL to about 26 ng/mL. In a further embodiment, the second $C_{\max}$ of the base compound achieved in plasma of the subject ranges from about 30 ng/mL to about 44 ng/mL. In another embodiment, the second optional dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered within about three weeks of the first dose. In another embodiment, the second optional dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered within about two weeks of the first dose. In a further embodiment, the second optional dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered three to seven days after the first dose. In an additional embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered in successive periodic doses during the acute induction phase of treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound ranging from about 26 ng/mL to about 44 ng/mL. In another embodiment, the successive periodic doses during the acute induction phase of treatment achieve subsequent to each dose a $C_{\max}$ of base compound ranging from about 18 ng/mL to about 44 ng/mL. In an embodiment, the optional successive periodic doses of the acute induction phase of treatment occur at intervals ranging from about every two weeks to about every two months commencing after the administration of the second dose of the pharmaceutical composition. In another embodiment,

only the first dose of base compound is administered. In a further embodiment, only the first and second doses of base compound are administered. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six months from the administration of the first dose. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six weeks from the administration of the first dose. In an even further embodiment, additional pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor is optionally administered in periodic successive doses in an amount effective to achieve subsequent to each administration a $C_{\max}$ of the base compound in plasma of the subject ranging from about 5 ng/mL to about 44 ng/mL during a maintenance phase of treatment. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about every two weeks to about every twelve weeks, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound in plasma of the subject ranging from about 22 ng/mL to about 44 ng/mL. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about every two weeks to about six months, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL. In another embodiment, a dose of a pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about every week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound in plasma of the subject ranging from about 5 ng/mL to about 22 ng/mL. In another embodiment, a dose of a pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about twice per week to about every two weeks during the maintenance phase of

treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound in plasma of the subject ranging from about 5 ng/mL to about 22 ng/mL. In another embodiment, a dose of a pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each dose a $C_{\max}$ of base compound in plasma of the subject ranging from about 5 ng/mL to about 16 ng/mL.

In an embodiment, the present disclosure comprises a method of treating a mood disorder or pain in a subject in need of such treatment comprising administering to the subject a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor during an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose of the pharmaceutical composition comprising base compound is administered in an amount effective to achieve subsequent to its administration a first area under the base compound in the plasma versus time curve of the subject (AUC) ranging from about 18 h·ng/mL to about 48 h·ng/mL, wherein the optional second dose is administered in an amount effective to achieve subsequent to its administration a second AUC in plasma ranging from about 27 h·ng/mL to about 57 h·ng/mL, wherein the optional successive periodic doses are administered in an amount effective to achieve subsequent to each administration an AUC in the plasma ranging from about 22 h·ng/mL to about 57 h·ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine. In another embodiment, the first dose of the pharmaceutical composition comprising base compound achieves subsequent to its administration a first AUC ranging from about 18 h·ng/mL to about 48 h·ng/mL, the optional second dose achieves subsequent to its administration a second AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL, and the optional successive periodic doses achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL. In an embodiment, the first AUC of base compound achieved in plasma of the subject ranges from about 22 h·ng/mL to about 27

h·ng/mL. In another embodiment, the first AUC of base compound achieved in plasma of the subject ranges from about 20 h·ng/mL to about 27 h·ng/mL. In a further embodiment, the first AUC of base compound achieved in plasma of the subject ranges from about 42 h·ng/mL to about 51 h·ng/mL. In a further embodiment, the first AUC of base compound achieved in plasma of the subject ranges from about 40 h·ng/mL to about 51 h·ng/mL. In an even further embodiment, the optional second dose of base compound is administered and achieves an AUC in plasma of the subject ranging from about 42 h·ng/mL to about 51 h·ng/mL. In an even further embodiment, the optional second dose of base compound is administered and achieves an AUC in plasma of the subject ranging from about 40 h·ng/mL to about 51 h·ng/mL. In an embodiment, the second dose is administered to the subject within about three weeks of the first dose. In an embodiment, the second dose is administered to the subject within about two weeks of the first dose. In an embodiment, the second dose is administered to the subject three to seven days after the first dose. In an embodiment, the optional successive periodic doses of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof are administered to the subject during the acute induction phase of treatment in an amount effective to achieve subsequent to each administration an AUC of base compound in the plasma ranging from about 27 h·ng/mL to about 51 h·ng/mL. In an embodiment, the optional successive periodic doses achieve subsequent to each administration an AUC of base compound in the plasma ranging from about 20 h·ng/mL to about 51 h·ng/mL. In an embodiment, the optional successive periodic doses of the pharmaceutical composition during the acute induction phase of treatment occur at intervals ranging from about every two weeks to every two months commencing after the administration of the optional second dose of pharmaceutical composition during the acute induction phase of treatment. In another embodiment, only the first dose of base compound is administered. In another embodiment, only the first and second doses of base compound are administered. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six months from the administration to the subject of the first dose. In a further embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered during the acute induction phase of treatment over a period of about six weeks from the administration to the subject of the first dose. In an

embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject in periodic successive doses in an amount effective to achieve subsequent to each administration an AUC of base compound in plasma of the subject ranging from about 6 h·ng/mL to about 57 h·ng/mL during a maintenance phase of treatment. In another embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject in periodic successive doses in an amount effective to achieve subsequent to each administration an AUC of base compound in plasma of the subject ranging from about 5 h·ng/mL to about 60 h·ng/mL during a maintenance phase of treatment. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about every two weeks to about every twelve weeks, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 27 h·ng/mL to about 51 h·ng/mL. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about every two weeks to about every six months, or about every two weeks to about every four weeks, during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 51 h·ng/mL. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about every week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 6 h·ng/mL to about 22 h·ng/mL. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 5 h·ng/mL to about 22 h·ng/mL. In another embodiment, a dose of the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered to the subject at intervals ranging from about twice per

week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 5 h·ng/mL to about 16 h·ng/mL.

In an embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor is administered intravenously, intramuscularly, by inhalation, intranasally, subcutaneously, or orally. In another embodiment, the pharmaceutical composition is administered intravenously, intramuscularly, or by inhalation. In another embodiment, the pharmaceutical composition is administered intravenously or intramuscularly. In another embodiment, the pharmaceutical composition is administered intravenously. In another embodiment, the pharmaceutical composition is administered intramuscularly.

In an embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered concurrently or simultaneously with another active ingredient. In an embodiment, it is administered simultaneously with the other active ingredient. The other active ingredient and the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof may be administered together by mixing the other active ingredient with substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof in the same pharmaceutical composition or they may be administered separately. The other active ingredient and the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof may be administered concurrently or simultaneously by the same mode of administration or by a different mode of administration, or the other active ingredient may be mixed with the substantially pure base compound or pharmaceutically acceptable salt thereof prior to the administration of same. The concurrent or simultaneous administration of the other active ingredient may occur during the acute induction phase or during the maintenance treatment phase or both phases for treating a mood disorder or pain. In an embodiment, the other active ingredient is an antidepressant. In an embodiment, the antidepressant to be used simultaneously or concurrently with the pharmaceutical composition comprising a substantially pure base compound or a pharmaceutically acceptable salt thereof blocks the serotonin transporter. In another embodiment, the antidepressant to be used concurrently or simultaneously 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 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, noreclomipramine, opipramol, protriptyline, trimipramine, mitrazapine, mianserin, or setiptiline. In another embodiment, the antidepressant is bupropion. In another embodiment, the antidepressant is a monoamine oxidase inhibitor (MAOI). In a further embodiment, the MAOI is isocarboxazid, hydracarbazine, phenelzine, tranylcypromine, bifemelane, methylthioninium chloride, moclobemide, pirlindole, rasagiline, selegiline, or safinamide. In a further embodiment, the antidepressant is gepirone. In an embodiment, the antidepressant is S-ketamine (esketamine), R-ketamine (arketamine), or racemic ketamine. A combination of any of the aforementioned active ingredients, such as the antidepressants, may be used concurrently or simultaneously with the substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. Thus, in an embodiment, one or more of S-ketamine, R-ketamine, or racemic ketamine may be used concurrently or simultaneously with the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof.

In additional embodiments, treatment with the base compound or a pharmaceutically acceptable salt thereof concurrently or simultaneously with S-ketamine, R-ketamine, or racemic ketamine or a combination thereof, for example, may occur during a maintenance treatment phase, or during an acute induction treatment. As indicated hereinabove, the antidepressant may be administered by the same route or by a different route than the base compound or pharmaceutically acceptable salt thereof. For example, the base compound or a pharmaceutically acceptable salt thereof may be administered intramuscularly, while S-ketamine, R-ketamine, or racemic ketamine is administered intravenously, intranasally, intramuscularly, subcutaneously,

sublingually, or orally during the acute induction phase of treatment. For example, in an embodiment, S-ketamine is administered intranasally, R-ketamine is administered subcutaneously, and racemic ketamine is administered intravenously.

In an embodiment, the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof is administered concurrently or simultaneously with racemic ketamine, S-ketamine, or R-ketamine or a pharmaceutically acceptable salt thereof in an amount relative to the free base form of ketamine, S-ketamine, or R-ketamine of about 10 mg to about 100 mg IV, IM, or IN in the case of racemic ketamine and S-ketamine, or about 20 mg to about 200 mg IV, IM, or IN in the case of R-ketamine, within about 3 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In another embodiment, the racemic ketamine, S-ketamine, or R-ketamine is administered within about 1 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In another embodiment, the racemic ketamine, S-ketamine, or R-ketamine is administered at about the same time as the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In an embodiment, the racemic ketamine, S-ketamine, or R-ketamine and the substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof are administered together as a single IV or IM injection. In another embodiment, the racemic ketamine, S-ketamine, or R-ketamine is administered IV. For example, the racemic ketamine, S-ketamine, or R-ketamine is administered IV over a period of about 60 minutes or less, such as, for instance over a period of about 15 minutes or less. In another embodiment, the racemic ketamine, S-ketamine, or R-ketamine is administered IM concurrently or simultaneously with the administration of and the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In a further embodiment, the racemic ketamine, S-ketamine, or R-ketamine is administered IN concurrently or simultaneously with the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a

pharmaceutically acceptable salt thereof. In another embodiment, the S-ketamine is administered IN at a dose of about 56 mg to about 84 mg.

In an embodiment, the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is administered concurrently or simultaneously with an NMDAR antagonist. The NMDAR antagonist and the pharmaceutical composition comprising substantially pure base compound or a pharmaceutically acceptable salt thereof may be administered together by mixing the NMDAR antagonist with substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof in the same pharmaceutical composition or they may be administered separately. The NMDAR antagonist and the pharmaceutical composition comprising substantially pure base compound or pharmaceutically acceptable salt thereof may be administered to the subject concurrently or simultaneously by the same mode of administration or by a different mode of administration.

In an embodiment, the NMDAR antagonist is (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof, which are described in US patent No. 11,344,510, WO 2022/272174, and co-pending application having USSN 63/599,280 (SSMP DOCKET 42446), entitled **METHODS OF TREATING PSYCHIATRIC DISORDERS OR PAIN USING (R)-2-(4-FLUOROPHENYL)-2-(METHYLAMINO)CYCLOHEXAN-1-ONE OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF**, the contents of all of which are incorporated herein by reference. In an embodiment, the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is administered concurrently or simultaneously with (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof via IM or IV or PO. This could be given as two separate administrations or as a combination product by mixing both together and administering both together in the same pharmaceutical composition for treating mood disorders or pain. In an embodiment, the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof is administered concurrently or simultaneously with (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof, with the latter being administered at a dose relative to the free base form of (*R*)-2-(4-

fluorophenyl)-2-(methylamino)cyclohexan-1-one of about 40 mg to about 360 mg PO or about 13 mg to about 120 mg IV or about 20 mg to about 180 mg IM, within about 3 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In an embodiment, the dose of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or pharmaceutically acceptable salt thereof is about 60 mg to about 220 mg PO or about 20 mg to about 73 mg IV or about 30 mg to about 110 mg IM. In a further embodiment, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is administered within about 1 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In an embodiment, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is administered at about the same time as the administration of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In a further embodiment, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one and the substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof are administered together as a single IV or IM injection. In an embodiment, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IV concurrently or simultaneously with the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. For example, both are administered by IV concurrently. In an embodiment, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IV over a period of about 15 minutes or less. In another embodiment, in the concurrent or simultaneous administration with the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IM. In a further embodiment, in the concurrent or simultaneous administration with the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered PO.

In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof. In an embodiment, the solution has a pH of about 2 to about 11, and in another embodiment, the solution has a pH of about 5 to about 8. In another embodiment, the sterile solution comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof additionally comprises buffering agents to maintain the pH in the aforesaid ranges. In an embodiment, the buffering agent is a phosphate buffer. In a further embodiment, the concentration of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine in the sterile solution relative to the base compound is about 10 mg to about 80 mg per milliliter. In another embodiment the concentration of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is about 10 mg to about 40 mg per milliliter. In another embodiment, the osmolality of the aforesaid solution ranges from about 250 mOsm/kg to about 325 mOsm/kg.

In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof and substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof. In an embodiment, the solution has a pH of about 2 to about 11, and in another embodiment, the solution has a pH of about 5 to about 8. In another embodiment, the sterile solution comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof and substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof additionally comprises buffering agents to maintain the pH in the aforesaid ranges. In an embodiment, the buffering agent is a phosphate buffer. In another embodiment, the osmolality of the aforesaid solution ranges from about 250 mOsm/kg to about 325 mOsm/kg.

In an embodiment of any of the methods of pharmaceutical compositions disclosed herein, the *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is in the form of the hydrochloride salt or the fumarate salt. In an embodiment of any of the methods of pharmaceutical compositions disclosed herein, the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one is in the form of the hydrochloride salt.

Without wishing to be bound, it is believed that the combination of an NMDAR antagonist, such as (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof, and the 5-HT_{2A} receptor agonist *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof induces an intense psychedelic experience in a subject through two mechanisms, NMDAR antagonism and 5-HT_{2A} receptor agonism, which is distinct from the experience of either drug alone and is more therapeutic for treating depression and other mood disorders. Further, the combination is believed to act synergistically, i.e., synergistic neuroplasticity mechanisms downstream of both receptor targets that drive efficacy and support a durable response. Moreover, since 5-HT_{2A} receptor agonism blocks the neurotoxic effects of NMDAR antagonists, so co-administering these drugs is believed to be neuroprotective with respect to the NMDAR antagonist component.

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.

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

EXAMPLES

EXAMPLE 1. Human Pharmacokinetic Results

The following example describes a double-blind, placebo-controlled human study to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of single doses of base compound administered intravenously as a 10-minute infusion. The study was conducted on human subjects ranging in age from 19 to 53 years with a mean age of 25.1 years, a mean body mass of 71.1 kg, and a mean body mass index (BMI) of 22.6 kg/m², ranging from 19 to 29 kg/m². There were a total of 49 subjects tested, 18 of which were female and 44 of which were white, and 1 of which in the placebo group had a dosing error and was replaced with an alternative subject. 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 IV dose of base compound at the following dose levels: 0.34 mg, 1 mg, 3.33 mg, 10 mg, 15 mg, or 20 mg. The doses indicated are relative to the free base compound and corrected for salt counterion mass.

A cohort of 12 subjects were added separately as a second part to the Phase 1 study wherein 9 subjects received a 10 mg dose of the base compound and 3 subjects placebo as an *IM* formulation. Aside from dosing route, procedures and assessments were the same as those conducted for the 6 *IV* cohorts described above.

The subjects in the *IM* cohort ranged in age from 18 to 55 years with a mean age of 24.9 years, a mean body mass of 73.4 kg, and a mean BMI of 22.8 kg/m², ranging from 19.6-26.5 kg/m². There were a total number of 12 subjects tested, 5 of which were female and 7 male. All 12 subjects were white.

Blood was drawn from each subject at multiple time points post dose, processed to plasma by standard methods, and analyzed for base compound using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The values of area under the plasma concentration versus time curve from time 0 to 24 hours post dose (AUC₀₋₂₄) 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} (Hours)	Median t _{max} (Hours)
0.34	6	--	--	--	--	--	--	--	--
1	6	1.21	70.4	2.74	1.49	50.3	2.63	--	0.33
3.3	6	6.59	42.1	10	5.46	29.4	7.10	0.87	0.33
10	6	22.4	40.8	38.8	22.03	49.8	41.8	0.75	0.25
15	6	44.6	61.7	70.9	44.42	42.6	68.2	0.65	0.17
20	6	56.8	16.2	68	43.82	20.5	60.7	0.79	0.33
10 (<i>IM</i>)	9	25.97	37.8	44	19.92	46	40.6	0.74	0.47

Abbreviations: AUC₀₋₂₄=area under the curve from time 0 to 24 hours; C_{max}=maximum plasma concentration;

ICV%=coefficient of variation; t_{1/2}=half-life; t_{max}=time of maximum plasma concentration; *IM*=intramuscular route of administration

As shown in Table 1, mean C_{max} in the two highest dose groups was about 44 ng/mL, while t_{1/2} was about 0.7 to about 0.9 h across dose groups, indicating a short duration of action.

Regarding safety, there were no deaths or serious treatment emergent adverse events (TEAE) in any of the groups. A dose-dependent increase in TEAEs occurred.

EXAMPLE 2. 5-Dimensional Altered States of Consciousness Scale

The 5-Dimensional Altered States of Consciousness Scale (5D-ASC) is a validated measure for quantifying the intensity and nature of the subjective effects on thought and perception induced by psychedelic drugs such as 5-HT_{2A} receptor agonists. It is a subject-rated outcome measure that consists of 94 questions where the subject rates his/her experience retrospectively after the psychedelic experience has completely subsided by responding to questions/prompts such as “I felt elated”. The questions are answered by a marking on a 100 mm visual analogue scale with two anchors of “No, not more than usually” on one end and “Yes, much more than usually” on the other end. Factor analyses have identified five main dimensions in this scale: (1) oceanic boundlessness, (2) anxious ego dissolution, (3) visionary restructuralization, (4) auditory alterations, and (5) reduction of vigilance. In the Phase 1 clinical trial described in Example 1, the 5D-ASC was recorded in all subjects administered the base compound by the *IV* route according to the following methods, with the results summarized in Figure 1. For the 10 mg *IM* cohort, results from the 5D-ASC are summarized in Figure 12, where they are also compared directly to the results from the 10 mg *IV*-dosed cohort

Methods. All healthy male and female subjects entering this trial were required to provide a self-report of at least one prior hallucinatory drug experience that included a meaningful altered state of consciousness in the last 5 years with a range of potential drugs, such as psilocybin, LSD, DMT, ayahuasca, mescaline, ibogaine, and/or ketamine. The subjects filled out the 5D-ASC approximately 4 hours after administration of the base compound, when all psychedelic effects had subsided. Scores were determined for each of the individual main five dimensions of the 5D-ASC, as well as the total score, as described above.

Results. Base compound generally induced dose-related increases in the 5D-ASC (Figure 1) as quantified by percent score maxima for both total score and the subdimensions. The effects of the lowest 2 doses (0.34 and 1.0 mg) were similar to the effects of placebo for the anxious ego dissolution, auditory alterations, oceanic boundlessness, reductions of vigilance, and visionary restructuralization dimensions. The 3.3 mg dose induced a modest increase in effect compared to placebo but did not produce a full psychedelic experience. In contrast, the effects of the 10, 15, and 20 mg doses were substantial, with scores of each dimension for these top 3 doses generally at least 2-fold greater than those for the 3.3 mg dose. The effects of the 15 and 20 mg doses appear to be similar to historical values for 30 mg psilocybin or 100 to 200 µg lysergic acid diethylamide (LSD; (Holze *et al.*, *Neuropsychopharmacology*, 47(6), 1180-1187 (2022)), which

are widely regarded as fully psychedelic doses of these compounds. However, the top dose of 20 mg tended to produce increased anxiety in subjects, as suggested by the increase in the anxious ego dissolution dimension of the 5D-ASC, and thus, may be less preferred in a therapeutic context compared to the 10 and 15 mg doses.

EXAMPLE 3. Mystical Experience Questionnaire-30

The Mystical Experience Questionnaire-30 (MEQ-30) is a validated subject-rated outcome measure for quantifying the intensity and nature of the subjective effects on thought and perception induced by psychedelic drugs such as 5-HT_{2A} receptor agonists. This scale consists of 30 questions/prompts, such as experience of oneness in relation to an “inner world”, in response to which the subject rates the intensity of their experience on a scale of 0 to 5 as follows: 0 – none; not at all; 1 – so slight cannot decide; 2 – slight; 3 – moderate; 4 – strong (equivalent in degree to any other strong experience); 5 – extreme (more than any other time in my life and stronger than 4). A factor analysis has identified sub-factors of (1) Mystical, (2) Positive Mood, (3) Transcendence of Time and Space, (4) Ineffability that can be scored individually in addition to the MEQ-30 Total Score. In the Phase 1 clinical trial described in Example 1, the MEQ-30 was recorded in all subjects in the 6 cohorts where the base compound was administered by the IV route, according to the following methods, with the results summarized in Figure 2. For the 10 mg *IM* cohort, results from MEQ are summarized in Figure 13, where they are also compared directly to the results from the 10 mg *IV*-dosed cohort

Methods. As described above, all healthy male and female subjects entering this trial were required to provide a self-report of at least one prior hallucinatory drug experience that included a meaningful altered state of consciousness in the last 5 years with a range of potential drugs, such as LSD, DMT, ayahuasca, mescaline, ibogaine, and/or ketamine. The subjects filled out the MEQ-30 about 4 hours after administration of the base compound when all psychedelic experiences had subsided. Scores were determined for each of the individual four main sub-factors of the MEQ-30, as well as the Total Score, as described above.

Results. Base compound generally induced dose-related increases in the MEQ-30 Total Score and especially the MEQ-30 Transcendence of Time and Space Score (Figure 2). The effects of the lowest dose (0.34 mg) were similar to the effects of placebo on all scores. The 1.0 and 3.3 mg doses induced a modest increase in effect compared to placebo but did not produce a

full psychedelic experience. In contrast, the effects of the 10, 15, and 20 mg doses were substantial, with scores of each sub-factor for these top 3 doses generally much greater than those for the 3.3 mg dose. The effects of the 15 and 20 mg doses on the MEQ-30 sub-factors appear to be similar to historical values for 30 mg psilocybin or 100 to 200 µg lysergic acid diethylamide (LSD) (Holze *et al.*, Neuropsychopharmacology, 47(6), 1180-1187 (2022)), which are widely regarded as fully psychedelic doses of these compounds.

EXAMPLE 4. Drug Effects Questionnaire

The Drug Effects Questionnaire (DEQ) is a validated, subject rated outcome measure for quantifying the intensity and nature of the subjective effects induced by psychoactive drugs. It is a simple and rapid assessment, allowing repeated administration during the acute phase of a drug's effects and therefore, it is useful for assessing the time course of those effects. The DEQ consists of five questions, where the subject quantifies their answers on a 100 mm visual analogue scale. The five questions are: (1) do you feel a drug effect right now?; (2) do you dislike any of the effects you are feeling right now?; (3) are you high right now?; (4) do you like any of the effects you are feeling right now?; and (5) would you like more of the drug you took right now? In the Phase 1 clinical trial described in Example 1, DEQ scores were recorded in all subjects at multiple time points according to the following methods, with the results of the question "do you feel a drug effect right now?" summarized in Figure 3 for the 6 cohorts dosed by the *IV* route. Data are not shown for the *IM* cohort.

Methods. As described above, all healthy male and female subjects entering this trial were required to provide a self-report of at least one prior hallucinatory drug experience that included a meaningful altered state of consciousness in the last 5 years with a range of potential drugs such as LSD, DMT, ayahuasca, mescaline, ibogaine, and/or ketamine. The subjects recorded their answers to the DEQ questions (not at all = 0 mm all the way up to very much so = 100 mm) at 0.33, 0.67, 1, 2, 4, 8, and 24 h after receiving the base compound.

Results. Base compound generally induced dose-related and time-dependent increases on the DEQ question "do you feel a drug effect right now?" (Figure 3). The effects of the lowest dose (0.34 mg) were similar to the effects of placebo for almost all time points, including the 0.33, 0.67, and 1 h time points. The 1.0 and 3.3 mg doses induced a modest increase in effect to about 50-60 mm at the 0.33 h time point and returned to baseline within approximately 2 h.

Importantly, the DEQ score at these intermediate doses was substantially stronger than in the 5D-ASC and MEQ-30 relative to the scores produced by the higher doses in each measure, suggesting that these intermediate doses are detectable as psychoactive by subjects, as quantified by the DEQ, but do not produce the full psychedelic effect necessary to substantially increase scores on the 5D-ASC or MEQ-30. The 10-20 mg doses resulted in >75 mm responses at the early time points, consistent with the strong effects of these doses on the 5D-ASC and MEQ-30 and the rapid rise of plasma concentrations to $C_{\max}$ following the 10-minute IV infusion used in this trial. The peak effects of 10-20 mg doses dropped rapidly, consistent with the short plasma half-life of the base compound (see Example 1), and were below the maximal effect of the lower doses of 1 and 3.3 mg by the 2 h time point, suggesting that the main psychedelic effects had resolved by this time point.

EXAMPLE 5. Human EEG

Resting-state electroencephalography (EEG) is very sensitive to central actions of pharmacologically active 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 utilizes 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 of the eyes closed recordings 20 minutes after administration of base compound summarized in Figure 4.

Methods. For the resting-state EEG setup, 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 the AFz EEG location. All signals were sampled at a sampling rate of 1024 Hz and were filtered prior to storage using a first order recursive high-pass filter with a cut-off frequency at 0.1 Hz. 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 eyeblinks. Each

recording employed alternating periods with eyes opened and closed with a duration of 64-seconds per period. This was 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. A 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-referenced 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 a 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 of 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. EEG data was collected at the following time points relative to administration of base compound: -2 h, -1 h, +20 min, +1 h, +1.5 h, +3 h, +4.5 h, +6 h.

Results. The EEG results at different dose levels of base compound in the eyes closed state 20 minutes after drug administration (near C_{max}) are presented in Figure 4. The base compound induced dose-dependent effects across several frequency bands, with the most prominent effects seen in the theta (4-8 Hz) and alpha (8-13) EEG bands, where EEG power was attenuated starting at 1 mg dose. Additional effects were observed in gamma bands, especially the fast gamma (65-95 Hz) EEG band, where EEG power was increased starting at the 10 mg

dose. The results suggest that psychoactive effects can be observed at doses (e.g., 1 and 3.3 mg) below those required to induce a full psychedelic experience (e.g., 10 mg and up).

Additional examples are provided to support the efficacy of the compounds of the present disclosure for treating psychiatric diseases.

EXAMPLE 6. Rat Head Twitch Response

Background. When rats are administered 5-HT_{2A} receptor agonist compounds they perform very distinctive behaviors. The first is referred to as a ‘wet dog shake’ (WDS), where the rat’s body spontaneously oscillates rapidly. The second is a head twitch response (HTR), where the rat will perform a spontaneous, rapid, side-to-side rotational movement of its head. The potency of a compound to produce these behaviors in rodents has been shown to predict the hallucinogenic potency of compounds in humans, as described in the article by Halberstadt et al. Neuropharmacology, 167, 107933 (2020).

Animals. Male Sprague-Dawley rats ~8 weeks of age (~250 g) were used in the experiments. Animals were housed in groups of 2 under controlled temperature (22 ± 3 °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 salts of the base compound and the positive control 2,5-dimethoxy-4-propylamphetamine (DOPR), in a saline vehicle, were administered subcutaneously (SC), with doses calculated based on the free base of each compound. All compounds were administered at a volume of 5 mL/kg. Treatment groups were balanced for body weight. Test compounds or vehicle were administered immediately prior to beginning observation of behaviors.

Head Twitch/Wet Dog Shakes (HTR/WDS). Rats (n=6/group) were dosed with base compound (0.032-10 mg/kg, SC), DOPR (0.32 mg/kg, SC), or vehicle (saline). Immediately after dosing, rats were placed (one at a time) in an open field observation box (40 cm x 20 cm x 36 cm), and observed manually to count the number of head twitch responses (HTR) and wet dog shakes (WDS) for 20 min.

Statistical Analysis. Data are presented as the mean $\pm$ standard error of the mean (SEM). Non-linear curve fitting to determine ED₅₀ doses was performed using GraphPad Prism 9 or 10.

Results. The positive control DOPR induced increases in HTR and WDS (8.5 counts/20 min). Base compound (0.032 - 10 mg/kg, SC) produced robust dose-dependent increases in both HTR and WDS with a peak effect of 7.7 counts/20 min at the 1 mg/kg dose (Figure 5). The ED₅₀ values for base compound to induce behavioral effects were as follows: HTR = 0.43 mg/kg, WDS = 0.02 mg/kg and the combination of HTR + WDS = 0.07 mg/kg. The C_{max} plasma exposure of base compound associated with peak HTR (1 mg/kg) was 41.3 ng/mL based on results of rat PK assessment in a separate study. This plasma exposure was similar to the C_{max} in plasma in human subjects administered base compound at doses of 15 and 20 mg IV, which induced intense psychedelic effects.

EXAMPLE 7. Rat 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 ± 3°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 the base compound, in a saline vehicle, and the positive control desipramine were administered subcutaneously (SC), with doses calculated based on the free base of each compound. All compounds were administered at a volume of 5 mL/kg. Test compounds or 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 ± 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.

Results. The results are depicted in Figure 6. It shows the effect of acute administration of base compound (0.1-3.2 mg/kg, SC) on immobility time in naive rats tested in the FST 24 h after dosing ($n \geq 10$ /group). A one-way ANOVA revealed a significant main effect of treatment ($(F_{5,54})=14.09$, $p < 0.0001$). Asterisks indicate a significant difference from the vehicle treated group using Dunnett's post-hoc test. The active comparator, desipramine (20 mg/kg, SC), 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. Base compound dosed at 1 ($p=0.0089$) and 3.2 mg/kg ($p < 0.0001$) produced significant reductions in immobility time. The minimum efficacious dose was 1 mg/kg, which in a separate PK study in rats produced a $C_{\max}$ exposure of 41.3 ng/mL. Accordingly, the results suggest that human doses that achieve similar plasma exposure at $C_{\max}$ (i.e., about 40 ng/mL or greater) will possess antidepressant effects.

EXAMPLE 8. Rat Chronic Mild Stress (CMS)

Animals. Male Wistar Kyoto rats (Charles River, Sulzfeld, Germany) were brought into the laboratory at the age of 5 weeks (around 100 g) approximately one month before the start of the experiment. Except for the first 10 days after arrival, when the animals were housed in groups of 10, they were singly housed with food and water freely available and maintained on a 12-h light/dark cycle in a constant temperature (22 ± 2 °C) and humidity ($45 \pm 5\%$) conditions. All procedures used in this study conformed to the rules and principles of the 86/609/EEC Directive and were approved by the Local Bioethical Committee at the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.

Procedure. A CMS study was carried out 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 of which relating to the procedures for conducting this protocol being incorporated by reference. Figure 7A depicts an overview of the experimental schedule for CMS studies. Short arrows (with ☉) represent weekly sucrose drinking tests (Tuesdays). Long arrows (with 📌) show when animals received weekly drug treatments (Mondays). The black arrow labelled with EPM shows the timing for the EPM (Wednesday), and the grey arrow labelled with NOR shows the timing for the NOR test (Thursday). For each treatment group n=8 rats were exposed to CMS stressors, and n=8 rats were unstressed controls.

Drugs and Drug Administration. The hydrochloride salt of the base compound, and its saline vehicle, were administered subcutaneously (SC), and the active comparator, ketamine (also dissolved in saline) was administered by the intraperitoneal route (IP) with doses calculated based on the free base of each compound. All compounds were administered at a volume of 2 mL/kg.

Statistical analysis. All sucrose intake data were analyzed by ANOVA, with post-hoc multiple comparisons tests using GraphPad Prism. EPM and NOR data were analyzed by 2-way ANOVA with Šidák's multiple comparisons tests to compare Stress and Control for each treatment.

Results. Figure 7B shows the effect of base compound (0.3 or 1 mg/kg, SC) and (*rac*)-ketamine (10 mg/kg, IP) 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. 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 7B). In the first week of base compound testing (week 3 of stress), administration of ketamine (10 mg/kg, IP) or base compound (0.3 or 1 mg/kg, SC) reversed the deficit in sucrose intake in stressed rats measured 24 h after dosing. In weeks 4-7, ketamine and base compound (0.3 or 1 mg/kg, SC) maintained the reversed the effects of CMS on sucrose intake. 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 7C shows the percent time spent in the open arms in the Elevated Plus Maze (EPM), which was conducted 48 h after the third weekly drug 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 ($F(3,56)=4.238$, $p=0.0091$), a significant main effect of Stress ($F(1,56)=10.95$, $p=0.0016$), and a trend towards a significant interaction ($F(3,56)=2.436$, $p=0.0742$). Post-hoc testing with Šídák's multiple comparisons test revealed significant differences between stressed and unstressed groups treated with vehicle ($p = 0.0004$) indicating an increase in anxiety due to exposure to CMS. In rats dosed with base compound at 0.3 or 1 mg/kg (SC) or ketamine (10 mg/kg IP), anxiety levels were not higher in stressed vs control rats, indicating that drug treatment had reduced CMS-induced anxiety.

Figure 7D shows the results from the Novel Object Recognition task (NOR). The NOR was conducted 72 h after the third weekly drug 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 Stress ($F(1,56)=10.47$, $p=0.0020$), but the effect of Treatment and the interaction did not reach significance. In rats dosed with base compound at 0.3 mg/kg, 1 mg/kg (SC) or ketamine (10 mg/kg, IP), recognition indices were not different in control vs stressed

rats, indicating that drug treatment had reduced CMS-induced impairment of recognition memory.

Administration of 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. At the lowest dose of base compound (0.3 mg/kg, SC) tested that was efficacious the peak plasma concentration is expected to be 12.4 ng/mL based on extrapolation from a separate rat PK study. Accordingly, the results suggest that human doses that achieve similar plasma exposure at $C_{\max}$ (i.e., about 12 ng/mL or greater) will possess antidepressant effects.

EXAMPLE 9. Rat EEG Studies

Animals. A cohort of 8 male Sprague-Dawley rats, aged 8-18 weeks, were used in the experiments. Prior to surgery rats 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. After surgery, rats were singly housed. All efforts were made to minimize suffering.

Procedure. The effects of base compound (0.32-3.2 mg/kg, SC, doses based on the free base) 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., (Kantor *et al.*, 2023), the contents of which related to the protocol are incorporated by reference.

Effects of base compound (0.32-3.2 mg/kg, SC) on the amplitude of cortical EEG oscillations were assessed for 30 min prior to and 180 min post-injection (Figure 8).

Results. Base compound produced a dose-dependent reduction in low frequency EEG power (Figure 8A), especially in the theta (5-12 Hz) EEG band. Compared to vehicle, the effects were significantly different for the 1 mg/kg group ($t(8) = -3.4$, $p = 0.01$) and 3.2 mg/kg group ($t(8) = -9.2$, $p = 3.7\text{e-}5$; Figure 8B). The effects lasted ~60 min in the 1 mg/kg group and ~120 min in the 3.2 mg/kg group (Figure 8A). The MED for decreasing low frequency power was 1

mg/kg, which, based on subcutaneous rat PK, was associated with a peak plasma concentration of 41.3 ng/mL.

EEG is a quantitative translational biomarker of target engagement. The reduction of low frequency activity with base compound demonstrates clear target engagement, consistent with 5-HT2A receptor activation. A dose of 1 mg/kg (SC), which was an efficacious in CMS, was sufficient to affect this biomarker of 5-HT2A receptor activation, which demonstrates that this dose of base compound results in significant engagement of 5-HT2A receptors *in vivo*.

EXAMPLE 10. Rat 5-HT2A Receptor Occupancy

Animals. Adult male Sprague-Dawley rats (250-300 g; Charles River) were used in the experiments. Rats were group-housed 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.

Procedure. Rats were pre-treated with base compound at doses of 1-10 mg/kg (SC, doses based on free base) or vehicle followed 10 min (for 1 & 3 mg/kg groups) or 30 min (vehicle and 10 mg/kg groups) later by intravenous administration of 13.3 ± 2 MBq of the radiolabeled 5-HT2A receptor agonist tracer [^{11}C]Cimbi-36. Thirty minutes post tracer injection, the frontal cortex, hippocampus and cerebellar lobules from one brain hemisphere were dissected, weighed, and counted for radioactivity by gamma counting. The remaining hemisphere was collected for bioanalysis of base compound exposure.

Results. Using the cerebellar lobules as a reference region, the pseudo non-displaceable binding potential in frontal cortex was calculated and plotted against drug concentration (Figure 9A). An ED_{50} value of 0.32 mg/kg was estimated for base compound (Figure 9B). Estimations of EC_{50} were modeled using PK plasma concentrations at appropriate time points resulting in a best modelled fit of the data estimating the EC_{50} to be 13.2 ng/mL.

EXAMPLE 11. Relationship Between Pharmacokinetics and Pharmacodynamics

Figure 10 provides an overview of the plasma concentrations of base compound associated with the pharmacodynamic effects of the drug in rats. Base compound plasma exposure of 13.2 ng/mL produced 50% occupancy of frontal cortex 5-HT2A receptors in rats. Published clinical data with psilocybin indicate that the dose (25 mg) which has been shown to

have antidepressant efficacy in patients with treatment-resistant depression and cause robust psychedelic effects achieves ~60-70% 5-HT_{2A} receptor occupancy (Madsen *et al.*, 2019; Goodwin *et al.*, 2022). These results are consistent with our findings showing that peak ‘psychedelic’ behavioral effects (HTR & WDS) in rats occur at a plasma exposure of 41.3 ng/mL, which achieves ~75% receptor occupancy in rats. Doses of 10-20 mg IV base compound, which achieved similar plasma exposures (22-44 ng/mL), were shown to cause robust psychedelic effects in healthy humans. In rats, plasma exposures achieving about 75% receptor occupancy produced signals of target engagement measured using EEG. The observation of robust effects on rat EEG at plasma concentrations ≥ 41.3 ng/mL was consistent with results in humans but suggests that human EEG is more sensitive for detecting changes in low frequency power, as in humans, significant dose-dependent reductions in alpha and theta power were observed at plasma concentrations ≥ 1.5 ng/mL. Finally, in rats, plasma exposures ≥ 12 ng/mL (which achieved ≥ 50 % 5-HT_{2A} receptor occupancy) produced antidepressant-like efficacy in CMS. These results, in combination with published results with psilocybin (mentioned above), suggest that base compound doses $\geq$ about 10 mg (IV) or those which achieve C_{max} exposures of $\geq$ about 12 ng/mL will have antidepressant efficacy in patients.

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.

Example 12. Real Time Intensity Scale

The Real Time Intensity Scale is a validated, subject-rated outcome measure for quantifying the intensity and nature of the experience induced by psychedelic drugs. It is a simple and rapid assessment, allowing repeated administration during the acute phase of a drug’s effects and therefore, it is useful for assessing the time course of those effects. The RTI requires subjects to verbally rate their experience in three dimensions: visual intensity, bodily intensity, and emotional intensity/metacognitive intensity, on a 0 to 10 scale, with 10 being the maximum possible effect. The real-time ratings provide the advantage of monitoring the effects of a psychedelic drug during the experience, as opposed to as a retrospective assessment, which is the

case with the 5D-ASC and MEQ. In the Phase 1 clinical trial described in Example 1, RTI scores were recorded in all subjects at multiple time points immediately following dosing.

Results from the RTI are shown in FIG. 15A-D for the 6 cohorts dosed by the *IV* route for the 3 subscales and total intensity for the RTI, and in FIG. 14A-D for the 9 subjects dosed with the 10 mg dose by the *IM* route, where data for 10 mg of the base compound by the *IV* route are also shown for comparison to illustrate the close correspondence in subjective intensity and time course elicited by the same dose given by both routes of administration.

Methods. As described above, all healthy male and female subjects dosed with placebo or the base compound by the *IV* or *IM* routes were asked at multiple timepoints following dosing to rate the intensity of their experience on each of the 3 subscales of the RTI.

Results. Base compound generally induced dose-related and time-dependent increases on all three subscales of the RTI. The effects of the lowest dose (0.34 mg) were similar to the effects of placebo for almost all time points, including the 0.33, 0.67, and 1 h time points near T_{max} . The 1.0 and 3.3 mg doses induced modest increases in effect across all subscales. The 10, 15, and 20 mg doses induced strong increases in all subscales. For all doses and both the *IV* and *IM* routes, psychedelic effects resolved within approximately 2 h.

WHAT IS CLAIMED IS:

1. A method of treating a mood disorder in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose administered is in an amount relative to the base compound ranging from about 8 mg to about 16 mg IV or inhaled or about 8 mg to about 24 mg IM, wherein the optional second dose administered is in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, wherein the optional successive periodic doses are administered each time in an amount relative to the base compound ranging from about 10 mg to about 20 mg IV or inhaled or about 10 mg to about 30 mg IM, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.
2. The method of claim 1 wherein the first dose is administered to the subject in an amount ranging from about 10 mg to about 12 mg IV or inhaled or about 10 mg to about 15 mg IM.
3. The method of claim 1 wherein the first dose is administered to the subject in an amount ranging from about 14 mg to about 16 mg IV or inhaled or about 14 mg to about 24 mg IM.
4. The method of any one of claims 1-3 wherein the optional second dose is administered to the subject and is in an amount ranging from about 10 mg to about 12 mg IV or inhaled or about 10 mg to about 15 mg IM.

5. The method of any one of claims 1-3 wherein the optional second dose is administered to the subject and is in an amount ranging from about 14 mg to about 16 mg IV or inhaled or about 14 mg to about 24 mg IM.
6. The method of any one of claims 1-5 wherein the second dose is administered to the subject within about 3 weeks of the first dose.
7. The method of any one of claims 1-5 wherein the second dose is administered to the subject within about 2 weeks of the first dose.
8. The method of any one of claims 1-5 wherein the second dose is administered to the subject three to seven days after the first dose.
9. The method of any one of claims 1-8 wherein the optional successive periodic doses during the acute induction phase of treatment are administered to the subject and are in an amount ranging from about 10 mg to about 16 mg IV or inhaled or about 10 mg to about 24 mg IM.
10. The method of any one of claims 1-9 wherein the optional successive periodic doses of the acute induction phase of treatment are administered to the subject and occur at intervals ranging from about every two weeks to every two months commencing after the administration of the second dose to the subject.
11. The method of any one of claims 1-3 wherein only the first dose is administered.
12. The method of any one of claims 1-8 wherein only the first and second doses are administered.
13. The method of any one of claims 1-12 wherein the acute induction phase of treatment lasts for a period of about six months from the administration of the first dose.
14. The method of any one of claims 1-12 wherein the acute induction phase of treatment lasts for a period of about six weeks from the administration of the first dose.
15. The method of any one of claims 1-14 additionally comprising administration of additional pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor to the subject in periodic successive doses in an amount relative to the base compound ranging from about 3 mg to about 20 mg IV or inhaled or about 3 mg to about 30 mg IM during a maintenance phase of treatment.

16. The method of claim 15 wherein doses are administered to the subject at intervals ranging from about every two weeks to about every six months during the maintenance phase of treatment in an amount ranging from about 10 mg to about 16 mg IV or inhaled or about 10 mg to about 24 mg IM.
17. The method of claim 15 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount ranging from about 3 mg to about 10 mg IV or inhaled or about 3 mg to about 15 mg IM.
18. The method of claim 15 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount ranging from about 3 mg to about 7 mg IV or inhaled or about 3 mg to about 10 mg IM.
19. The method of any one of claims 1-18 wherein all doses are administered IV.
20. The method of any one of claims 1-19 wherein each IV dose is administered to the subject in about 15 minutes or less.
21. The method of any one of claims 1-18 wherein all doses are administered to the subject by inhalation.
22. The method of any one of claims 1-18 wherein all doses are administered to the subject IM.
23. A method of treating a mood disorder in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in remission or substantially improved, wherein the first dose is administered in an amount effective to achieve subsequent to its administration a first $C_{\max}$ of base compound in plasma of the subject ranging from about 16 ng/mL to about 44 ng/mL, wherein the optional second dose is administered in an amount effective to achieve subsequent to its

administration a second $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL, wherein the optional successive periodic doses are administered in an amount effective to achieve subsequent to each administration a $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.

24. The method of claim 23 wherein the first $C_{\max}$ ranges from about 18 ng/mL to about 26 ng/mL.
25. The method of claim 23 wherein the first $C_{\max}$ ranges from about 30 ng/mL to about 44 ng/mL.
26. The method of any one of claims 23-25 wherein the optional second dose is administered to the subject and the second $C_{\max}$ ranges from about 18 ng/mL to about 26 ng/mL.
27. The method of any one of claims 23-25 wherein the optional second dose is administered to the subject and the second $C_{\max}$ ranges from about 30 ng/mL to about 44 ng/mL.
28. The method of any one of claims 23-27 wherein the second dose is administered to the subject within about three weeks of the first dose.
29. The method of any one of claims 23-27 wherein the second dose is administered to the subject within about two weeks of the first dose.
30. The method of any one of claims 23-27 wherein the second dose is administered to the subject three to seven days after the first dose.
31. The method of any one of claims 23-30 wherein the optional successive periodic doses during the acute induction phase of treatment are administered to the subject and are in an amount effective to achieve subsequent to each administration a $C_{\max}$ ranging from about 18 ng/mL to about 44 ng/mL.
32. The method of any one of claims 23-31 wherein the optional successive periodic doses of the acute induction phase of treatment are administered to the subject and occur at intervals ranging from about every two weeks to every two months commencing after the administration of the second dose to the subject.
33. The method of any one of claims 23-25 wherein only the first dose is administered.
34. The method of any one of claims 23-30 wherein only the first and second doses are administered.

35. The method of any one of claims 23-34 wherein the acute induction phase of treatment lasts for a period of about six months from the administration of the first dose.
36. The method of any one of claims 23-34 wherein the acute induction phase of treatment lasts for a period of about six weeks from the administration of the first dose.
37. The method of any of claims 23-36 additionally comprising administration of additional pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor to the subject in periodic successive doses in an amount effective to achieve subsequent to each administration a $C_{\max}$ of base compound in plasma of the subject ranging from about 5 ng/mL to about 44 ng/mL during a maintenance phase of treatment.
38. The method of claim 37 wherein doses are administered to the subject at intervals ranging from about every two weeks to about every six months during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration a $C_{\max}$ of base compound in plasma of the subject ranging from about 18 ng/mL to about 44 ng/mL.
39. The method of claim 37 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration a $C_{\max}$ in plasma of the subject ranging from about 5 ng/mL to about 22 ng/mL.
40. The method of claim 37 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration a $C_{\max}$ in plasma of the subject ranging from about 5 ng/mL to about 16 ng/mL.
41. A method of treating a mood disorder in a subject in need of such treatment comprising administering to the subject a pharmaceutical composition comprising a base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in a dosing regimen commencing with a first dose and an optional second dose and continuing with optional successive periodic doses of the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor in an acute induction phase of treatment that concludes when neuropsychiatric symptoms from the mood disorder are in

remission or substantially improved, wherein the first dose is administered in an amount effective to achieve subsequent to its administration a first area under the curve of base compound concentration in the plasma versus time of the subject (AUC) ranging from about 18 h·ng/mL to about 48 h·ng/mL, wherein the optional second dose is administered in an amount effective to achieve subsequent to its administration a second AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL, wherein the optional successive periodic doses are administered in an amount sufficient to achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 60 h·ng/mL, and wherein the base compound is substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine.

42. The method of claim 29 wherein the first AUC ranges from about 20 h·ng/mL to about 27 h·ng/mL.
43. The method of claim 29 wherein the first AUC ranges from about 40 h·ng/mL to about 51 h·ng/mL.
44. The method of any one of claims 41-43 wherein the optional second dose is administered to the subject and the second AUC ranges from about 20 h·ng/mL to about 27 h·ng/mL.
45. The method of any one of claims 41-43 wherein the optional second dose is administered to the subject and the second AUC ranges from about 40 h·ng/mL to about 51 h·ng/mL.
46. The method of any one of claims 41-45 wherein the second dose is administered to the subject within about three weeks of the first dose.
47. The method of any one of claims 41-45 wherein the second dose is administered to the subject within about two weeks of the first dose.
48. The method of any one of claims 41-45 wherein the second dose is administered to the subject three to seven days after the first dose.
49. The method of any one of claims 41-48 wherein the optional successive periodic doses during the acute induction phase of treatment are administered to the subject and are in an amount effective to achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 51 h·ng/mL.
50. The method of any one of claims 41-49 wherein the optional successive periodic doses of the acute induction phase of treatment are administered to the subject and occur at

intervals ranging from about every two weeks to every two months commencing after the administration of the second dose to the subject.

51. The method of any one of claims 41-43 wherein only the first dose is administered.
52. The method of any one of claims 41-48 wherein only the first and second doses are administered.
53. The method of any one of claims 41-52 wherein the acute induction phase of treatment lasts for a period of about six months from the administration of the first dose.
54. The method of any one of claims 41-52 wherein the acute induction phase of treatment lasts for a period of about six weeks from the administration of the first dose.
55. The method of any one of claims 41-54 additionally comprising administration of additional pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor to the subject in periodic successive doses in an amount sufficient to achieve subsequent to each administration an AUC of base compound in plasma of the subject ranging from about 5 h·ng/mL to about 60 h·ng/mL during a maintenance phase of treatment.
56. The method of claim 55 wherein doses are administered to the subject at intervals of about every two weeks to about every six months during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC ranging from about 20 h·ng/mL to about 51 h·ng/mL.
57. The method of claim 55 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC of base compound ranging from about 5 h·ng/mL to about 22 h·ng/mL.
58. The method of claim 55 wherein doses are administered to the subject at intervals ranging from about twice per week to about every two weeks during the maintenance phase of treatment in an amount effective to achieve subsequent to each administration an AUC of base compound ranging from about 5 h·ng/mL to about 16 h·ng/mL.
59. The method of any one of claims 23-58 wherein the pharmaceutical composition is administered intravenously, intramuscularly, by inhalation, intranasally, subcutaneously, or orally.

60. The method of claim 59 wherein the pharmaceutical composition is administered intravenously, intramuscularly, or by inhalation.
61. The method of claim 59 wherein the pharmaceutical composition is administered intravenously.
62. The method of claim 59 wherein the pharmaceutical composition is administered intramuscularly.
63. The method of any one of claims 1-62 additionally comprising administration to the subject of substantially pure (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof in an amount relative to the free base form of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one of about 40 mg to about 360 mg PO or about 13 mg to about 120 mg IV or about 20 mg to about 180 mg IM, within about 3 h of the administration to the subject of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
64. The method of claim 63 wherein the dose of (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is about 60 mg to about 220 mg PO or about 20 mg to about 73 mg IV or about 30 mg to about 110 mg IM.
65. The method of claim 63 or 64 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered within about 1 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
66. The method of any one of claims 63-65 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered at about the same time as the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
67. The method of any one of claims 63-66 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof and substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a

pharmaceutically acceptable salt thereof are administered together as a single IV or IM injection.

68. The method of any one of claims 63-67 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IV.
69. The method of any one of claims 63-68 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IV over a period of about 15 minutes or less.
70. The method of any one of claims 63-67 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered IM.
71. The method of any one of claims 63-66 wherein the (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof is administered PO.
72. The method of any one of claims 1-62 additionally comprising administration to the subject of racemic ketamine, S-ketamine, or R-ketamine or a pharmaceutically acceptable salt thereof in an amount relative to the free base form of racemic ketamine, S-ketamine, or R-ketamine of about 10 mg to about 100 mg IV, IM, or IN in the case of racemic ketamine and S-ketamine, or about 20 mg to about 200 mg IV, IM, or IN in the case of R-ketamine, within about 3 h of the administration to the subject of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
73. The method of claim 72 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered within about 1 h of the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
74. The method of claim 72 or 73 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered at about the same time as the administration of the pharmaceutical composition comprising substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.

75. The method of any one of claims 72-74 wherein the racemic ketamine, S-ketamine, or R-ketamine and the substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof are administered together as a single IV or IM injection.
76. The method of any one of claims 72-75 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered IV.
77. The method of any one of claims 72-76 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered IV over a period of about 15 minutes or less.
78. The method of any one of claims 72-76 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered IV over a period of about 60 minutes or less.
79. The method of any one of claims 72-75 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered IM.
80. The method of any one of claims 72-74 wherein the racemic ketamine, S-ketamine, or R-ketamine is administered IN.
81. The method of any one of claims 72-74 wherein S-ketamine is administered IN at a dose of about 56 mg to about 84 mg.
82. The method of any one of claims 1-81 wherein the mood disorder is major depressive disorder, treatment-resistant major depressive disorder, persistent depressive disorder, dysthymic disorder, adjustment disorder with depressed mood, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, a substance-related disorder, a substance-use disorder, an anxiety disorder, an obsessive-compulsive and related disorder, a trauma- and stressor-related disorder including post-traumatic stress disorder, a feeding and eating disorder, borderline personality disorder, attention-deficit/hyperactivity disorder, or an autism spectrum disorder.
83. The method of claim 82 wherein the mood disorder is major depressive disorder or treatment-resistant major depressive disorder.

84. The method of claim 82 wherein the mood disorder is an anxiety disorder selected from the group consisting of generalized anxiety disorder, panic disorder, and social anxiety disorder.
85. The method of claim 82 wherein the mood disorder is a substance use disorder selected from the group consisting of alcohol use disorder, opioid use disorder, amphetamine/methamphetamine use disorder, cocaine use disorder, tobacco/nicotine use disorder, and cannabinoid use disorder.
86. The method of any one of claims 1-85 wherein an antidepressant is administered concurrently with the pharmaceutical composition comprising the base compound or a pharmaceutically acceptable salt thereof during the acute induction phase of treatment or during the maintenance treatment phase or during both the acute induction phase of treatment and the maintenance treatment phase.
87. The method of claim 86 wherein the antidepressant blocks the serotonin transporter.
88. The method of claim 86 or 87 wherein the antidepressant is a selective serotonin reuptake inhibitor.
89. The method of claim 88 wherein the selective serotonin reuptake inhibitor is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, or vortioxetine.
90. The method of claim 86 or 87 wherein the antidepressant is a serotonin-norepinephrine reuptake inhibitor.
91. The method of claim 90 wherein the serotonin-norepinephrine reuptake inhibitor is duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.
92. The method of claim 86 or 87 wherein the antidepressant is fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, vortioxetine, duloxetine, venlafaxine, desvenlafaxine, milnacipran, or levomilnacipran.
93. The method of any one of claims 1-92 wherein *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine hydrochloride is administered to the subject.
94. A pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof.
95. The pharmaceutical composition of claim 94 wherein the solution has a pH of about 2 to about 11.

96. The pharmaceutical composition of claim 95 wherein the solution has a pH of about 5 to about 8.
97. The pharmaceutical composition of any one of claims 94-96 further containing buffering agents to maintain the pH in a desired range.
98. The pharmaceutical composition of claim 97 wherein the buffering agent is a phosphate buffer.
99. The pharmaceutical composition of any of claims 94-98 wherein the concentration of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine in the solution relative to the base compound is about 10 mg to about 80 mg per milliliter.
100. The pharmaceutical composition of claim 99 wherein the concentration of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine is about 10 mg to about 40 mg per milliliter.
101. The pharmaceutical composition of any one of claims 94-100 wherein the osmolality of the solution ranges from about 250 mOsm/kg to about 325 mOsm/kg.
102. A pharmaceutical composition comprising a sterile solution of substantially pure *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine or a pharmaceutically acceptable salt thereof and (*R*)-2-(4-fluorophenyl)-2-(methylamino)cyclohexan-1-one or a pharmaceutically acceptable salt thereof.
103. The pharmaceutical composition of claim 102 wherein the solution has a pH of about 2 to about 11.
104. The pharmaceutical composition of claim 103 wherein the solution has a pH of about 5 to about 8.
105. The pharmaceutical composition of any one of claims 102-104 further containing buffering agents to maintain the pH in a desired range.
106. The pharmaceutical composition of claim 105 wherein the buffering agent is a phosphate buffer.
107. The pharmaceutical composition of any one of claims 102-106 wherein the osmolality of the solution ranges from about 250 mOsm/kg to about 325 mOsm/kg.