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(54) **Title:** TREATMENT OF PSYCHIATRIC OR NEUROLOGICAL DISORDERS BY PARENTERAL ADMINISTRATION OF A SINGLE, EFFECTIVE PARENTERAL DOSE OF A SHORT-ACTING PSYCHEDELIC AGENT

(57) **Abstract:** The invention relates to a dosage regimen, method for treating, delivery device or parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient. In particular, the invention relates to the administration of a psychedelic agent.

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TREATMENT OF PSYCHIATRIC OR NEUROLOGICAL DISORDERS BY PARENTERAL ADMINISTRATION OF A SINGLE, EFFECTIVE PARENTERAL DOSE OF A SHORT-ACTING PSYCHEDELIC AGENT

FIELD OF THE INVENTION

The invention relates to a dosage regimen, method for treating, delivery device, parenteral formulation or kit for use in the treatment of a psychiatric or neurological disorder in a patient. In particular, the invention relates to the administration of a psychedelic agent.

BACKGROUND OF THE INVENTION

Classical psychedelics have shown preclinical and clinical promise in treating psychiatric disorders (Carhart-Harris and Goodwin, *Neuropsychopharmacology* 42, 2105-2113 (2017)). In particular, psilocybin has demonstrated significant improvement in a range of depression and anxiety rating scales in randomised double-blind studies (Griffiths et al. *Journal of Psychopharmacology*, 30(12), 1181-1197 (2016)). Efficacy of psilocybin has been shown in depression (R. L. Carhart-Harris *et al.*, *Psychopharmacology*, 2018, 235, 399-408), end of life anxiety (R. R. Griffiths *et al.*, *J. Psychopharmacol.*, 2016, 30, 12, 1181-1197) and addiction (M. W. Johnson, A. Garcia-Romeu and R. R. Griffiths, *Am. J. Drug Alcohol Abuse*, 2017, 43, 1, 55-60), and is currently being investigated for several other mental health disorders that are rooted in psychologically destructive patterns of thought processing (Anorexia Nervosa: NCT# NCT04052568).

N,N-dimethyltryptamine (DMT) is also proposed to hold therapeutic value as a short-acting psychedelic. A review of research into the biosynthesis and metabolism of DMT in the brain and peripheral tissues, methods and results for DMT detection in body fluids and the brain is provided by S. A. Barker in *Front. Neurosci.*, 12, 536, 1-17 (2018). Barker et al. suggest that '*Further characterization of DMT cellular distribution, receptors and general biochemistry may lead to new targets for more effective pharmaceutical substances and interventions*'. D. Nutt et al. (Cell. 2020 Apr 2;181(1):24-28. doi: 10.1016/j.cell.2020.03.020) suggest a possible therapeutic role for DMT: '*It is theoretically possible, however, that a short trip, such as with i.v. DMT, might "shake-up" and "reset" abnormal patterns of brain activity and so could have some therapeutic benefit*.' Both Barker et al. and Nutt et al. conclude that further research is required into the role and function of DMT.

Sanches et al and Palhano-Fontes et al report that in studies of patients with recurrent major depressive disorder (MDD) or treatment-resistant depression (TRD), a single oral dose of ayahuasca, a natural psychedelic-containing plant brew was associated with improvements in depressive symptoms (Sanches RF, de Lima Osorio F, dos Santos RG, et al. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A SPECT study. J Clin Psychopharmacol 2016;36(1):77-81 and Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial.

Psychol Med 2019;49(4):655-663). N,N-dimethyltryptamine (DMT) is the principal psychedelic compound contained in ayahuasca.

Good et al. discuss the results of a phase 1 study to investigate the pharmacokinetics of N,N-dimethyltryptamine fumarate in healthy subjects (Good, M., Joel, Z., Benway, T. et al. Pharmacokinetics of N,N-dimethyltryptamine in Humans. Eur J Drug Metab Pharmacokinet 48, 311–327 (2023). https://doi.org/10.1007/s13318-023-00822-y). No patients with a psychiatric or neurological disorder were included in the study. D'Souza et al report an '*exploratory study of the dose-related safety, tolerability, and efficacy of dimethyltryptamine (DMT) in healthy volunteers and major depressive disorder*' (Neuropsychopharmacology (2022) 47:1854 – 1862). Seven patients with major depressive disorder received two doses of DMT hemifumarate (0.1 mg/kg, followed by 0.3 mg/kg) at least 48 hours apart. The participants were administered DMT by intravenous push over 30–60 seconds, i.e., a bolus injection.

Goodwin et al report a phase 2 trial of psilocybin in adults with treatment resistant depression (N. Engl. J. Med. (2022) 387:1637-1648). Patients received a single oral dose of psilocybin, along with psychological support, with the administration session stated to last 6 to 8 hours. A sustained response at 12 weeks was reported for 20% of patients who received a 25mg dose.

WO2022195489 discusses methods for the use of psychedelics, in which an initial bolus injection is administered, followed by the administration of a lower maintenance dose. WO2022031566 discusses the intravenous administration of DMT.

Timmermann et al. discuss the results of a clinical trial to investigate the effects of intravenous DMT in healthy participants (Translational Psychiatry (2023) 13:172, published online on 23 May 2023).

Cybin Inc. have completed the Phase 1 part of a Phase 1/2a clinical trial evaluating a deuterated psilocybin compound (CYB003) in healthy participants with and without major depressive disorder (ClinicalTrials.gov Identifier: NCT05385783). In February 2023, Cybin Inc. announced that following a single oral dose of CYB003, psychedelic effects were seen within ≈ 15 minutes and the average duration of peak effects lasted ≈ 2 hours, data based on an interim analysis of CYB003 in healthy volunteers (https://cybin.com/cyb003/).

In May 2023, Cybin Inc. announced that the company is evaluating the intravenous administration of a deuterated dimethyltryptamine compound (CYB004) in healthy volunteers. Part C of the Phase 1 CYB004-E trial is a crossover study design which will evaluate IV bolus + infusion regimens of CYB004 in up to two cohorts.

With the growing interest in the potential use of psychedelic agents in psychiatry, such as psilocybin and DMT, there is an increasing need for methods of administering these agents in a safe and tolerable manner.

SUMMARY OF THE INVENTION

As a first aspect, the invention provides a dosage regimen for administering a short-acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a second aspect, the invention provides a method for treating a psychiatric or neurological disorder in a patient, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a third aspect, the invention provides a delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a fourth aspect, the invention provides a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one

time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a fifth aspect, the invention provides a kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for administration, preferably parenteral administration, of the parenteral formulation indicating that said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a sixth aspect, the invention provides a parenteral formulation comprising a single, effective parenteral dose of a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of the single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As a seventh aspect, the invention provides a parenteral formulation comprising a single, effective parenteral dose of a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

As an eighth aspect, the invention provides a dosage regimen for administering a short-acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most

once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

As a ninth aspect, the invention provides a method for treating a psychiatric or neurological disorder in a patient, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

As a tenth aspect, the invention provides a delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

As an eleventh aspect, the invention provides a kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for administration, preferably parenteral administration, of the parenteral formulation indicating that said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

FIGURES

Figure 1: NCT04673383, Part B study design. Figure 1 shows the clinical trial design for NCT04673383, Part B.

Figure 2: Percentage of subjects with ≥ 50% reduction from Baseline. Figure 2 shows the percentage of subjects with ≥ 50% reduction in Montgomery-Asberg Depression Rating Scale

(MADRS) score compared with baseline assessment for Group A (active) and Group P (placebo) at week 1 and week 2 following administration.

Figure 3: Percentage of subjects with a MADRS score ≤10. Figure 3 shows the percentage of subjects with a MADRS score ≤ 10 for Group A (active) and Group P (placebo) at week 1 and week 2 following administration.

Figure 4: Mean MADRS Score. Figure 4 shows the mean MADRS score for Group A (active) and Group P (placebo) at week 1 and week 2 following administration.

Figure 5: Durable Reduction in Mean MADRS Scores. Figure 5 shows the durable reduction in the mean MADRS score for Group A (active) and Group P (placebo) at weeks 1, 2, 4 and 12 following administration.

Figure 6: ≥ 50% reduction from baseline. Figure 6 shows the percentage of subjects with ≥50% reduction in MADRS score compared with baseline assessment for Group PA (placebo, active) and Group AA (active, active) at weeks 1, 2, 4 and 12 following open label dose.

Figure 7: MADRS score ≤10. Figure 7 shows the percentage of subjects with a MADRS score of ≤10 score for Group PA (placebo, active) and Group AA (active, active) at weeks 1, 2, 4 and 12 following open label dose.

DEFINITIONS

Throughout this specification, one or more aspects of the invention may be combined with one or more features described in the specification to define distinct embodiments of the invention.

In the detailed description, reference is made to a number of terms, which are to be understood to have the meanings provided below, unless a context expressly indicates to the contrary.

The nomenclature used herein for the psychedelic agents for use in the invention is as commonly used in the field. The compounds described herein, may also be referred to by nomenclature in accordance with the rules of the International Union of Pure and Applied Chemistry (IUPAC) for chemical compounds, specifically the "IUPAC Compendium of Chemical Terminology (Gold Book)" (see A. D. Jenkins et al., Pure & Appl. Chem., 1996, 68, 2287-2311). For the avoidance of doubt, if a rule of the IUPAC organisation is contrary to a definition provided herein, the definition herein is to prevail.

N,N-dimethyltryptamine is also known by the IUPAC name 2-(1H-indol-3-yl)-N,N-dimethylethanamine.

5-Methoxy- N,N-dimethyltryptamine is also known by the IUPAC name 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine.

4-Acetoxy-N,N-dimethyltryptamine is also known by the IUPAC name [3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] acetate.

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Psilocybin is also known by the IUPAC name [3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate.

Psilocin is also known by the IUPAC name 3-[2-(dimethylamino)ethyl]-1*H*-indol-4-ol.

As used herein the term 'deuterated analogues' of the psychedelic agent means that one or more hydrogen atom(s) in the structure of the psychedelic agent is replaced with a deuterium atom, wherein a deuterium atom is a hydrogen atom with an additional neutron. Substitution with deuterium may be at one or more of the α and β positions, on the methyl groups, and on the indole ring, and in certain compounds at a substituent to the indole ring, e.g., the methoxy group of 5-methoxy-N,N-dimethyltryptamine. In some embodiments, deuteration may be at the methyl groups, and at the α, and optionally the β positions. Preferably, deuteration is at the α positions.

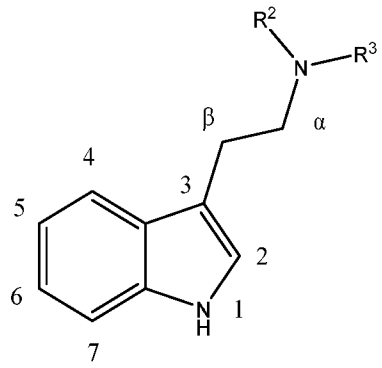
Where compounds described herein are indicated as being or described as deuterated analogues, the compound concerned is enriched beyond natural abundance with deuterium by an amount that is dependent on the percentage of deuterium available in the reagents from which the compounds are derived. For example, the d6-dimethylamino portions of compounds of formula I, wherein $–NR^2R^3$ is $–N(CD_3)_2$, may be derived from dimethyl-d7-amine, or dimethyl-d6-amine (commonly available as HCl salts), which are available from chemical vendors in purities of deuterium that range from 98% to 99%. The purity of deuterium in the resultant d6-dimethylamino substituents is consequently between 98% and 99%. This means, as the skilled person will understand, that not all compounds of formula I (for example) will comprise d6-dimethylamino substituents – some may comprise d0-d5dimethylamino, but the average purity of deuterium is about 98% to 99%.

In some embodiments, the psychedelic agent is substituted at position 5 with methoxy, or at position 4 with acetoxy or hydroxy, or with monohydrogen phosphate. The term "acetoxy" (often abbreviated to OAc) defines a univalent group derived from acetic acid by removal of a hydrogen atom from the OH moiety. The term "methoxy" (often abbreviated to OMe) defines a univalent group derived from methanol by removal of a hydrogen atom from the OH moiety. The term "hydroxy" (often abbreviated to OH) defines a univalent group derived from water by removal of a hydrogen atom from the H_2O moiety. The term monohydrogen phosphate defines a divalent group of formula HPO_4, derived from phosphoric acid by removal of a proton from two of the three OH moieties, and thus denotes a substituent of formula $-OP(O)(OH)O^-$.

When the dimethyltryptamine compound is substituted at position 4 with hydroxy, the psychedelic agent is referred to herein as psilocin. When the dimethyltryptamine compound is substituted at position 4 with monohydrogen phosphate, this is to reflect that psilocybin (also known as [3-(2-Dimethylaminoethyl)-1*H*-indol-4-yl] dihydrogen phosphate) in water generally has monohydrogen phosphate at the 4-position, this generally being understood to be the predominant form owing to the pKa values of the two terminal phosphate oxygen atoms being estimated as 1.3

and 6.5. It is further understood that the monohydrogen phosphate-containing form of psilocybin exists as a zwitterion (i.e., an internal salt) in which the nitrogen atom of the dimethylamino moiety is protonated. This form is thus, and psilocybin is to be regarded as, a salt of a dimethyltryptamine compound substituted at position 4 with monohydrogen phosphate.

For the avoidance of doubt, positions 4 and 5, and α and β, of the psychedelic agent refer to the positions labelled in the structure below (substitution not shown).



References herein to the dose or total dose of a psychedelic agent refer to the dose or total dose as the free base equivalent of that agent.

As used herein the term 'parenteral administration' or 'parenterally administering' means the administration of a dose of a psychedelic agent via any route other than oral, in one or more portions over the duration of the dosing period. The parenteral administration is preferably essentially continuous for a dosing period of from about 5 to about 15 minutes. In other embodiments, the parenteral administration may comprise an initial bolus administration of a psychedelic agent, that is a single dose of the psychedelic agent administered at a rapid rate, typically over about 30 to about 60 seconds, which single dose provides a fast onset breakthrough psychedelic experience, followed by an essentially continuous administration for a period of from about 5 to about 15 minutes. In other embodiments, the parenteral administration may comprise a bolus administration of a psychedelic agent, that is a single dose of an agent administered at a rapid rate, typically over about 30 to about 60 seconds.

As used herein the term 'effective dose' refers to a dose which is sufficient to elicit a psychedelic experience, i.e., a period in which the patient experiences one or more of intense reactions or emotions, altered state of perception, visual or other sensory hallucinations, spiritual experience, ego dissolution and dissociation. Ego dissolution describes a state in which the boundary between an individual and the outside world dissolves. Dissociation describes a state in which an individual experiences a sensation that different parts of the brain are not connected, such as a disconnect between mind and body.

The Mystical Experience Questionnaire (MEQ) was designed to address experiences occasioned specifically by hallucinogens and allows researchers to understand the characteristically incomprehensible subjective experiences associated with psychedelics. The MEQ consists of 30 questions; participants are asked to answer each question according to one's feelings, thoughts, and experiences at the time of the session, each item being rated on a 0-5 scale (0-None/not at all to 5-Extreme, more than any other time in my life). The minimum score is 0 and the maximum score is 150 with higher scores indicating a greater degree of mystical experience. The MEQ total score is computed by taking the average response to all items. In some embodiments, a 'psychedelic experience' is an experience which has a percentage score of at least 40% on the Mystical Experience Questionnaire (MEQ), for example 40% or more, 45% or more, 50% or more, 55% or more, or 60% or more points on the MEQ.

'Breakthrough psychedelic experience' means an intense and immersive psychedelic experience in which almost all connection to the real world is lost. In some embodiments breakthrough psychedelic experience is an experience which scores 50% or more, 55% or more, or 60% or more on the MEQ.

Fast onset means a psychedelic experience which peaks less than two minutes following the start of administration of the psychedelic agent, such as is observed following bolus intravenous administration or inhaled administration.

A 'month' as used herein is defined as a period of 30 days. Thus, one month is 30 days, two months is 60 days, 3 months is 90 days, six months is 180 days, nine months is 270 days and twelve months is 360 days, and so on.

'Administration occurs only one time in any one-month period' as used herein means an interval of at least 30 days is present between administrations. Likewise, 'administration occurs only one time in any two-month period' as used herein means an interval of at least 60 days is present between administrations, and so on.

'Administration occurs at most once a month' means at least one month, i.e. 30 days pass between administrations. Likewise, 'administration occurs at most once every two months' means at least two months, i.e. 60 days pass between administrations, and so on.

References herein to a singular of a noun encompass the plural of the noun, and vice-versa, unless the context implies otherwise.

Throughout this specification the word 'comprise', or variations such as 'comprises' or 'comprising', will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of

element', integers or steps. The term 'comprising' includes within its ambit the term 'consisting" or 'consisting essentially of'.

The term 'consisting' or variants thereof is to be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, and the exclusion of any other element, integer or step or group of elements, integers or steps.

The term 'consisting essentially of' or variants thereof is to be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, and that further components may be present, but only those not materially affecting the essential characteristics of the embodiment of the invention.

The term 'about' herein, when qualifying a number or value, is used to refer to values that lie within ± 5% of the value specified. For the avoidance of doubt, where a number or value is specified herein in the absence of the term 'about', the number or value should be understood according to standard numeric rounding conventions according to the number of decimal places. For example, a whole number, such as 6, is understood to encompass values ≥ 5.5 and < 6.5. Likewise, a number specified to one decimal place, such as 5.3, is understood to encompass values ≥ 5.25 and < 5.35.

Where a range of values is provided, the range includes the end point values. For example, the range 20 to 28, or from 20 to 28, would include the values 20, 21, 22, 23, 24, 25, 26, 27 and 28; the range 5 to 15, or from 5 to 15, would include the values 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15.

As used herein, the term 'patient' preferably refers to a mammal. Typically, the mammal is a human, but may also refer to a domestic mammal. The term does not encompass laboratory mammals.

As used herein, the term 'in combination with psychotherapy' refers to the treatment of a psychiatric disorder by psychological means, which are enhanced by the dosing regimen, method for treating, delivery device, or parenteral formulation for use of the invention.

The term 'treatment' defines the therapeutic treatment of a patient, in order to reduce or halt the rate of progression of a disorder, or to ameliorate or cure the disorder. Prophylactic treatment of a patient having a diagnosed psychiatric or neurological disorder is also included. Such prophylactic treatment, also referred to as secondary prevention, aims to reduce the impact of the disorder and/or to hinder development of the disorder through treatment in accordance with the invention.

As used herein, the term 'improvement' refers to a clinically meaningful reduction in symptom severity over a period of time, compared to baseline assessment, or as assessed by patient reported outcomes. Improvement may be assessed by patient reported outcomes or clinician reported outcomes, such as a structured patient interview or questionnaire. The term 'clinician' refers to a

qualified and/or registered doctor or healthcare professional and includes therapists, psychiatrists and psychologists.

Patient reported outcomes or clinician reported outcomes may comprise assessments using rating scales, which include, but are not limited to the Clinical Global Impression scale (CGI), an observer rated scale consisting of one or more of three different measures – severity of illness (CGI-S), global improvement (CGI-I) and the efficacy index (CGI-E); the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 point diagnostic questionnaire; the 17-item Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Ruminative Response Scale (RRS-22), a self-reported measure consisting of 22 items and three factors – depression, brooding and reflection; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A); the State-Trait Anxiety Inventory (STAI); the General Anxiety Disorder-7 Assessment (GAD-7); the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; and suicidality rating scales such as the Beck Scale for Suicidal Ideation (BSS), Columbia-Suicide Severity Rating Scale (C-SSRS), or the suicidal thoughts item of the MADRS for suicidal ideation or the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale. Patient reported outcomes may also include the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), a 16-item self-administered questionnaire; the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); and/or the Patient Global Impression of Improvement scale (PGI-I). A combination of the rating scales may be used. Clinician or patient reported outcomes may comprise weight gain for anorexia nervosa; frequency of binge-purge episodes for bulimia nervosa, or frequency of binge episodes for binge eating disorder.

Measurement of a clinically meaningful reduction in symptom severity will be assessed in accordance with the rating scale or other clinician or patient reported outcomes, including:

Typically for the Clinical Global Impression scale (CGI), a response score of 0, 1, 2 or 3 indicates improvement, preferably 0, 1 or 2.

Typically, for rating scales such as the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD17), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Beck Scale for Suicidal Ideation (BSS), Columbia-Suicide Severity Rating Scale (C-SSRS), Hamilton Anxiety Scale (HAM-A), State-Trait Anxiety Inventory (STAI-T), Yale-Brown Obsessive Compulsive Scale, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); EQ-5D-5L descriptive system and EQ VAS, and Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS) ; a 15% or greater, reduction in the score compared with baseline assessment indicates improvement, preferably 20% or greater, 30% or greater, preferably 50% or greater. A reduction of less than 15% is not considered a clinically meaningful improvement.

Alternatively, clinically meaningful reduction in symptom severity may be assessed by the point reduction on the rating scale. For example, improvement is indicated by the following point reductions: for the MADRS scale, a point reduction of -6 or greater; for the HAMD-17 scale, a point reduction of 4 or greater; for the Beck Depression Inventory-II (BDI-II) scale, a point reduction of 12 or greater. Alternatively, a reduction in the severity category indicates improvement, for example from severe to moderate.

Typically for the Columbia-Suicide Severity Rating Scale (C-SSRS), a reduction in the number of questions answered 'yes' indicates improvement. Alternatively, a reduction in the intensity category indicates improvement, for example a reduction from very severe to severe, or from severe to moderately severe.

Typically, for the Patient Global Impression of Severity scale (PGI-S), a reduction in the severity rating assessed by the patient indicates improvement, e.g., a reduction in the severity rating from 6 (severely ill) to 4 (moderately ill).

Typically for the Patient Global Impression of Improvement scale (PGI-I), a rating of 3 (minimally improved) or below indicates improvement, preferably a score of 2 (much improved) or below. The PGI-I scale is not assessed in comparison with the baseline assessment, but is a post-dosing only assessment.

As used herein, the term 'remission' refers to a reduction in the symptoms of the psychiatric or neurological disorder to a level which indicates mild symptoms, or that the patient is in the healthy range, i.e., the patient is not experiencing symptoms indicative of a clinical condition. For depressive disorders, remission is typically considered to be a score of 13 or below on the MADRS rating score, preferably 10 or below; or 7 or below on the HAMD17 rating scale; or 19 or below on the Beck Depression Inventory – II scale; or 15 or below on the Beck Anxiety Inventory scale; or 17 or below on the Hamilton Anxiety scale; or 15 or below on the Yale Brown Obsessive Compulsive scale; or 3 or below on the Patient Global Impression – Severity Scale (PGI-S). Remission is typically considered to apply to a patient who answers no to each question on the Columbia-Suicide Severity Rating Scale (C-SSRS), or a score of 10 or below (moderate), preferably 6 or below.

As used herein, the term 'short-acting psychedelic agent' or 'short-acting psychedelic' refers to a psychedelic agent which, following parenteral administration, elicits a psychedelic experience with a duration of about 3 hours or less, about 2 hours or less, or about 1 hour or less when administered parenterally. Preferably, the duration of psychedelic experience is about 3 hours or less, or about 2 hours or less when the psychedelic agent is deuterated. Preferably, the duration of psychedelic experience is about 2 hours or less, about 1 hour or less, more preferably about 45 minutes or less, yet more preferably about 30 minutes or less when the psychedelic agent is undeuterated.

As used herein 'neurological disorder' refers to a disorder which may be associated with a dysfunction in the brain or nervous system, and which may result in physical and/or psychological symptoms. As used herein, the term 'psychiatric disorder' is characterised by a clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour, and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom.

Diagnostic criteria for psychiatric or neurological disorders referred to herein are provided in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5).

As used herein the term 'psychedelic assisted psychotherapy', is defined as any psychotherapeutic practice that is provided alongside a dose of a psychedelic therapeutic formulation, including for example any dose as defined in the present invention. The term 'psychedelic assisted psychotherapy' includes support therapy providing preparation, psychological support and therapeutic integration to patients around and during administration of the psychedelic agent.

As used herein the term 'obsessive-compulsive disorder' (OCD) is defined by the presence of either obsessions or compulsions, but commonly both. The symptoms can cause significant functional impairment and/or distress. An obsession is defined as an unwanted intrusive thought, image or urge that repeatedly enters the person's mind. Compulsions are repetitive behaviours or mental acts that the person feels driven to perform. Typically, OCD manifests as one or more obsessions, which drive adoption of a compulsion. For example, an obsession with germs may drive a compulsion to clean or an obsession with food may drive a compulsion to overeat, eat too little or throw up after eating (i.e., an obsession with food may manifest itself as an eating disorder). A compulsion can either be overt and observable by others, such as checking that a door is locked, or a covert mental act that cannot be observed, such as repeating a certain phrase in one's mind. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) rating scale may be used to assess OCD.

As used herein, the term 'eating disorder' is defined by severe and persistent disturbance in eating behaviours and associated distressing thoughts and emotions. The term 'eating disorder' includes anorexia nervosa and bulimia nervosa, binge eating disorder, avoidant restrictive food intake disorder, other specified feeding and eating disorder, pica and rumination disorder. Assessment of eating disorders may be by assessing weight gain, frequency of binge-purge episodes, and/or frequency of binge episodes.

Eating disorders often co-occur with anxiety disorders and obsessive compulsive disorder. Neziroglu and Sandler differentiate between OCD and an eating disorder: '*Whereas patients with*

eating disorders are primarily driven by concerns of physical appearance, and consequently alter their eating patterns in order to lose weight accordingly. OCD patients may be restricting their eating for reasons very different than body image concerns' (https://iocdf.org/expert-opinions/expert-opinion-eating-disorders-and-ocd/).

The term "eating disorder" includes anorexia nervosa, bulimia and binge eating disorder (BED). The symptoms of anorexia nervosa include eating too little and/or exercising too much in order to keep weight as low as possible. The symptoms of bulimia include eating a lot of food in a very short amount of time (i.e., binging) and then being deliberately sick, using laxatives, eating too little and/or exercising too much to prevent weight gain. The symptoms of BED include regularly eating large portions of food until uncomfortably full, and consequently feeling upset or guilty.

As used herein the term 'depressive disorder' includes major depressive disorder, persistent depressive disorder, bipolar disorder, bipolar depression, and depression in terminally ill patients.

As used herein the term 'major depressive disorder' (MDD, also referred to as major depression or clinical depression) is defined as the presence of five or more of the following symptoms over a period of two-weeks or more (also referred to herein as a 'major depressive episode'), most of the day, nearly every day:

- depressed mood, such as feeling sad, empty or tearful (in children and teens, depressed mood can appear as constant irritability);
- significantly reduced interest or feeling no pleasure in all or most activities;
- significant weight loss when not dieting, weight gain, or decrease or increase in appetite (in children, failure to gain weight as expected);
- insomnia or increased desire to sleep;
- either restlessness or slowed behaviour that can be observed by others;
- fatigue or loss of energy;
- feelings of worthlessness, or excessive or inappropriate guilt;
- trouble making decisions, or trouble thinking or concentrating;
- recurrent thoughts of death or suicide, or a suicide attempt.

At least one of the symptoms must be either a depressed mood or a loss of interest or pleasure.

Persistent depressive disorder, also known as dysthymia, is defined as a patient exhibiting the following two features:

A. has depressed mood for most of the time almost every day for at least two years. Children and adolescents may have irritable mood, and the time frame is at least one year.

B. While depressed, a person experiences at least two of the following symptoms:

- Either overeating or lack of appetite.
- Sleeping too much or having difficulty sleeping.
- Fatigue, lack of energy.
- Poor self-esteem.
- Difficulty with concentration or decision-making.

As used herein the term 'treatment resistant major depressive disorder' describes MDD that fails to achieve an adequate response to treatment with standard of care therapy.

As used herein, 'bipolar disorder', also known as manic-depressive illness, is a disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.

There are two defined sub-categories of bipolar disorder; all of them involve clear changes in mood, energy, and activity levels. These moods range from periods of extremely "up," elated, and energised behaviour (known as manic episodes, and defined further below) to very sad, "down," or hopeless periods (known as depressive episodes). Less severe manic periods are known as hypomanic episodes.

Bipolar I Disorder — defined by manic episodes that last at least 7 days, or by manic symptoms that are so severe that the person needs immediate hospital care. Usually, depressive episodes occur as well, typically lasting at least 2 weeks. Episodes of depression with mixed features (having depression and manic symptoms at the same time) are also possible.

Bipolar II Disorder — defined by a pattern of depressive episodes and hypomanic episodes, but not the full-blown manic episodes described above.

As used herein 'bipolar depression' is defined as an individual who is experiencing depressive symptoms with a previous or coexisting episode of manic symptoms, but does not fit the clinical criteria for bipolar disorder.

Depressive disorders are typically assessed using a rating scale selected from Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Depression Rating Scale (HAMD-17) ; the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); suicidality rating scales such as the Beck Scale for Suicidal Ideation (BSS), Columbia-Suicide Severity Rating Scale (C-SSRS), the suicidal thoughts item of the MADRS for suicidal ideation, the

Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale, or the Columbia-Suicide Severity Rating Scale (C-SSRS); and combinations of these scales. Depressive disorders may also be assessed using patient reported outcomes selected from the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); and combinations of these outcome assessments.

Depressive disorders are preferably assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS), the Beck Depression Inventory-II, the Beck Scale for Suicidal Ideation (BSS), the Montgomery-Asberg Depression Rating Scale (MADRS), and/or the 17-item Hamilton Depression Rating Scale (HAMD-17).

As used herein, the term 'anxiety disorder' includes generalised anxiety disorder, phobia, panic disorder, social anxiety disorder, and post-traumatic stress disorder. Anxiety disorders are typically assessed using a rating scale selected from the Beck Anxiety Inventory (BAI), Hamilton Anxiety Scale (HAM-A), State-Trait Anxiety Inventory (STAI-T), Generalised Anxiety Disorder Assessment (GAD-7), and combinations of these scales. Anxiety disorders may also be assessed using patient reported outcomes, as described above.

'Generalised anxiety disorder' (GAD) as used herein means a chronic disorder characterised by long-lasting anxiety that is not focused on any one object or situation. Those suffering from GAD experience non-specific persistent fear and worry, and become overly concerned with everyday matters. GAD is characterised by chronic excessive worry accompanied by three or more of the following symptoms: restlessness, fatigue, concentration problems, irritability, muscle tension, and sleep disturbance.

'Phobia' is defined as a persistent fear of an object or situation the affected person will go to great lengths to avoid, typically disproportional to the actual danger posed. If the feared object or situation cannot be avoided entirely, the affected person will endure it with marked distress and significant interference in social or occupational activities.

A patient suffering from a 'panic disorder' is defined as one who experiences one or more brief attack(s) (also referred to as a panic attack) of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, and/or difficulty breathing. A panic attack is defined as a fear or discomfort that abruptly arises and peaks in less than ten minutes.

'Social anxiety disorder' is defined as an intense fear and avoidance of negative public scrutiny, public embarrassment, humiliation, or social interaction. Social anxiety often manifests specific physical symptoms, including blushing, sweating, and difficulty speaking.

'Post-traumatic stress disorder' (PTSD) is an anxiety disorder that results from a traumatic experience. Post-traumatic stress can result from an extreme situation, such as combat, natural disaster, rape, hostage situations, child abuse, bullying, or even a serious accident. Common symptoms include hypervigilance, flashbacks, avoidant behaviours, anxiety, anger and depression.

The Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS) may be used to assess PTSD symptoms.

As used herein, the term "post-partum depression" (PPD, also known as postnatal depression) is a form of depression experienced by either parent of a newborn baby. Symptoms typically develop within 4 weeks of delivery of the baby and often include extreme sadness, fatigue, anxiety, loss of interest or pleasure in hobbies and activities, irritability, and changes in sleeping or eating patterns.

As used herein, the term 'substance abuse' means a patterned use of a drug in which the user consumes the substance in amounts or with methods that are harmful to themselves or others.

As used herein, the term 'gambling disorder' means persistent and recurrent problematic gambling behaviour leading to clinically significant impairment or distress. The disorder has similarities with substance abuse.

As used herein, the term 'an avolition disorder' refers to a disorder that includes as a symptom the decrease in motivation to initiate and perform self-directed purposeful activities.

As used herein, the term 'breakthrough psychedelic experience' refers to an immersive and intense experience in which almost all connection to the real world is lost.

As used herein, 'slow onset breakthrough psychedelic experience' is a breakthrough psychedelic experience which peaks at least about two minutes, preferably at least about 5 minutes, more preferably at least about 10 minutes after the start of the parenteral administration. The peak may occur at different time points depending on the mode of administration. For example, while following intravenous administration the psychedelic experience may peak at least about 5 or at least about 10 minutes after the start of the administration, following intramuscular administration, the psychedelic experience may peak at least about 20, or at least about 25 minutes, or at least about 30 minutes after the start of the administration.

DETAILED DESCRIPTION

The dosage regimen, method for treating, delivery device, parenteral formulation for use or kit of the invention is based on the surprising discovery that a significant reduction in the symptoms of psychiatric and neurological disorders, such as Major Depressive Disorder, can be achieved by

administering to the patient a single, effective dose of a short-acting psychedelic such as N,N-dimethyltryptamine and deuterated N,N-dimethyltryptamine, demonstrating a durable response at three months post dosing.

Accordingly, the first aspect of the invention provides, as embodiment 1, a dosage regimen for administering a short-acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

The second aspect of the invention provides, as embodiment 2, a method of treating a psychiatric or neurological disorder in a patient, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one month, two month, or three-month, or six-month, or nine-month, or twelve-month period.

The third aspect of the invention provides, as embodiment 3, a delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

The fourth aspect of the invention provides, as embodiment 4, a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, the treatment comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

The fifth aspect of the invention provides, as embodiment 5, a kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for administration, preferably parenteral administration, of the parenteral formulation indicating that said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

The sixth aspect of the invention provides, as embodiment 6, a parenteral formulation comprising a single, effective parenteral dose of a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

As embodiment 7, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein said administration occurs (i) only one time in any one-month, or two-month, or three-month period or (ii) only one time in any three-month period. Preferably, said administration occurs only one time in any one-month period.

As embodiment 8, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein said administration occurs only one time in any six-month period or any nine-month period.

As embodiment 9, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein said administration occurs only one time in any twelve-month period.

The seventh aspect of the invention provides, as embodiment 10, a parenteral formulation comprising a single, effective parenteral dose of a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most

once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

The eighth aspect of the invention provides, as embodiment 11, a dosage regimen for administering a short-acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

The ninth aspect of the invention provides, as embodiment 12, a method for treating a psychiatric or neurological disorder in a patient, comprising the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

The tenth aspect of the invention provides, as embodiment 13, a delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

The eleventh aspect of the invention provides, as embodiment 14, a kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for administration of the parenteral formulation indicating that said administration occurs at most once a month, or at most

once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

As embodiment 15, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 10 to 14, wherein said administration occurs (i) at most once a month, or at most once every two months, or at most once every three months or (ii) at most once every three months. Preferably, said administration occurs at most once every three months.

As embodiment 16, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 10 to 15, wherein said administration occurs at most once every six months or at most once every nine months.

As embodiment 17, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 10 to 16, wherein said administration occurs at most once every twelve months.

As embodiment 18, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, which further comprises the parenteral administration of a second single effective dose of the short-acting psychedelic agent in the period three to twelve months following the administration of the first single effective dose.

As embodiment 19, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 18 which comprises the parenteral administration of a second single, effective dose of the short-acting psychedelic agent in the period three to nine months following the administration of the first single, effective dose.

As embodiment 20, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 18 or embodiment 19, wherein the administration of the first single, effective dose and the second single, effective dose occurs only one time in any twelve-month period.

As embodiment 21, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 18 or embodiment 19, wherein the administration of both the first single, effective dose and the second single, effective dose occur at most once every twelve months.

As embodiment 22, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, which further comprises the steps of and/or instructions for

(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes;

(ii) parenteral administration to the patient of a single effective dose of a short-acting psychedelic agent, wherein the psychedelic agent is selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and

(iii) post-dosing assessment of the patient.

As embodiment 23, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 22, further comprising the steps of :

(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes, before parenteral administration to the patient; and

(ii) post-dosing assessment of the patient, following parenteral administration to the patient.

As embodiment 24, the invention provides a dosage regimen, method for treating, delivery device parenteral formulation for use, or kit, according to embodiment 22 or embodiment 23, wherein the baseline assessment is by a rating scale selected from the Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A);the State-Trait Anxiety Inventory (STAI); the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); and combinations thereof; or by assessment of weight , frequency of binge-purge episodes, and/or frequency of binge episodes.

As embodiment 25, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 22 to 24, wherein the post-dosing assessment is by a rating scale selected from the Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); the Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A); the State-Trait Anxiety Inventory (STAI); Generalised Anxiety Disorder Assessment (GAD-7), the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-

Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); the clinical global improvement scale (CGI-I); the Patient Global Impression of Improvement scale (PGI-I); and combinations thereof; or by assessment of weight , frequency of binge-purge episodes , and/or frequency of binge episodes.

As embodiment 26, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 22 to 25, wherein the psychiatric or neurological disorder is depressive disorder, and wherein the baseline and post-dosing assessment is carried out using a depression rating scale selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD17), Beck Depression Inventory-II, and combinations thereof.

As embodiment 27, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the parenteral administration comprises:

parenterally administering to the patient a dose of the psychedelic agent for a dosing period of from about 5 to about 15 minutes,

wherein the parenteral administration is essentially continuous.

'Essentially continuous' as used herein means administration without a material break in administration. Optionally the parenteral administration is continuous.

As embodiment 28, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the parenteral administration is selected from the group consisting of intravenous, intramuscular, subcutaneous, intranasal, transmucosal, sublingual, rectal, and transdermal administration and inhalation.

As embodiment 29, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the parenteral administration is by intravenous infusion, preferably wherein the intravenous administration is conducted using a syringe pump.

As embodiment 30, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the parenteral administration is by a two-phase intravenous infusion.

As embodiment 31, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 29, wherein the parenteral administration is by a single-phase intravenous infusion.

As embodiment 32, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 27 to 31, wherein the dosing period is from about 8 to about 12 minutes.

As embodiment 33, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 27 to 31, wherein the dosing period is from about 9 to about 11 minutes, or about 10 minutes.

As embodiment 34, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the single effective dose of the psychedelic agent is selected from the group consisting of:

- about 20 to about 70 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 15 to about 30 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 10 to about 20 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 5 to about 15 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 10 to about 30 mg of 5-methoxy-*N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof
- about 1 to about 5 mg of psilocybin, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 3 to about 15 mg of 4-acetoxy- *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof; and
- about 1 to about 5 mg, or about 3 to about 25 mg of psilocin, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

As embodiment 35, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, comprising the parenteral administration of a total dose of about 20 to about 29 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

As embodiment 36, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, comprising the

parenteral administration of a total dose of about 20 to about 23 mg, or a total dose of about 26 to about 29 mg, of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

As embodiment 37, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 7 to about 10 mg.

As embodiment 38, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 34, wherein the administration is by a two-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 23 mg, or about 10 to about 20 mg.

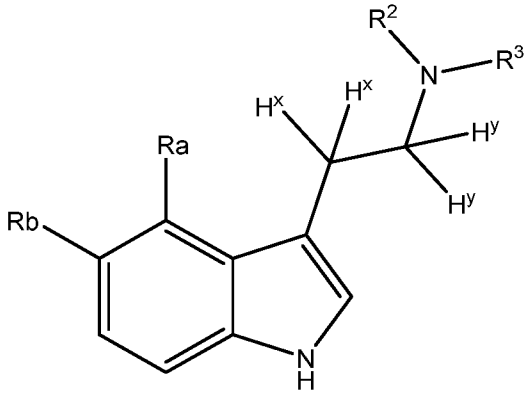
As embodiment 39, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 35, wherein the administration is by a single-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 26 to about 29 mg.

As embodiment 40, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 29 and 32 to 37, wherein the administration is by intramuscular administration.

As embodiment 41, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 70 mg, preferably about 50 to about 70 mg.

As embodiment 42, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 34 and 40, comprising the parenteral administration of a total dose of about 1.5 to about 3 mg of psilocybin, a deuterated analogue, or a pharmaceutically acceptable salt thereof, or about 1.5 to about 3 mg of psilocin, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

As embodiment 43, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the psychedelic agent is a compound of formula I, or a pharmaceutically acceptable salt thereof:



Formula I

Ra is selected from H, D, -OH, -OAc and -PO_3OH, and Rb is H or D; or

Ra is H or D, and Rb is selected from H, D, -OMe, and -OCD_3;

R^2 and R^3 are each independently selected from -$C(H^z)_3$; and

each H^x, H^y and H^z is independently selected from protium and deuterium.

As embodiment 44, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 43, wherein R^2 and R^3 are each independently selected from -$C(H)_3$ and -$C(D)_3$.

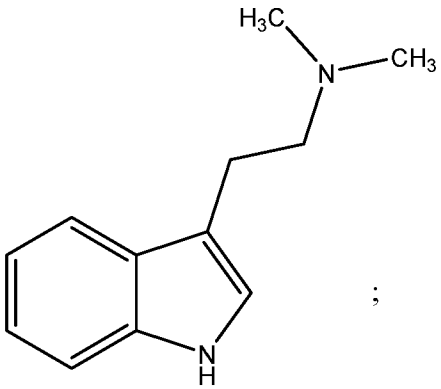
As embodiment 45, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 43, wherein R^2 and R^3 are both -$C(H)_3$, or R^2 and R^3 are both -$C(D)_3$, or R^2 is -$C(H)_3$ and R^3 is -$C(D)_3$.

As embodiment 46, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 45, wherein each H^x is H, or each H^x is D, or one H^x is H and one H^x is D.

As embodiment 47, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 46, wherein each H^y is H, or each H^y is D, or one H^y is H and one H^y is D. Preferably, each H^y is D.

As embodiment 48, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 47 and 34, wherein each H^x, H^y and H^z is deuterium.

As embodiment 49, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 48, wherein the psychedelic agent is selected from the group consisting of:



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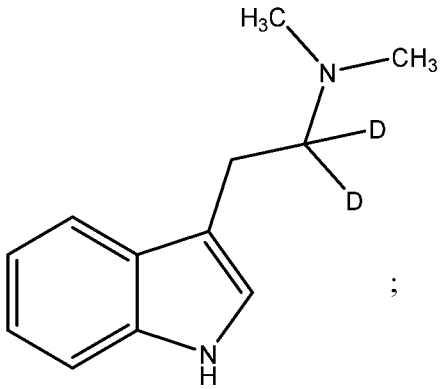

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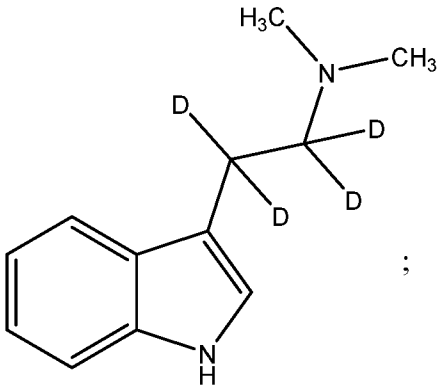

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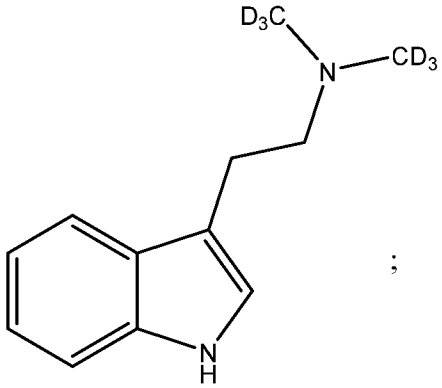

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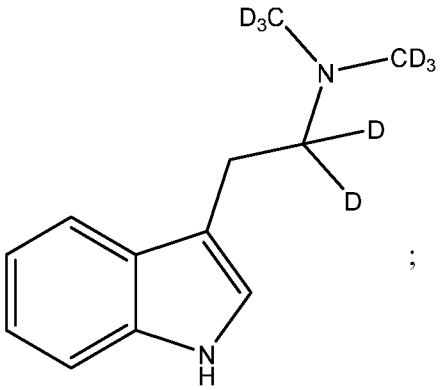

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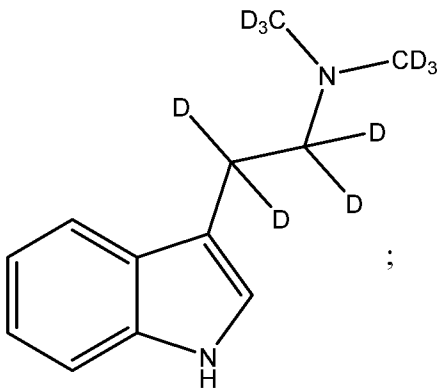
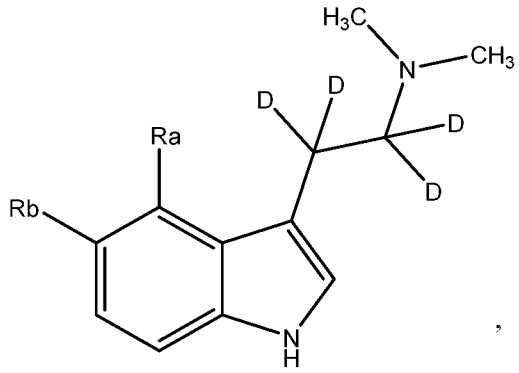


;

or a pharmaceutically acceptable salt thereof.

As embodiment 50, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 48, wherein the psychedelic agent is selected from the group consisting of:



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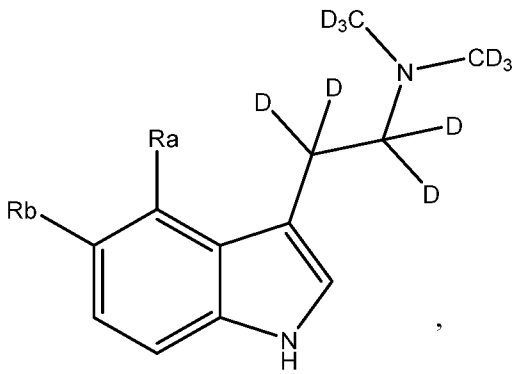

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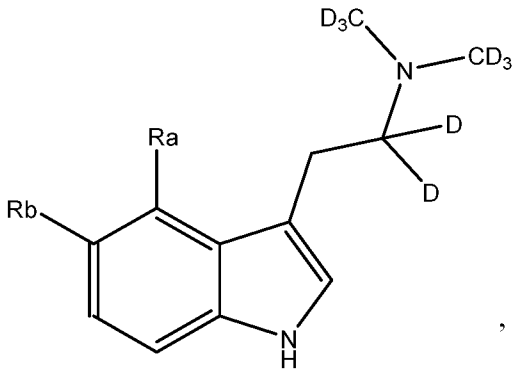

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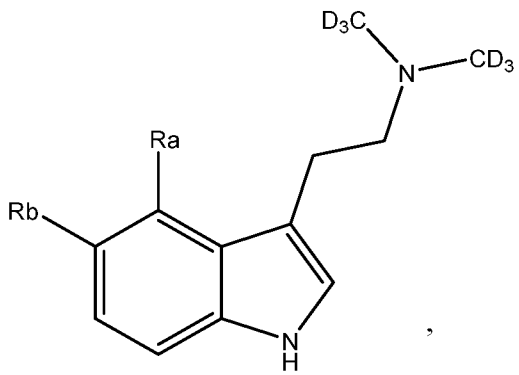

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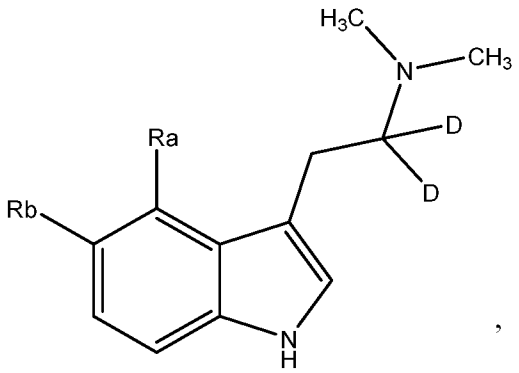

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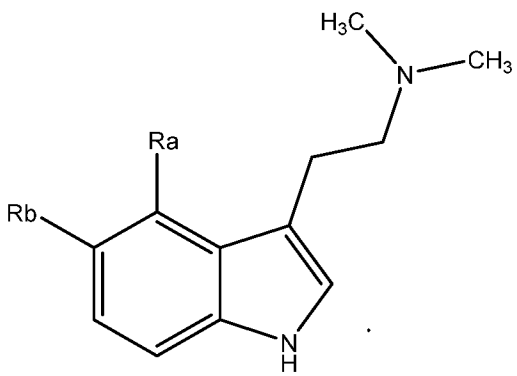

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or a pharmaceutically acceptable salt thereof, wherein Ra and Rb are as defined in embodiment 43.

As embodiment 51, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 48 and 49 to 50, wherein Ra is H or Ra is D.

As embodiment 52, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 43 to 48 and 49 to 50, wherein Rb is H or Rb is D.

As embodiment 53, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 39 and 41 to 52, wherein the parenteral administration comprises intravenous infusion by one or two syringe pumps.

As embodiment 54, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiments, wherein the psychiatric or neurological disorder is selected from the group consisting of (i) an obsessive compulsive disorder, (ii) a depressive disorder, (iii) an anxiety disorder, (iv) substance abuse and gambling disorders and (v) an avolition disorder. Often, the disorder is selected from the group consisting of major depressive disorder, treatment resistant major depressive disorder, post-partum depression, an obsessive compulsive disorder and an eating disorder such as a compulsive eating disorder. Preferably the psychiatric or neurological disorder is selected from the group consisting of a depressive disorder and an anxiety disorder.

As embodiment 55, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiments, wherein the psychiatric or neurological disorder is a depressive disorder or an anxiety disorder.

As embodiment 56, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiments, wherein the psychiatric or neurological disorder is major depressive disorder.

As embodiment 57, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein, the duration of the psychedelic experience is about 3 hours or less, or about 2 hours or less, or about 1 hour or less.

As embodiment 58, the invention provides a dosage regimen, method for treating, delivery device or parenteral formulation for use, according to any preceding embodiment, wherein, the duration of the psychedelic experience is:

- From about 15 to about 30 minutes, or from about 30 to about 90 minutes when the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof; or

- From about 15 to about 45 minutes, or about 45 minutes to about 180 minutes when the psychedelic agent is selected from psilocybin, 4-acetoxy- *N,N*-dimethyltryptamine , 5-methoxy- *N,N*-dimethyltryptamine, psilocin, a deuterated analogue thereof, or a pharmaceutically acceptable salt thereof; or
- From about 20 to about 30 minutes wherein the psychedelic agent is *N,N*-dimethyltryptamine or a pharmaceutically acceptable salt thereof; or
- From about 60 to about 90 minutes wherein the psychedelic agent is a deuterated analogue of *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof.

As embodiment 59 the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 1 to 58, wherein the psychedelic agent is *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about is about 20 to about 30 minutes, preferably about 20 minutes; ; or the psychedelic agent is a deuterated analogue of *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about 60 to about 90 minutes.

As embodiment 60, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any one of embodiments 57 to 59, wherein the duration of experience is assessed by an attending clinician, preferably a psychiatrist, psychologist or therapist.

As embodiment 61, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, further comprising the steps of and/or instructions for:

a. Preparation Stage, comprising preparing the patient for a psychedelic experience;

b. Administration Stage, comprising the dosage regimen or method of treatment or parenteral formulation for use according to any preceding embodiment; and

c. Integration Stage, comprising a psychiatrist or therapist led interview or discussion with the patient focussed on the psychedelic experience.

As embodiment 62, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment wherein the treatment of a psychiatric or neurological disorder in a patient comprises psychedelic assisted psychotherapy.

As embodiment 63, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment wherein the single, effective dose is sufficient to achieve a breakthrough psychedelic experience in the patient.

As embodiment 64, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to any preceding embodiment, wherein the patient is assessed as having moderate or severe symptoms on a rating scale for the psychiatric or neurological disorder at a baseline assessment.

As embodiment 65, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 64, wherein the psychiatric or neurological disorder is depressive disorder, and the rating scale is selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-17), the Beck Depression Inventory-II (BDI-II), and combinations thereof.

As embodiment 66, the invention provides a dosage regimen, method for treating, delivery device, parenteral formulation for use or kit, according to embodiment 65, wherein the patient is assessed as having a Montgomery-Asberg Depression Rating Scale score of 20 or higher, or a Hamilton Depression Rating Scale (HAMD-17) score of 17 or higher, or a Beck Depression Inventory-II score of 23 or higher at baseline assessment.

The psychedelic agents for use in the dosage regimen, method for treating, delivery device, or parenteral formulation for use of the invention may be prepared according to the synthetic processes described in WO2021/089873, US20210395201, WO2022/117359, US11242318, US11724985, and US20220202775, the disclosures of which are hereby incorporated by reference in their entireties.

The dose of psychedelic agent for use in the dosage regimen, method for treating, delivery device, or parenteral formulation for use of the invention may preferably be in the form of a pharmaceutically acceptable salt wherein the salt comprises an acid and the freebase of a psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, and deuterated analogues thereof. An example of a salt comprising an acid and dimethyltryptamine compound is *N,N*-dimethyltryptamine fumarate, which is the fumaric acid salt of N,N-dimethyltryptamine. P. H. Stahl and C. G. Wermuth provide an overview of pharmaceutical salts and the acids comprised therein in *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. The acids described in this review are suitable acids for inclusion within the salt of the formulation.

To be abundantly clear, when the phrase, “psychedelic agent is selected from *N,N*-dimethyltryptamine, 5-methoxy-*N,N*-dimethyltryptamine, 4-acetoxy-*N,N*-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof” is

used, this means that 1) any one of the listed compounds, 2) a pharmaceutically acceptable salt of any one of the listed compounds, 3) a deuterated analogue of any one of the listed compounds, and 4) a pharmaceutically acceptable salt of any one of the deuterated analogues of any one of the listed compounds is included. For instance, as a non-limiting example, the psychedelic agent would include *N,N*-dimethyltryptamine, a pharmaceutically acceptable salt of *N,N*-dimethyltryptamine, a deuterated analogue of *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt of a deuterated analogue of *N,N*-dimethyltryptamine. The same is true for the other listed compounds. A preferred psychedelic agent for use in any embodiment of the invention is selected from :

N,N-dimethyltryptamine;

α-protio, α-deutero-*N,N*-dimethyltryptamine;
α,α-dideutero-*N,N*-dimethyltryptamine;
α,α,β,β-tetradeutero-N,N-dimethyltryptamine;
N,N-di(trideuteromethyl)tryptamine;
α-protio, α-deutero-*N,N*- di(trideuteromethyl)tryptamine;
α,α-dideutero-*N,N*-di(trideuteromethyl)tryptamine;
α,α,β,β-tetradeutero-*N,N*-di(trideuteromethyl)tryptamine;
5-methoxy-*N,N*-dimethyltryptamine;
5-methoxy-α-protio, α-deutero-*N,N*-dimethyltryptamine;
5-methoxy- α,α-dideutero-*N,N*-dimethyltryptamine;
5-methoxy- α,α,β,β-tetradeutero-*N,N*-dimethyltryptamine;
5-methoxy-*N,N*-di(trideuteromethyl)tryptamine;
5-methoxy-α-protio, α-deutero-*N,N*- di(trideuteromethyl)tryptamine;
5-methoxy- α,α-dideutero-*N,N*-di(trideuteromethyl)tryptamine;
5-methoxy- α,α,β,β-tetradeutero-*N,N*-di(trideuteromethyl)tryptamine;
psilocybin;
α-protio, α-deutero- psilocybin;
α,α-dideutero- psilocybin;
α,α,β,β-tetradeutero- psilocybin;
4-(dihydrogen phosphate) -*N,N*-di(trideuteromethyl)tryptamine;
4-(dihydrogen phosphate)-α-protio, α-deutero-*N,N*-di(trideuteromethyl)tryptamine;
4-(dihydrogen phosphate)-α,α-dideutero-*N,N*-di(trideuteromethyl)tryptamine;
4-(dihydrogen phosphate)-α,α,β,β-tetradeutero-*N,N*-di(trideuteromethyl)tryptamine;
psilocin;
α-protio,α-deutero- psilocin;
α,α-dideutero- psilocin;
α,α,β,β-tetradeutero- psiloin;

4-hydroxy-*N,N*-di(trideuteromethyl)tryptamine;
4- hydroxy-α-protio, α-deutero-*N,N*-di(trideuteromethyl)tryptamine;
4- hydroxy-α,α-dideutero-*N,N*-di(trideuteromethyl)tryptamine;
4- hydroxy-α,α,β,β-tetradeutero-*N,N*-di(trideuteromethyl)tryptamine; and
pharmaceutically acceptable salts thereof.

The salt may comprise an acid selected from the group consisting of fumaric acid, tartaric acid, citric acid, acetic acid, lactic acid, gluconic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, galactaric acid, gentisic acid, glucoheptonic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, thiocyanic acid, toluenesulfonic acid and undecylenic acid.

Preferably, the pharmaceutically acceptable salt is selected from fumarate, tartarate, citrate and hydrochloride. More preferably, the pharmaceutically acceptable salt is fumarate.

More preferably, the pharmaceutically acceptable salt of the psychedelic agent is the fumarate salt.

Parenteral routes of administration include intravenous, intramuscular, subcutaneous, intranasal, transmucosal, sublingual, rectal, and transdermal administration, and inhalation. Any parenteral route capable of administration over a period of 5 to 15 minutes are suitable for use in the present invention. Parenteral routes capable of bolus administration over a period of less than 5 minutes, or less than 1 minute, are suitable for use in the present invention. Preferred routes of parenteral administration according to any aspect of the present invention are selected from intravenous infusion, intramuscular infusion, subcutaneous infusion, intranasal, transmucosal, and transdermal administration, and inhalation. Intravenous infusion is a particularly preferred route of administration. Intramuscular administration is a particularly preferred route of administration. The skilled person will appreciate that the delivery device for use in the present invention is selected depending on the route of administration of the dose of a psychedelic agent.

When the parenteral route of administration is intravenous, the delivery device may comprise an infusion bag or a syringe, and may preferably further comprise a syringe pump. Where two

syringe pumps are used to administer the intravenous infusion, the syringe pumps may be joined via a 3-way tap into a single cannula. When the parenteral route of administration is intramuscular the delivery device may comprise a syringe. When the parenteral route is intranasal, the delivery device may comprise a pump-action spray means. When the parenteral route is transmucosal, the delivery device may comprise an oromucosal film. When the parenteral route is transdermal, the delivery device may comprise a transdermal patch. When the route of administration is inhalation, the delivery device may comprise a metered dose inhaler, or a vaporiser, or a nebuliser.

Dosage forms suitable for parenteral administration have a pH of about 3 to 9 and, for liquid formulations, an osmolality of about 250 to about 600 mOsm/Kg. pH values above 9 are reported by I. Usach *et al.* in *Adv. Ther.*, 36, 2986-2996 (2019) to relate to tissue necrosis (death of cells within the tissue), whereas values lower than 3 are reported to cause pain and phlebitis (inflammation of veins). Osmolality values greater than 600 mOsm/Kg are also reported to cause pain. Usach *et al* also recommend that parenteral formulations should be formulated as isotonic solutions (osmolality of about 300 mOsm/Kg), proposing an upper limit of 600 mOsm/Kg to minimise pain.

Osmolality is formally defined as the quotient of the negative natural logarithm of the rational activity of water and the molar mass of water, as represented by formula:

$$osmolality = \frac{-lna_w}{18.015};\ a_w = \frac{p}{p^*}$$

where p is the partial vapour pressure of water in the solution and p^* is the partial vapour pressure of pure water. In simpler terms, osmolality is the number of osmotically active particles (the number of solute particles) in 1 kg of a solution. Thus, osmolality is a function only of the number of particles, and is not related to particle molecular weight, size, shape, or charge (see D. K. Faria *et al.*, M. E. Mendes and N. M. Sumita, *J. Bras. Patol. Med. Lab.*, 53, 1, 38-45 (2017) for a review of the measurement of serum osmolality). For example, one mole of a non-dissociating substance (e.g., DMT as a free base) dissolved in 1 kg of water has an osmolality of 1 Osm/kg (1000 mOsm/kg), whilst one mole of a substance that dissociates into two separate species in solution (e.g., DMT fumarate) dissolved in 1 kg of water has an osmolality of 2 Osm/kg (2000 mOsm/kg).

Where a first solution is defined herein to be isotonic with a second solution, the solutions have the same osmolality. For example, where a formulation is defined to be isotonic with human blood serum, the formulation has the same osmolality as human blood serum. Human blood serum typically has an osmolality of about 275 to about 300 mOsm/Kg (L. Hooper *et al.*, *BMJ Open*, 2015; 5(10): e008846).

Suitable formulations for injection according to the present invention are described in WO2022/043227 and US11406619. Suitable formulations for administration by inhalation in accordance with the invention are described in WO2022/117640. Suitable formulations for

transdermal administration are described in US 20210346347 and 17/866,477. Other suitable formulations according to the present invention are described in co-pending patent application US17/574,424. The entire disclosures of each of these patent applications are hereby incorporated by reference in their entireties.

In some embodiments, the parenteral formulation for use in the present invention comprises a salt of the psychedelic agent, a base agent, water and optionally a buffer which is separate to the salt, wherein the formulation has a pH of from about 5 to about 6, a concentration of about 10 mg/ml as freebase or greater, and an osmolality of from about 250 to about 350 mOsm/Kg; and wherein the formulation comprises a dose of the optionally substituted dimethyltryptamine compound within a volume of 5 ml or less.

The base agent adjusts the pH of the formulation to the required pH range, for example from pH 5 to pH 6. The pH of a formulation including the optionally substituted dimethyltryptamine salt, water, and a buffer is often low, e.g., less than pH 5, and so a pH adjustment with a base agent may be required. The skilled person is able to assess suitable base agents to adjust the pH of the solution without risk of degradation of the optionally substituted dimethyltryptamine salt. The base agent may be sodium hydroxide or potassium hydroxide.

The parenteral formulation optionally comprises a buffer, which is separate to the salt, i.e., the buffer is not merely a counterion to the psychedelic agent. For example, where the salt is *N,N*-dimethyltryptamine fumarate (i.e., the fumaric acid salt of *N,N*-dimethyltryptamine), an amount of buffer may be required over and above the buffer effect provided by the fumarate salt. The term "buffer" is well known in the art and refers to a chemical which, on inclusion within a formulation, resists a change in pH on addition of acid or base to the formulation. As used herein, the term 'buffer' refers to the buffer system or the buffer agent. Within a formulation, a buffer comprises a weak acid and its conjugate base. A suitable buffer comprises an acid with a pKa value that lies within ±1 of the desired pH of the formulation. For example, if the desired pH of the formulation is about 5.0, a suitable buffer comprises a weak acid with a pKa value of from about 4.0 to about 6.0. If the acid of a buffer has more than one pKa value (i.e., each molecule of the acid is able to donate more than one proton), in order for the buffer to be suitable, at least one of the pKa values lies within the desired pH range.

The weak acid and conjugate base of the buffer are in equilibrium with one another. In accordance with Le Chatelier's principle (if a constraint (such as a change in concentration of a reactant) is applied to a system in equilibrium, the equilibrium will shift so as to counteract the effect of the constraint), addition of acid or base to the formulation shifts the position of equilibrium in favour of the conjugate base or weak acid, respectively. Consequently, the concentration of free protons in the formulation (and thus the pH) is relatively unchanged.

Suitable buffer systems comprise an acetate salt and acetic acid (pKa = 4.75); a citrate salt and citric acid (pKa = 3.13, 4.76 and 6.40); and a phosphate salt and phosphoric acid (pKa = 2.14, 7.20 and 12.37); or mixtures thereof. The pKa values cited herein are those reported at 25 °C in water. Typically, the buffer comprises only one of the pairs listed above, i.e., one acid and its conjugate base.

In some embodiments, the buffer comprises an acetate salt and acetic acid; a citrate salt and citric acid; or a phosphate salt and phosphoric acid. Sometimes, the buffer comprises an acetate salt and acetic acid; or a citrate salt and citric acid. In some embodiments, the buffer comprises an acetate salt and acetic acid, often sodium acetate and acetic acid, or potassium acetate and acetic acid.

The concentration of buffer within the formulation is typically sufficient to resist significant pH change of the formulation on storage of the formulation for two weeks (i.e., the pH typically fluctuates less than about 0.1 pH unit), The skilled person is able to assess suitable buffer concentrations and to achieve this. Often, the concentration of buffer is from about 15 mM to about 75 mM, such as about 20 mM to about 30 mM. In some embodiments, the concentration of the buffer is about 25 mM.

As used herein, the term 'buffer agent' refers to the weak acid or weak base. Any pharmaceutically acceptable buffer agent may be used in the formulations of the invention, including phosphoric acid, citric acid, acetic acid, phosphate salt, citrate salt, and acetate salt. In some embodiments, the buffer comprises sodium phosphate, sodium citrate, or sodium acetate.

Sometimes, the concentration of psychedelic agent and optional buffer in the formulation gives rise to the desired osmolality. Alternatively, the desired osmolality may be achieved by inclusion of one or more tonicity agents in the formulation. Thus, in some embodiments, the formulation further comprises a tonicity agent. A tonicity agent is defined herein as a chemical that, on inclusion within a formulation, increases the osmolality of the formulation. As described above, the osmolality is the number of osmotically active particles (the number of solute particles) in 1 kg of a solution. Thus, a chemical that acts as a solute when incorporated into the formulation lies within the definition of a tonicity agent.

In some embodiments, the formulation comprises a tonicity agent. The concentration of tonicity agent depends on the concentration of other components within the formulation, such as the psychedelic agent and buffer. For example, where the formulation without tonicity agent has an osmolality of about 60 mOsm/kg, at least about 190 mOsm/kg would be provided by a tonicity agent (e.g., 95 mM of sodium chloride). M. F. Powell, T. Nguyen and L. Baloian provide a review of excipients suitable for parenteral administration (administration other than by the mouth or alimentary canal) in *PDA J. Pharm. Sci. Technol.*, 52, 238-311 (1998). All soluble excipients listed in this review

article that can be given by the intravenous route will, when added to the formulation, contribute to the osmolality and thus can be considered tonicity agents.

Suitable excipients for use in the dose of a psychedelic agent when used in accordance with the invention may be selected from the group consisting of ethanol, citric acid, trisodium citrate, benzalkonium chloride, microcrystalline cellulose, carboxymethylcellulose sodium, chlorobutanol, edetate disodium, glycerin, hydrochloric acid, methylparaben, polyethylene glycol, propylene glycol, propylparaben, saccharin sodium, sodium bicarbonate, sodium bisulphate, sodium bisulphite, sodium chloride, sodium hydroxide, sodium metabisulphite, sodium phosphate, sodium citrate, sulphuric acid, trisodium citrate, tromethamine, and mixtures thereof.

Some excipients may act as a cosolvent. Suitable solvents or cosolvents for use in the formulations of the invention may be selected from ethanol, polyethylene glycol, propylene glycol, and mixtures thereof. In some embodiments, the formulation comprises a cosolvent. In some embodiments, the formulation does not comprise a cosolvent. In particular, when the salt of the optionally substituted dimethyltryptamine compound is a fumarate, for example N,N-dimethyltryptamine fumarate or α,α-dideutero-N,N-dimethyltryptamine fumarate, the formulation does not comprise a cosolvent.

The onset and cessation of the psychedelic experience may be assessed by the attending clinician, psychiatrist or therapist. 'Duration of the psychedelic experience' as used herein refers to the time from the start of the continuous parenteral administration to the cessation of the psychedelic experience.

Therapeutic improvement may be assessed using a rating scale commonly used in the field. For patients with a depressive disorder such as MDD or TRD, the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAMD-17) may be used. The rating scale is used prior to administration of the psychedelic agent, to provide a baseline assessment, and again after administration of the psychedelic agent (post-dosing) to assess the therapeutic effect. Preferably post-dosing assessment occurs from about 24 hours to about one month after administration of the psychedelic agent, preferably about one week, about two weeks, about three weeks and/or about four weeks after administration of the psychedelic agent. A reduction in symptoms to an essentially asymptomatic level is considered to indicated remission. Remission may be assessed by a MADRS score of 13 or below, or 10 or below, a HAMD-17 score of 10 or below, preferably 8 or below, or a BDI-II score of 13 or below, preferably 11 or below.

In some embodiments, the psychedelic agent may be administered as a two-phase IV infusion through a venous cannula over 6–11 min. In some embodiments, the psychedelic agent may be administered as a two-phase IV infusion through a venous cannula, wherein each phase comprises a 5-minute infusion. In some embodiments, the psychedelic agent may be administered as a single-

phase IV infusion through a venous cannula over 6–11 min, preferably about 10 minutes. Where a two-phase IV infusion is used, suitably the syringe pumps are joined via a 3-way tap into a single cannula: once infusion is complete on the first pump, the 3-way tap is turned to allow infusion to continue from the second pump.

The term 'single-phase' IV infusion refers to the administration of an IV infusion by one syringe pump, with the administration of the psychedelic agent from a single syringe pump. The term 'two-phase' IV infusion refers to the administration of an IV infusion by two syringe pumps, with the first phase comprising administration of the psychedelic agent from the first syringe pump, followed by the second phase comprising administration of the psychedelic agent from the second syringe pump. The two-phase IV infusion is essentially continuous, with a non-material break in the infusion to change administration from the first syringe pump to the second syringe pump.

In some embodiments, the psychedelic agent may be administered by intramuscular administration.

In some embodiments, the kit is a kit for treating a psychiatric or neurological disorder in a patient, and the kit includes a) a container comprising a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and b) a label or package insert on or associated with the container comprising instructions for administration of the parenteral formulation, indicating that the administration occurs only one time in any one-month, or two-month, or three-month period.

EXAMPLES

A double-blind, randomised, placebo-controlled study of intravenous doses of DMT fumarate, was carried out in patients with major depressive disorder (ClinicalTrials.gov Identifier: NCT04673383, Part B). The protocol, as shown in Figure 1, comprised the steps of:

Day -1

- MADRS assessment by an independent assessor

Day 1

- Administration of either a placebo or a dose of DMT fumarate by continuous intravenous infusion over a dosing period of about 10 minutes.
- Tolerability assessment following cessation of the psychedelic experience.

Day 8 , Day 14 , Day 22 (±1 day), Day 29 (± 2 days), Day 45 (± 2 days), Day 105 (± 5 days)

- MADRS assessment

The administration of the study drug, DMT fumarate (SPL026), in NCT04673383, Part B was in accordance with the present invention.

Data from the Day 8, Day 14, Day 22, and Day 29 time points are presented in **TABLE 1**. Group A received one dose of active and were assessed at Day 8 and Day 14. Group P received a placebo on Day 1, and were also assessed at Day 8 and Day 14. Group PA received placebo on Day 1, followed by one dose of active on Day 15, and were assessed at Day 22 and Day 29

TABLE 1

	A		P		PA	
Time from active dose (or placebo dose for Group P)	1 week	2 weeks	1 week	2 weeks	1 week	2 weeks
study day	Day 8	Day 14	Day 8	Day 14	Day 22	Day 29
Number of dosed subjects	17	17	17	17	16	16
Number of datapoints	16	17	16	17	14	16
Mean Baseline MADRS	26.3		25.5		23.5	
Mean change from baseline	-12.7	-11.0	-1.9	-3.6	-10.6	-10.8
mean % reduction	-48.2	-41.0	-6.0	-15.8	-40.6	-36.7
% of subjects with ≥ 50% reduction from BL	43.8	35.3	6.3	11.8	42.9	43.8
% of subjects with MADRS score ≤ 10	43.8	29.4	12.5	11.8	42.9	31.3

BL = baseline assessment

These data demonstrate a clear rapid mean improvement in symptoms for subjects who received one dose of active (Groups A and PA) compared with subjects who received placebo only (Group P); with a statistically significant difference in mean change from baseline between Group A and Group P at Day 8 of -10.8 points (p=0.002); and a statistically significant difference of -7.4 points at Day 15 (p=0.02). Data demonstrating the percentage of subjects in Groups A and P with ≥ 50% reduction in MADRS from baseline and the percentage of subjects with a MADRS score ≤10 are presented in Figures 2 and 3, respectively.

Data from the Day 22, Day 29, Day 45, and Day 105 time points are presented in **TABLE 2**. Group A received one dose of active on Day 1. Group PA received placebo on Day 1, followed by one dose of active (open label) on Day 15. Group AA received one dose of active on Day 1 and a second dose of active (open label) on Day 15.

TABLE 2

	AA				PA				A			
Week post open label dose	1	2	4	12	1	2	4	12	1	2	4	12
study day	Day22	Day29	Day45	Day105	Day22	Day29	Day45	Day105	Day22	Day29	Day45	Day105
Number of dosed subjects	13	13	13	13	16	16	16	16	4	4	4	4
Number of datapoints	12	12	12	12	14	16	16	14	4	4	4	4
Mean Baseline MADRS	25.1				23.5				30.3			
Mean change from baseline	-13.4	-13.3	-12.4	-7.8	-10.6	-10.8	-13.9	-15.4	-7.0	-15.8	-14.8	-11.0
mean % reduction	-52.2	-50.7	-45.4	-28.2	-40.6	-36.7	-46.9	-53.7	-19.6	-52.4	-49.1	-36.4
% of subjects with ≥ 50% reduction from BL	58.3	58.3	50.0	41.7	42.9	43.8	50.0	50.0	25.0	50.0	50.0	50.0
% of subjects with a MADRS score ≤10	58%	50%	50%	33%	43%	31%	50%	57%	25.0	50.0	50.0	50.0

BL = baseline assessment

These data demonstrate a clear, durable mean improvement in symptoms for all treated groups at Day 22 through to Day 105. At Day 105, 50.0 % of Group PA and Group A subjects had a ≥ 50% reduction in MADRS scores compared with the baseline assessment; and 57% of Group PA subjects and 50.0% of Group A patients had a MADRS score ≤10 (remission). Data demonstrating the mean reduction in MADRS score are shown in Figure 5. Data demonstrating the percentage of subjects in Groups AA and PA with ≥ 50% reduction in MADRS from baseline and the percentage of subjects with a MADRS score ≤10 at weeks 1, 2, 4, and 12 post-open label dose are presented in Figures 6 and 7, respectively. The data further surprisingly show no significant difference in improvement between subjects who received two doses (Group AA) and subjects who received one dose of active (Group PA and Group A). This unexpected result is commercially beneficial in that a single dose of a treatment is less expensive in terms of (at least) starting materials, processing, and medical/administrative burden. Additionally, a one dose regimen may decrease the burden on patients and increase patient convenience and compliance.

Data are presented in **TABLE 3** showing the reduction in severity category on the MADRS rating scale at Day 8 (D8), D14, D29, D45 and D105 for subjects who received placebo on Day 1, followed by one dose of active at Day 15 (Group PA).

TABLE 3

	1 dose (PA), N	**D8**	**D14**	**D29**	**D45**	**D105**
	1 step	3	4	5	3	4
	2+ step	0	1	5	7	5
	At least 1 step	3	5	10	10	9
	n	*16*	*17*	*16*	*16*	*14*
	1 step	18.8%	23.5%	31.3%	18.8%	28.6%
	2+ step	0.0%	5.9%	31.3%	43.8%	35.7%
	At least 1 step	18.8%	29.4%	62.5%	62.5%	64.3%
	N					
(1 step)	Mild to symptom absent	0	1	0	1	0
(1 step)	Moderate to mild	2	2	4	2	3
(1 step)	Severe to moderate	1	1	1	0	1
(2 steps)	Moderate to symptom absent	0	1	4	5	4
(2 steps)	Severe to mild	0	0	1	1	0
(3 steps	Severe to symptom absent	0	0	0	1	1
	%					
(1 step)	Mild to symptom absent	-	5.9%	-	6.3%	-
(1 step)	Moderate to mild	12.5%	11.8%	25.0%	12.5%	21.4%
(1 step)	Severe to moderate	6.3%	5.9%	6.3%	-	7.1%
(2 steps)	Moderate to symptom absent	-	5.9%	25.0%	31.3%	28.6%
(2 steps)	Severe to mild	-	-	6.3%	6.3%	-
(3 steps)	Severe to symptom absent	-	-	-	6.3%	7.1%

Symptom Severity Categories defined by MADRS score ranges:	*Lower*	*Upper*
Symptom absent	0	6
Mild	7	19
Moderate	20	34
Severe	34	

At Day 45, 62.5% of subjects experienced at least a one-step reduction in symptom severity category on the MADRS scale, and 64.3% of subjects experienced at least a one-step reduction at Day 105. 43.8% of subjects experienced a two-step or three-step reduction at Day 45, while 35.7 experienced a two-step or three-step reduction at Day 105. At Day 105, 28.6% of subjects experienced a two-step reduction from moderate to symptoms absent, while at Day 45, 31.3% of subjects also experienced a two-step reduction from moderate to symptoms absent. Furthermore, at Day 45, 6.3% of subjects experienced a three-step reduction from severe to symptom absent while at Day 105 7.1% of subjects experienced a three-step reduction from severe to symptom absent. These data demonstrate that administration of a psychedelic agent in accordance with the present invention achieved a reduction of at least a one-step in symptom severity category for a significant percentage of subjects, particularly for subjects assessed as moderate at baseline.

Analysis of patient-reported depression scores corroborated the MADRS assessments conducted by independent clinical raters. Improvements in depression scores from baseline were observed across all study timepoints in patients receiving at least a single dose of active in accordance with the invention, as measured by the Beck Depression Inventory ("BDI"). This includes a statistically significant improvement in depression symptoms compared to placebo at two-weeks post-dose (p=0.002). The efficacy outcomes on the BDI were consistent with MADRS, providing additional support for the rapid and sustained therapeutic profile of DMT fumarate for the treatment of MDD, when administered in accordance with the invention.

Measures assessing patients' anxiety and wellbeing, areas which are often negatively impacted by depression, were also analyzed across the study. Following administration of one dose of active, in accordance with the invention, with supportive therapy, patients demonstrated a rapid and sustained improvement in anxiety symptoms as measured by the State-Trait Anxiety Inventory-Trait ("STAI-T") scale. A statistically significant improvement in anxiety symptoms was observed compared to placebo at two-weeks post-dose (p=0.03). At 12-weeks following the open label dose (Group PA), a -14.2 mean change from baseline ("CFB") was demonstrated in the patient group receiving one dose (Group PA).

Further, a rapid and sustained improvement in wellbeing was observed following at least one dose of active, administered in accordance with the invention, with supportive therapy, as measured by the Warwick-Edinburgh Mental Wellbeing Scale ("WEMWBS"). The results at two-weeks following the blinded dose of active or placebo (Groups A and P) showed a 10.1 mean CFB in Group A compared to 0.9 in Group P.

Statistical analysis was conducted on the MADRS open label data. A statistically significant difference in mean total MADRS score was observed for both the PA and AA Groups across all open-label study timepoints ($p<0.05$). Further analysis was conducted to assess the difference in total MADRS scores between the PA and AA groups using a mixed model of repeated measures for all subjects across all timepoints. No statistical difference (p=ns) was demonstrated between these dose regimens across all time points to 12-weeks. This analysis provides further support that one dose of active is sufficient to elicit a rapid and durable antidepressant effect. The data are presented in Table 4.

Table 4

	Blinded Phase (Week 2)*		*Open Label Phase (Week 12*)*	
	P	*A*	*PA*	*AA*
Self-Reported Depression (BDI CFB)	-3.8	-17.4	-19.7	-17.1
p value (BDI CFB active vs. placebo)	p=0.002		n/a	
Anxiety (STAI-T CFB)	-3.4	-11.0	-14.2	-9.1
p value (STAI-T CFB active vs. placebo)	p=0.03		n/a	
Wellbeing (WEMWBS CFB)	0.9	10.1	9.8	8.9
MADRS (PA vs AA regimen)	n/a		p=ns	

**refers to weeks following administration of dose in either blinded or open-label phase*

CLAIMS

1. A parenteral formulation comprising a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, the treatment comprising the parenteral administration to the patient of a single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

2. The parenteral formulation for use according to claim 1, wherein said administration occurs (i) only one time in any one-month, or two-month, or three-month period or (ii) only one time in any three-month period.

3. The parenteral formulation for use according to any preceding claim, wherein said administration occurs only one time in any six-month or any nine-month period.

4. The parenteral formulation for use according to any preceding claim, wherein said administration occurs only one time in any twelve-month period.

5. A parenteral formulation comprising a single, effective parenteral dose of a short-acting psychedelic agent for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the treatment comprises the administration, preferably parenteral administration, to the patient of a single, effective parenteral dose of the short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

6. The parenteral formulation for use according to claim 5, wherein said administration occurs (i) at most once a month, or at most once every two months, or at most once every three months or (ii) at most once every three months.

7. The parenteral formulation for use according to claim 5 or claim 6, wherein said administration occurs at most once every six months or at most once every nine months.

8. The parenteral formulation for use according to any one of claims 5 to 7, wherein said administration occurs at most once every twelve months.

9. The parenteral formulation for use according to any preceding claim, further comprising the parenteral administration of a second single, effective dose of the short-acting psychedelic agent in the period three to twelve months following the administration of the first single, effective dose.

10. The parenteral formulation for use according to claim 9, comprising the parenteral administration of a second single, effective dose of the short-acting psychedelic agent in the period three to nine months following the administration of the first single, effective dose.

11. The parenteral formulation for use according to claim 9 or claim 10, wherein the administration of the first single, effective dose and the second single, effective dose occurs only one time in any twelve-month period.

12. The parenteral formulation for use according to claim 9 or claim 10, wherein the administration of both the first single, effective dose and the second single, effective dose occur at most once every twelve months.

13. The parenteral formulation for use according to any preceding claim, further comprising the steps of :

(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes;

(ii) parenteral administration to the patient of a single effective dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and

(iii) post-dosing assessment of the patient.

14. The parenteral formulation for use according to any one of claims 1 to 12, further comprising the steps of :

(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes, before parenteral administration to the patient; and

(ii) post-dosing assessment of the patient, following parenteral administration to the patient.

15. The parenteral formulation for use according to claim 13 or claim 14, wherein the baseline assessment is by a rating scale selected from the Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A);the State-Trait Anxiety Inventory (STAI); Generalised Anxiety Disorder Assessment (GAD-7), the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); and combinations thereof; or by assessment of weight , frequency of binge-purge episodes, and/or frequency of binge episodes.

16. The parenteral formulation for use according to any one of claims 13 to 15, wherein the post-dosing assessment is by a rating scale selected from the Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); the Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A); the State-Trait Anxiety Inventory (STAI); Generalised Anxiety Disorder Assessment (GAD-7), the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); the clinical global improvement scale (CGI-I); the Patient Global Impression of Improvement scale (PGI-I); and combinations thereof; or by assessment of weight, frequency of binge-purge episodes, and/or frequency of binge episodes.

17. The parenteral formulation for use according to any one of claims 13 to 16, wherein the psychiatric or neurological disorder is depressive disorder, and wherein the baseline and post-dosing assessment is carried out using a depression rating scale selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD17), Beck Depression Inventory-II, and combinations thereof.

18. The parenteral formulation for use according to any preceding claim, wherein the parenteral administration comprises:
parenterally administering to the patient a dose of the psychedelic agent for a dosing period of from about 5 to about 15 minutes,
wherein the parenteral administration is essentially continuous.

19. The parenteral formulation for use according to any preceding claim, wherein the parenteral administration is selected from the group consisting of intravenous, intramuscular, subcutaneous, intranasal, transmucosal, sublingual, rectal, and transdermal administration and inhalation.

20. The parenteral formulation for use according to any preceding claim, wherein the parenteral administration is by intravenous infusion or by intramuscular administration, preferably wherein the intravenous administration is conducted using a syringe pump.

21. The parenteral formulation for use according to any preceding claim, wherein the parenteral administration is by a two-phase intravenous infusion.

22. The parenteral formulation for use according to any one of claims 1 to 20, wherein the parenteral administration is by a single-phase intravenous infusion.

23. The parenteral formulation for use according to any one of claims 18 to 22, wherein the dosing period is from about 8 to about 12 minutes.

24. The parenteral formulation for use according to any one of claims 18 to 22, wherein the dosing period is from about 9 to about 11 minutes, or about 10 minutes.

25. The parenteral formulation for use according to any preceding claim, wherein the single effective dose of the psychedelic agent is selected from the group consisting of:

- about 20 to about 70 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 15 to about 30 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 10 to about 20 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;

- about 5 to about 15 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 10 to about 30 mg of 5-methoxy-*N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof
- about 1 to about 5 mg of psilocybin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 3 to about 15 mg of 4-acetoxy- *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 1 to about 5 mg of psilocin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof; and
- about 3 to about 25 mg of psilocin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof.

26. The parenteral formulation for use according to any preceding claim, comprising the parenteral administration of a total dose of about 20 to about 29 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

27. The parenteral formulation for use according to any preceding claim, comprising the parenteral administration of a total dose of about 20 to about 23 mg, or a total dose of about 26 to about 29 mg, of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

28. The parenteral formulation for use according to any preceding claim, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 7 to about 10 mg.

29. The parenteral formulation for use according to claim 25, wherein the administration is by a two-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 23 mg, or about 10 to about 20 mg.

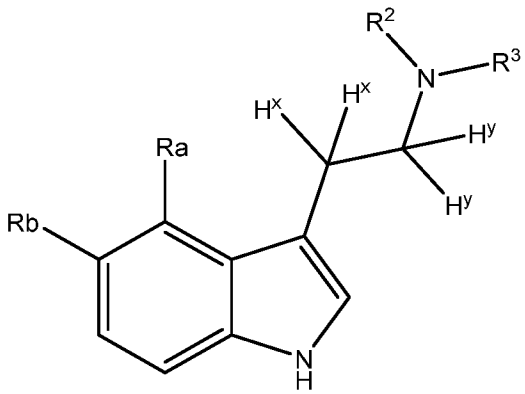
30. The parenteral formulation for use according to claim 26, wherein the administration is by a single-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 26 to about 29 mg.

31. The parenteral formulation for use according to any one of claims 1 to 20 and 23 to 28, wherein the administration is by intramuscular administration.

32. The parenteral formulation for use according to any preceding claim, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 70 mg.

33. The parenteral formulation for use according to any one of claims 1 to 25 and 31, comprising the parenteral administration of a total dose of about 1.5 to about 3 mg of psilocybin, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

34. The parenteral formulation for use according to any preceding claim, wherein the psychedelic agent is a compound of formula I, or a pharmaceutically acceptable salt thereof:



Formula I

Ra is selected from H, D, -OH, -OAc and -PO_3OH, and Rb is H or D; or

Ra is H or D, and Rb is selected from H, D, -OMe, and -OCD_3;

R^2 and R^3 are each independently selected from -$C(H^z)_3$; and

each H^x, H^y and H^z is independently selected from protium and deuterium.

35. The parenteral formulation for use according to claim 34, wherein R^2 and R^3 are each independently selected from -$C(H)_3$ and -$C(D)_3$.

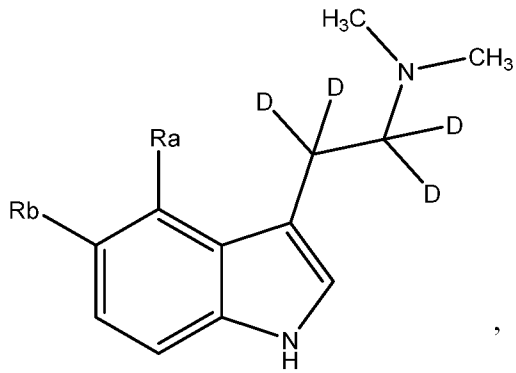
36. The parenteral formulation for use according to claim 34, wherein R^2 and R^3 are both -$C(H)_3$, or R^2 and R^3 are both -$C(D)_3$, or R^2 is -$C(H)_3$ and R^3 is -$C(D)_3$.

37. The parenteral formulation for use according to any one of claims 34 to 36, wherein each H^x is H, or each H^x is D, or one H^x is H and one H^x is D.

38. The parenteral formulation for use, according to any one of claims 34 to 37, wherein each H^y is H, or each H^y is D, or one H^y is H and one H^y is D.

39. The parenteral formulation for use according to any one of claims 34 to 38, wherein each H^x, H^y and H^z is deuterium.

40. The parenteral formulation for use, according to any one of claims 34 to 39, wherein the psychedelic agent is selected from the group consisting of:



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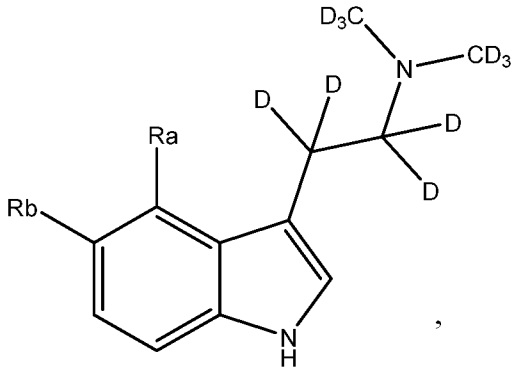

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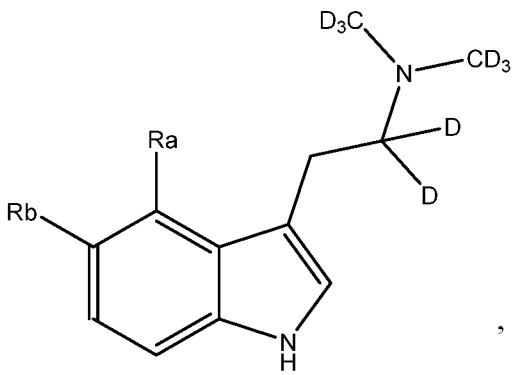

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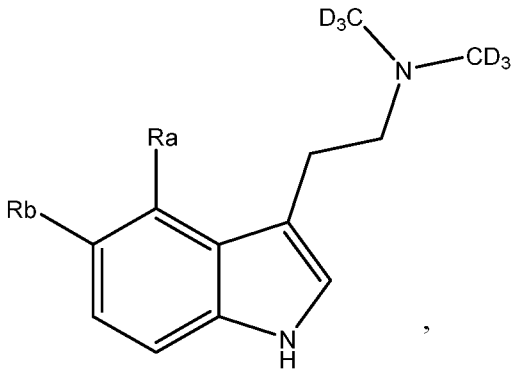

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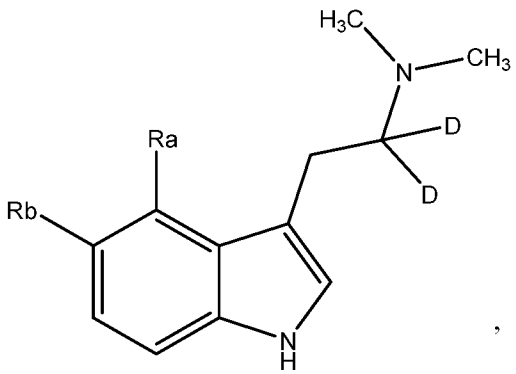

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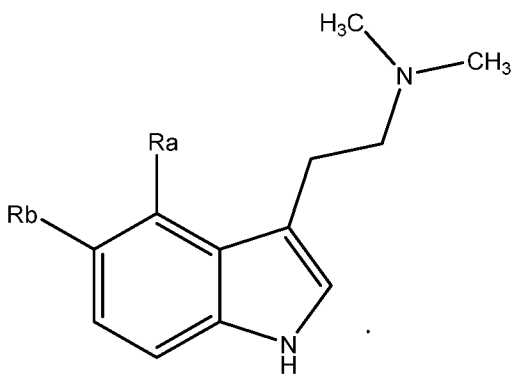

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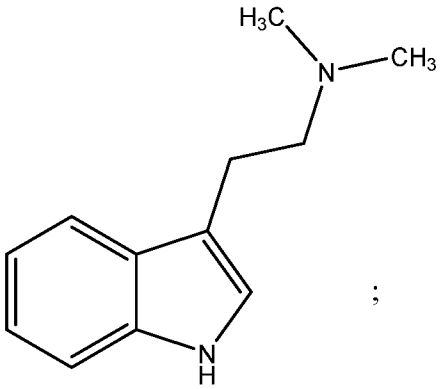
or a pharmaceutically acceptable salt thereof; wherein Ra and Rb are as defined in claim 34.

41. The parenteral formulation for use according to any one of claims 34 to 40, wherein Ra is H or Ra is D.

42. The parenteral formulation for use according to any one of claims 34 to 41, wherein Rb is H or Rb is D.

43. The parenteral formulation for use according to any one of claims 34 to 42, wherein the psychedelic agent is selected from the group consisting of: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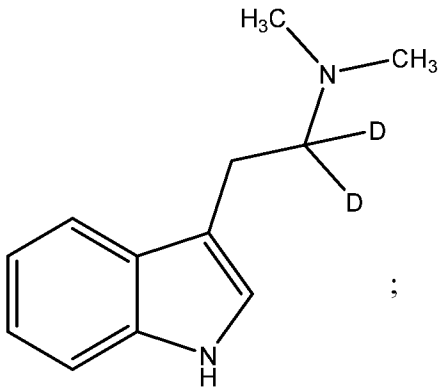
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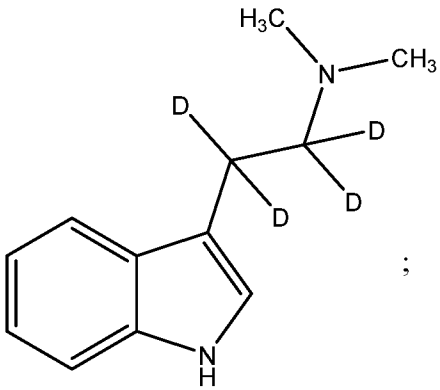
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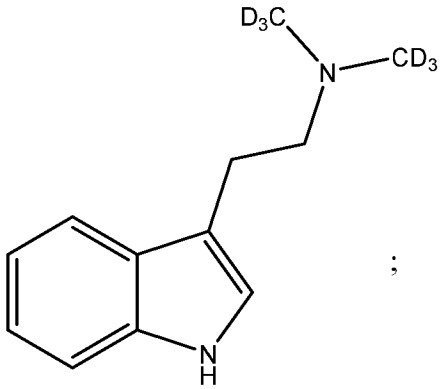
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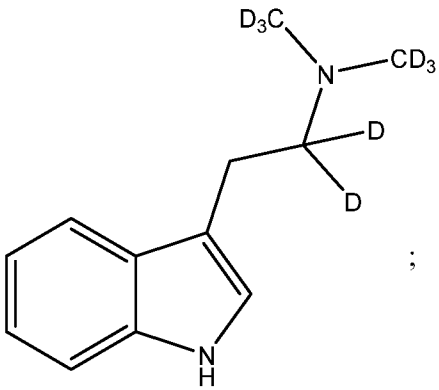
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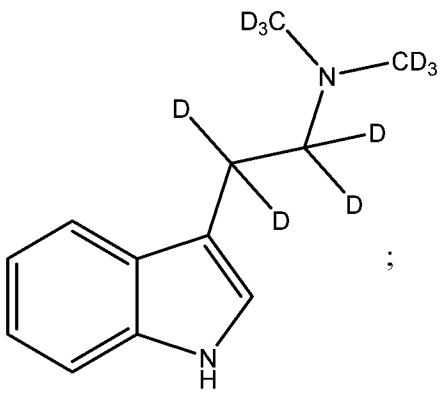
;

or a pharmaceutically acceptable salt thereof.

44. The parenteral formulation for use or according to any one of claims 1 to 30 and 32 to 43, wherein the parenteral administration comprises intravenous infusion by one or two syringe pumps.

45. The parenteral formulation for use according to any preceding claims, wherein the psychiatric or neurological disorder is selected from the group consisting of (i) an obsessive compulsive disorder, (ii) a depressive disorder, (iii) an anxiety disorder, (iv) substance abuse and gambling disorders and (v) an avolition disorder; preferably a depressive disorder or an anxiety disorder.

46. The parenteral formulation for use according to any preceding claims, wherein the psychiatric or neurological disorder is a depressive disorder or an anxiety disorder.

47. The parenteral formulation for use according to any preceding claims, wherein the psychiatric or neurological disorder is major depressive disorder.

48. The parenteral formulation for use according to any preceding claims, wherein the duration of the psychedelic experience is about 3 hours or less, or about 2 hours or less, or about 1 hour or less.

49. The parenteral formulation for use according to any preceding claim, wherein the duration of the psychedelic experience is:

From about 15 to about 30 minutes, or from about 30 to about 90 minutes when the psychedelic agent is N,N-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof; or

From about 15 to about 45 minutes, or about 45 minutes to about 180 minutes when the psychedelic agent is selected from psilocybin, 4-acetoxy- N,N-dimethyltryptamine , 5-methoxy-N,N-dimethyltryptamine, psilocin, a deuterated analogue thereof, or a pharmaceutically acceptable salt thereof; or

From about 20 to about 30 minutes wherein the psychedelic agent is N,N-dimethyltryptamine or a pharmaceutically acceptable salt thereof; or

From about 60 to about 90 minutes wherein the psychedelic agent is a deuterated analogue of N,N-dimethyltryptamine, or a pharmaceutically acceptable salt thereof.

50. The parenteral formulation for use according to any one of claims 1 to 49, wherein the psychedelic agent is *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about is about 20 to about 30 minutes, preferably about 20 minutes; or the psychedelic agent is a deuterated analogue of *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about 60 to about 90 minutes.

51. The parenteral formulation for use according to any one of claims 48 to 50, wherein the duration of experience is assessed by an attending clinician, preferably a psychiatrist, psychologist or therapist.

52. The parenteral formulation for use according to any preceding claim, further comprising the steps of:

a. Preparation Stage, comprising preparing the patient for a psychedelic experience;

b. Administration Stage, comprising the parenteral formulation for use according to any preceding claim; and

c. Integration Stage, comprising a psychiatrist or therapist led interview or discussion with the patient focussed on the psychedelic experience.

53. The parenteral formulation for use according to any preceding claim wherein the treatment of a psychiatric or neurological disorder in a patient comprises psychedelic assisted psychotherapy.

54. The parenteral formulation for use according to any preceding claim wherein the single, effective dose is sufficient to achieve a breakthrough psychedelic experience in the patient.

55. The parenteral formulation for use according to any preceding claim, wherein the patient is assessed as having moderate or severe symptoms on a rating scale for the psychiatric or neurological disorder at a baseline assessment.

56. The parenteral formulation for use according to claim 55, wherein the psychiatric or neurological disorder is depressive disorder, and the rating scale is selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-17), the Beck Depression Inventory-II (BDI-II), and combinations thereof.

57. The parenteral formulation for use according to claim 56, wherein the patient is assessed as having a Montgomery-Asberg Depression Rating Scale score of 20 or higher, or a Hamilton Depression Rating Scale (HAMD-17) score of 17 or higher, or a Beck Depression Inventory-II score of 23 or higher at baseline assessment.

58. A dosage regimen for administering a short acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the parenteral administration to

the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

59. A method of treating a psychiatric or neurological disorder in a patient, comprising the parenteral administration to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

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60. A delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the parenteral administration to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

61. A kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for parenteral administration of the parenteral formulation indicating that said administration occurs only one time in any one-month, or two-month, or three-month, or six-month, or nine-month, or twelve-month period.

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62. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 61, wherein said administration occurs (i) only one time in any one-month, or two-month, or three-month period or (ii) only one time in any three-month period.

63. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 62, wherein said administration occurs only one time in any six-month or any nine-month period.

64. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 63, wherein said administration occurs only one time in any twelve-month period.

65. A dosage regimen for administering a short-acting psychedelic agent to a patient for the treatment of a psychiatric or neurological disorder, comprising the parenteral administration to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

66. A method for treating a psychiatric or neurological disorder in a patient, comprising the parenteral administration to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

67. A delivery device for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the delivery device is configured to deliver the parenteral administration to the patient of a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; wherein said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

68. A kit comprising a parenteral formulation for use in the treatment of a psychiatric or neurological disorder in a patient, wherein the parenteral formulation comprises a single, effective parenteral dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and further comprising instructions for parenteral administration of the parenteral formulation indicating that said administration occurs at most once a month, or at most once every two months, or at most once every three months, or at most once every six months, or at most once every nine months, or at most once every twelve months.

69. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 65 to 68, wherein said administration occurs (i) at most once a month, or at most once every two months, or at most once every three months or (ii) at most once every three months.

70. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 65 to 69, wherein said administration occurs at most once every six months or at most once every nine months.

71. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 65 to 70, wherein said administration occurs at most once every twelve months.

72. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 71, further comprising the parenteral administration of a second single, effective dose of the short-acting psychedelic agent in the period three to twelve months following the administration of the first single, effective dose.

73. The dosage regimen, method for treating, delivery device, or kit, according to claim 72, which comprises the parenteral administration of a second single effective dose of the short-acting psychedelic agent in the period three to nine months following the administration of the first single effective dose.

74. The dosage regimen, method for treating, delivery device, or kit, according to claim 72 or claim 73, wherein the administration of the first single effective dose and the second single effective dose occurs only one time in any twelve-month period.

75. The dosage regimen, method for treating, delivery device, or kit, according to claim 72 or claim 73, wherein the administration of both the first single, effective dose and the second single, effective dose occur at most once every twelve months.

76. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 75, further comprising the steps of and/or instructions for

(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes;

(ii) parenteral administration to the patient of a single effective dose of a short-acting psychedelic agent selected from N,N-dimethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, 4-acetoxy-N,N-dimethyltryptamine, psilocybin, psilocin, deuterated analogues thereof, and pharmaceutically acceptable salts thereof; and

(iii) post-dosing assessment of the patient.

77. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 75, which further comprises the steps of and/or instructions for
(i) baseline assessment of the patient using a rating scale and/or clinician reported outcomes and/or patient reported outcomes, before parenteral administration to the patient; and
(iii) post-dosing assessment of the patient, following parenteral administration to the patient.

78. The dosage regimen, method for treating, delivery device or kit, according to claim 76 or claim 77, wherein the baseline assessment is by a rating scale selected from the Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A);the State-Trait Anxiety Inventory (STAI); Generalised Anxiety Disorder Assessment (GAD-7), the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); and combinations thereof; or by assessment of weight , frequency of binge-purge episodes, and/or frequency of binge episodes.

79. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 76 to 78, wherein the post-dosing assessment is by a rating scale selected from the

Clinical Global Impression scale (CGI); the Montgomery-Asberg Depression Rating Scale (MADRS); the Hamilton Depression Rating Scale (HAMD17); the Beck Depression Inventory-II; the Beck Anxiety Inventory (BAI); the Hamilton Anxiety Scale (HAM-A); the State-Trait Anxiety Inventory (STAI); Generalised Anxiety Disorder Assessment (GAD-7), the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS); the Yale-Brown Obsessive Compulsive Scale; the Beck Scale for Suicidal Ideation (BSS); Columbia-Suicide Severity Rating Scale (C-SSRS); the suicidal thoughts item of the MADRS for suicidal ideation; the Clinical Global Impression of Severity of Suicidality - Revised (CGI-SS-R) scale; the Beck Depression Inventory (BDI-II); the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF); the EQ-5D-5L descriptive system and EQ VAS; the Patient Global Impression of Severity scale (PGI-S); the clinical global improvement scale (CGI-I); the Patient Global Impression of Improvement scale (PGI-I); and combinations thereof; or by assessment of weight, frequency of binge-purge episodes, and/or frequency of binge episodes.

80. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 76 to 79, wherein the psychiatric or neurological disorder is depressive disorder, and wherein the baseline and post-dosing assessment is carried out using a depression rating scale selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD17), Beck Depression Inventory-II, and combinations thereof.

81. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 80, wherein the parenteral administration comprises:
parenterally administering to the patient a dose of the psychedelic agent for a dosing period of from about 5 to about 15 minutes,
wherein the parenteral administration is essentially continuous.

82. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 81, wherein the parenteral administration is selected from the group consisting of intravenous, intramuscular, subcutaneous, intranasal, transmucosal, sublingual, rectal, and transdermal administration and inhalation.

83. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 82, wherein the parenteral administration is by intramuscular administration, or by intravenous infusion, preferably wherein the intravenous administration is conducted using a syringe pump.

84. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 83, wherein the parenteral administration is by a two-phase intravenous infusion.

85. The dosage regimen, method for treating, delivery device or kit, according to any one of claims 58 to 83, wherein the parenteral administration is by a single-phase intravenous infusion.

86. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 81 to 85, wherein the dosing period is from about 8 to about 12 minutes.

87. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 81 to 85, wherein the dosing period is from about 9 to about 11 minutes, or about 10 minutes.

88. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 87, wherein the single effective dose of the psychedelic agent is selected from the group consisting of:

- about 20 to about 70 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 15 to about 30 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 10 to about 20 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof;
- about 5 to about 15 mg of *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 10 to about 30 mg of 5-methoxy-*N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof
- about 1 to about 5 mg of psilocybin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 3 to about 15 mg of 4-acetoxy- *N,N*-dimethyltryptamine, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof;
- about 1 to about 5 mg of psilocin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof; and
- about 3 to about 25 mg of psilocin, a deuterated analogue, and/or a pharmaceutically acceptable salt thereof.

89. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 88, comprising the parenteral administration of a total dose of about 20 to about 29 mg of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

90. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 89, comprising the parenteral administration of a total dose of about 20 to about 23 mg, or a total dose of about 26 to about 29 mg, of *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

91. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 90, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 7 to about 10 mg.

92. The dosage regimen, method for treating, delivery device, or kit, according to claim 88, wherein the administration is by a two-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 23 mg, or about 10 to about 20 mg.

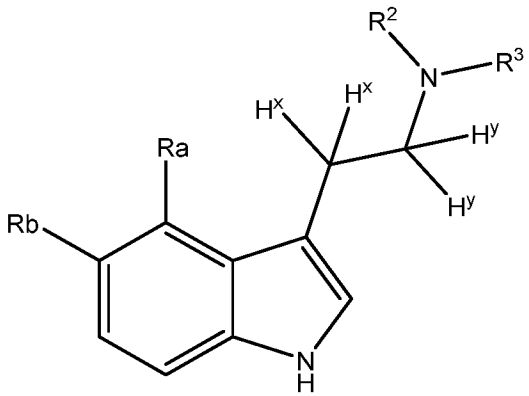
93. The dosage regimen, method for treating, delivery device, or kit, according to claim 89, wherein the administration is by a single-phase intravenous infusion, the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 26 to about 29 mg.

94. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 83 and 86 to 91, wherein the administration is by intramuscular administration.

95. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 94, wherein the psychedelic agent is *N,N*-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof, and the total dose is about 20 to about 70 mg, preferably about 50 to about 70 mg.

96. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 88 and 94, comprising the parenteral administration of a total dose of about 1.5 to about 3 mg of psilocybin, a deuterated analogue, or a pharmaceutically acceptable salt thereof.

97. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 96, wherein the psychedelic agent is a compound of formula I, or a pharmaceutically acceptable salt thereof:



Formula I

Ra is selected from H, D, -OH, -OAc and -PO_3OH, and Rb is H or D; or

Ra is H or D, and Rb is selected from H, D, -OMe, and OCD_3;

R^2 and R^3 are each independently selected from -$C(H^z)_3$; and

each H^x, H^y and H^z is independently selected from protium and deuterium.

98. The dosage regimen, method for treating, delivery device, or kit, according to claim 97, wherein R^2 and R^3 are each independently selected from -$C(H)_3$ and -$C(D)_3$.

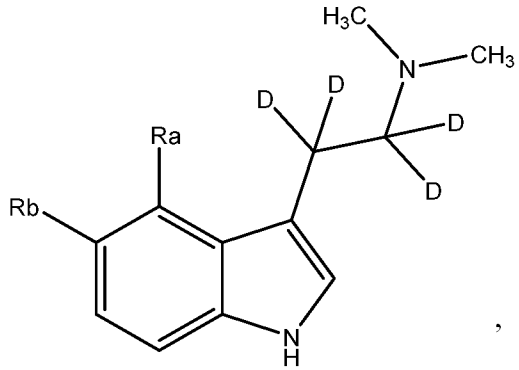
99. The dosage regimen, method for treating, delivery device, or kit, according to claim 97, wherein R^2 and R^3 are both -$C(H)_3$, or R^2 and R^3 are both -$C(D)_3$, or R^2 is -$C(H)_3$ and R^3 is -$C(D)_3$.

100. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 99, wherein each H^x is H, or each H^x is D, or one H^x is H and one H^x is D.

101. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 100, wherein each H^y is H, or each H^y is D, or one H^y is H and one H^y is D.

102. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 101, wherein each H^x, H^y and H^z is deuterium.

103. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 102, wherein the psychedelic agent is selected from the group consisting of:



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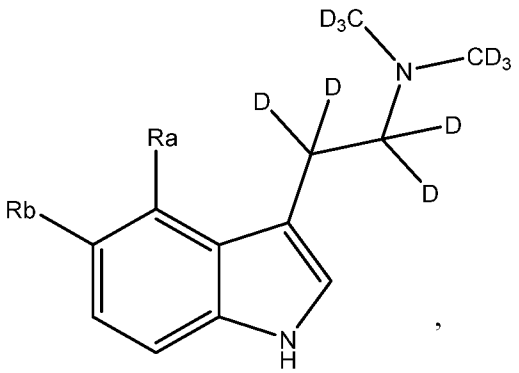

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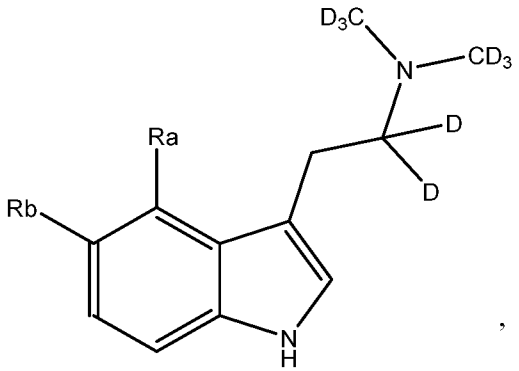

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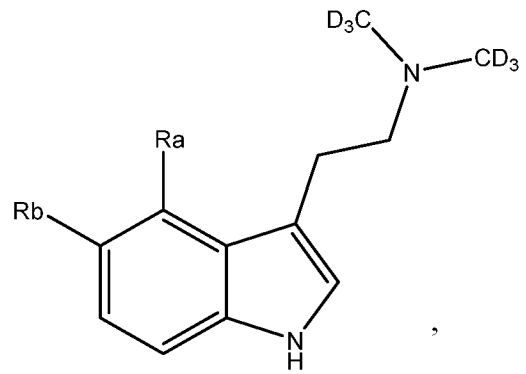

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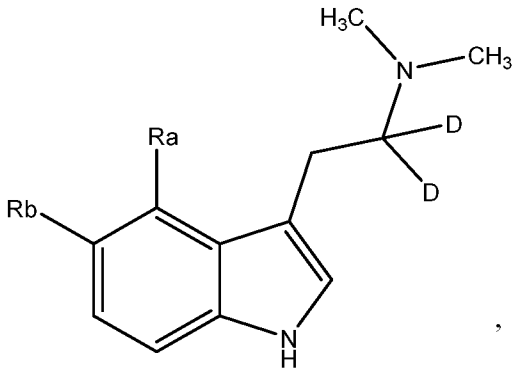

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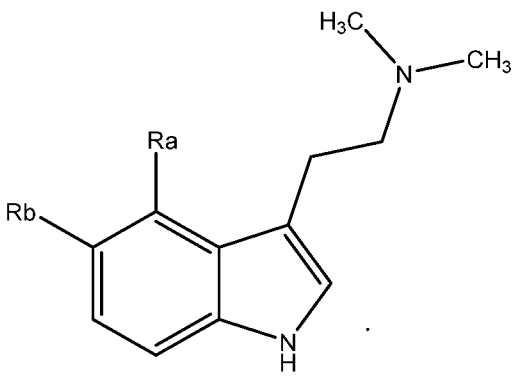


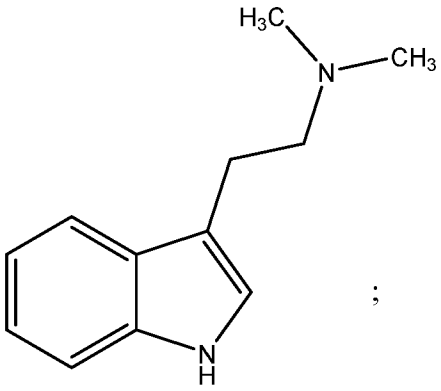
.

or a pharmaceutically acceptable salt thereof; wherein Ra and Rb are as defined in claim 97.

104. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 103, wherein Ra is H or Ra is D.

105. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 104, wherein Rb is H or Rb is D.

106. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 97 to 105, wherein the psychedelic agent is selected from the group consisting of: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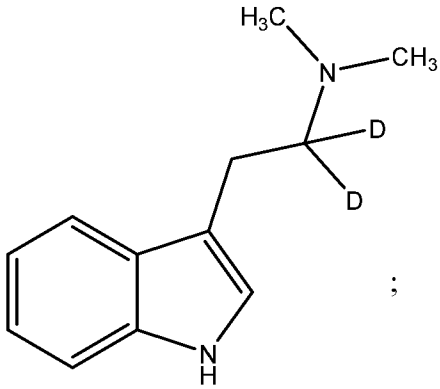
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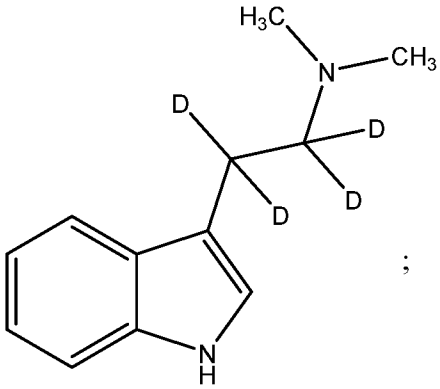
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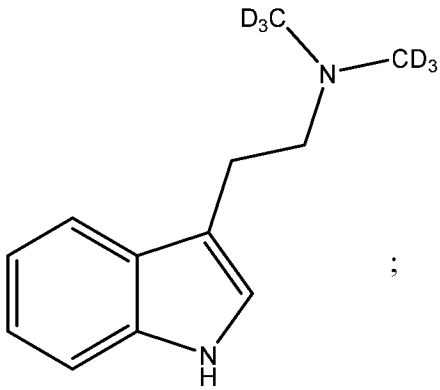
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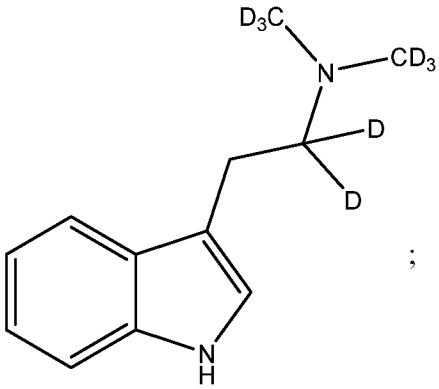
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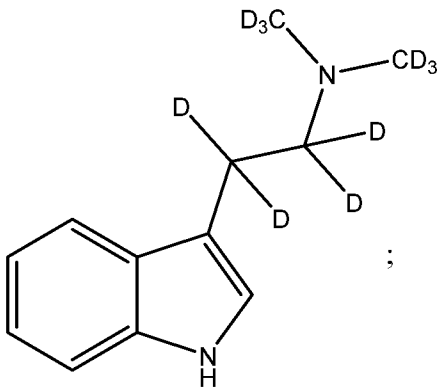
or a pharmaceutically acceptable salt thereof.

107. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 93 and 95 to 106, wherein the parenteral administration comprises intravenous infusion by one or two syringe pumps.

108. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 107, wherein the psychiatric or neurological disorder is selected from the group consisting of (i) an obsessive compulsive disorder, (ii) a depressive disorder, (iii) an anxiety disorder, (iv) substance abuse and gambling disorders and (v) an avolition disorder; preferably a depressive disorder or an anxiety disorder.

109. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 108, wherein the psychiatric or neurological disorder is a depressive disorder or an anxiety disorder.

110. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 109, wherein the psychiatric or neurological disorder is major depressive disorder.

111. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 110, wherein, the duration of the psychedelic experience is about 3 hours or less, or about 2 hours or less, or about 1 hour or less.

112. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 111, wherein, the duration of the psychedelic experience is:

- From about 15 to about 30 minutes, or from about 30 to about 90 minutes when the psychedelic agent is N,N-dimethyltryptamine, a deuterated analogue, or a pharmaceutically acceptable salt thereof; or
- From about 15 to about 45 minutes, or about 45 minutes to about 180 minutes when the psychedelic agent is selected from psilocybin, 4-acetoxy- N,N-dimethyltryptamine , 5-methoxy- N,N-dimethyltryptamine, psilocin, a deuterated analogue thereof, or a pharmaceutically acceptable salt thereof; or
- From about 20 to about 30 minutes wherein the psychedelic agent is N,N-dimethyltryptamine or a pharmaceutically acceptable salt thereof; or
- From about 60 to about 90 minutes wherein the psychedelic agent is a deuterated analogue of N,N-dimethyltryptamine, or a pharmaceutically acceptable salt thereof..

113. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 57 to 112, wherein the psychedelic agent is *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about is about 20 to about 30 minutes, preferably about 20 minutes; or the psychedelic agent is a deuterated analogue of *N,N*-dimethyltryptamine, or a pharmaceutically acceptable salt thereof, and the duration of the psychedelic experience is about 60 to about 90 minutes.

114. The dosage regimen, method for treating, delivery device, or kit, according to claim 112 or claim 113, wherein the duration of experience is assessed by an attending clinician, preferably a psychiatrist, psychologist or therapist.

115. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 114, further comprising the steps of and/or instructions for:

a. Preparation Stage, comprising preparing the patient for a psychedelic experience;

b. Administration Stage, comprising the dosage regimen or method of treatment according to any preceding claim; and

c. Integration Stage, comprising a psychiatrist or therapist led interview or discussion with the patient focussed on the psychedelic experience.

116. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 115 wherein the treatment of a psychiatric or neurological disorder in a patient comprises psychedelic assisted psychotherapy.

117. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 116 wherein the single, effective dose is sufficient to achieve a breakthrough psychedelic experience in the patient.

118. The dosage regimen, method for treating, delivery device, or kit, according to any one of claims 58 to 117, wherein the patient is assessed as having moderate or severe symptoms on a rating scale for the psychiatric or neurological disorder at a baseline assessment.

119. The dosage regimen, method for treating, delivery device, or kit, according to claim 118, wherein the psychiatric or neurological disorder is depressive disorder, and the rating scale is selected from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD-17), the Beck Depression Inventory-II (BDI-II), and combinations thereof.

120. The dosage regimen, method for treating, delivery device, or kit, according to claim 119, wherein the patient is assessed as having a Montgomery-Asberg Depression Rating Scale score of 20 or higher, or a Hamilton Depression Rating Scale (HAMD-17) score of 17 or higher, or a Beck Depression Inventory-II score of 23 or higher at baseline assessment.

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Figure 1

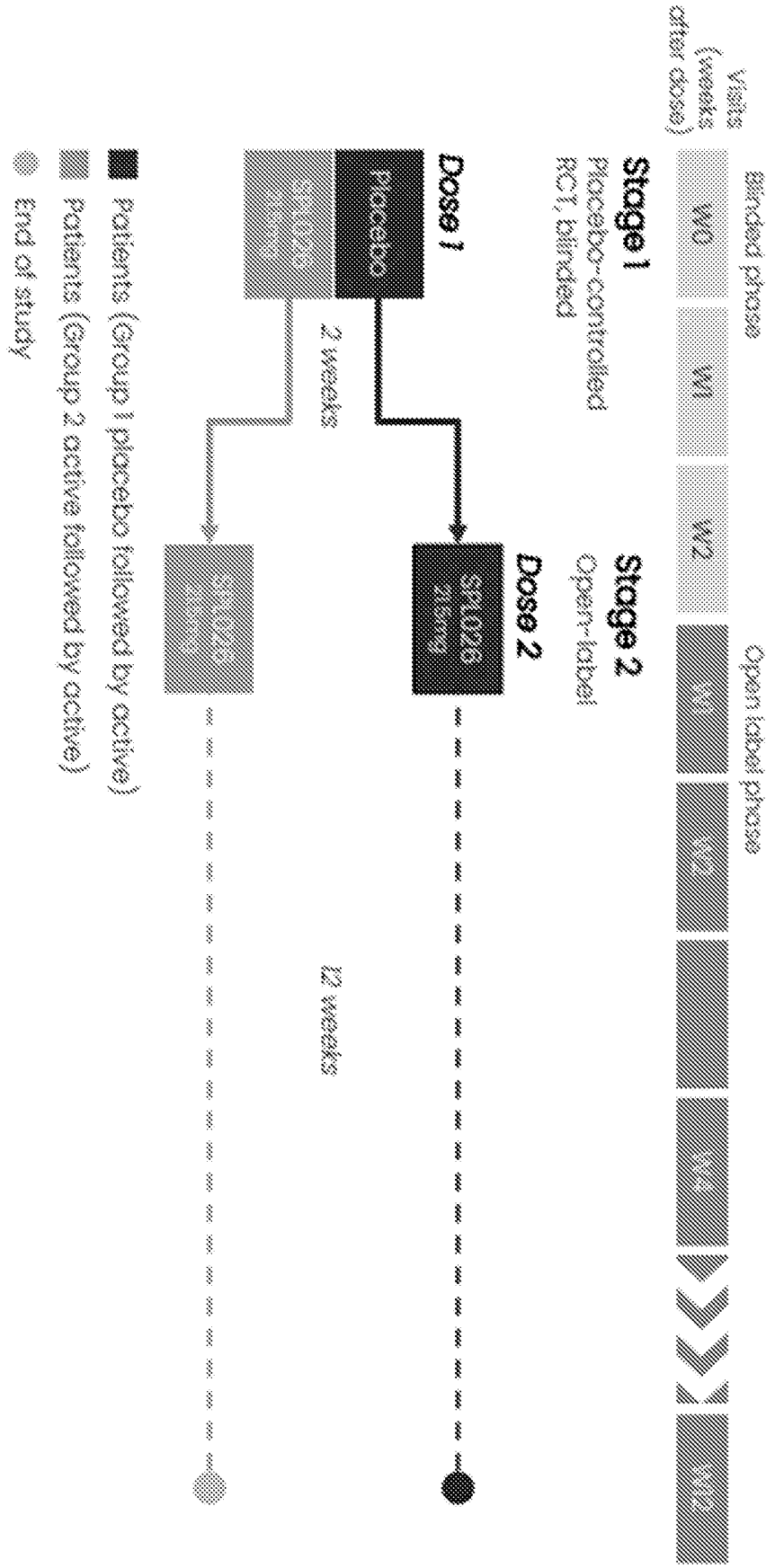

Visits (weeks after dose)
W0
W1
W2
Stage 1
Placebo-controlled RCT, blinded
Stage 2
Open-label
Dose 1
Dose 2
2 weeks
12 weeks
Patients (Group 1 placebo followed by active)
Patients (Group 2 active followed by active)
End of study

FIGURE 2

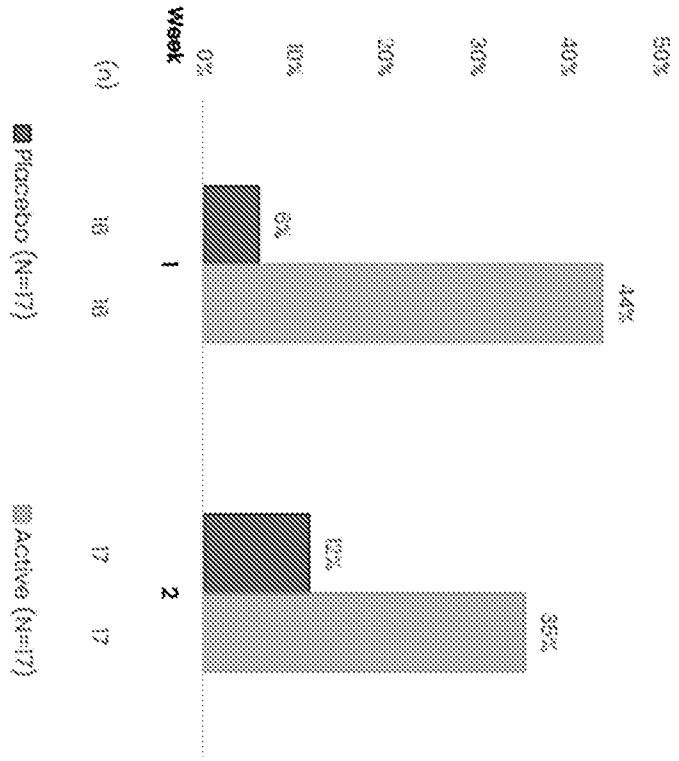


FIGURE 3

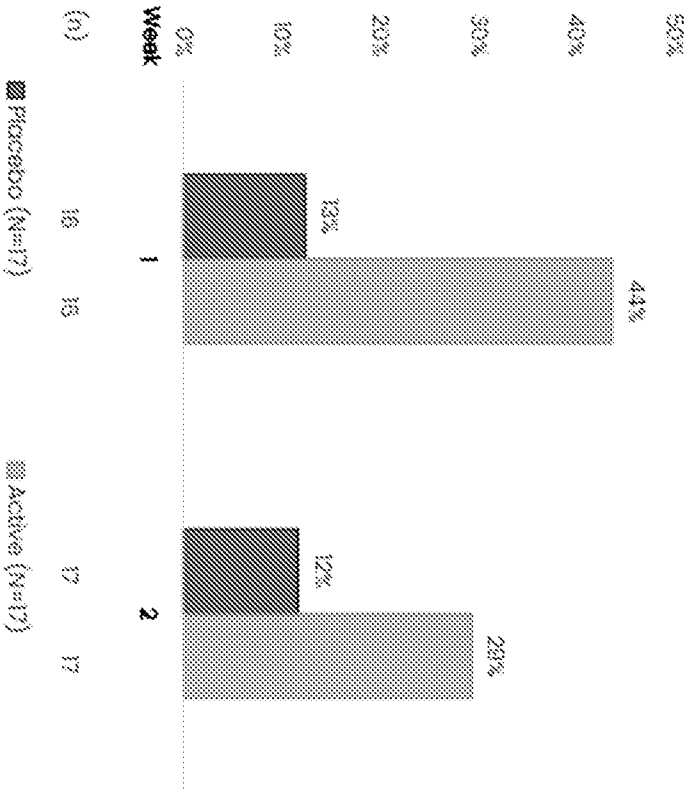


FIGURE 4

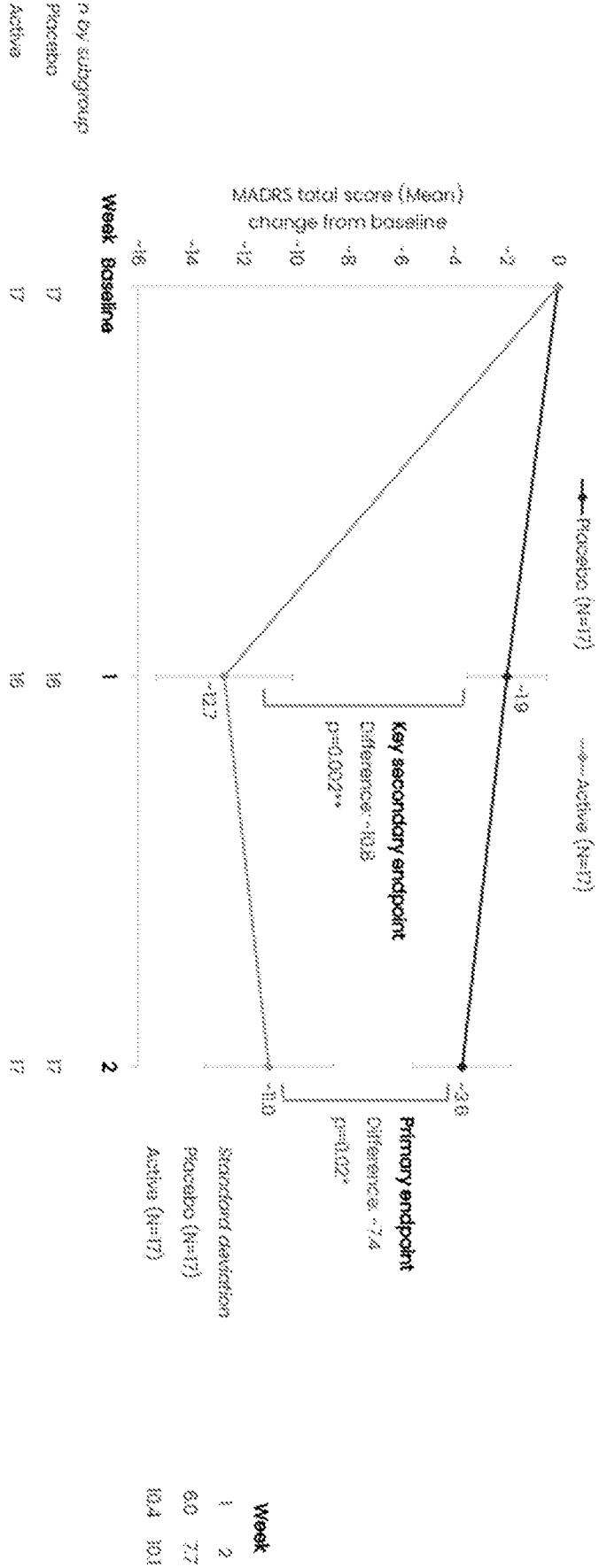
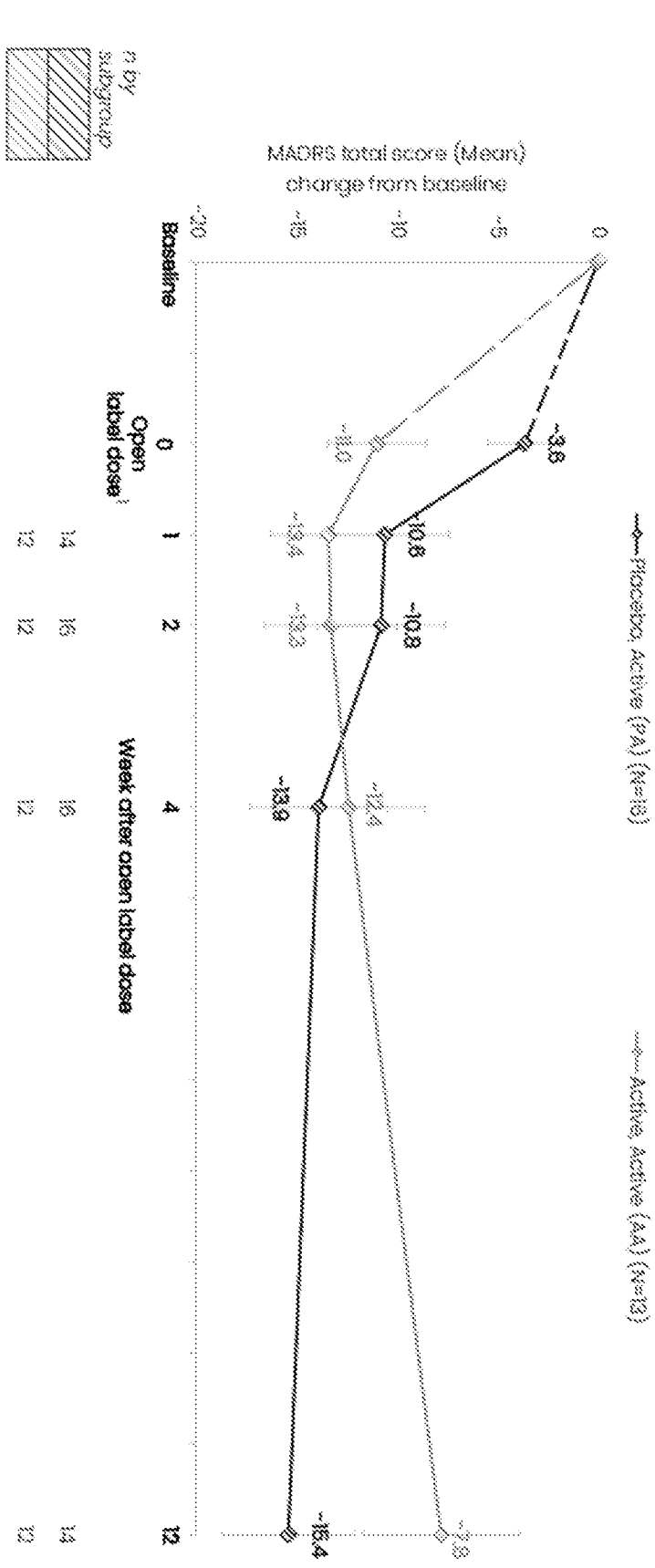

MADRS total score (Mean) change from baseline
0
-2
-4
-6
-8
-10
-12
-14
-16
Placebo (N=17)
Active (N=17)
-10.7
-18
-21.0
-26.6
Key secondary endpoint
Difference -10.8
p=0.002**
Primary endpoint
Difference -7.4
p=0.022*
Week
Baseline
1
2
n by subgroup
Placebo
Active
17
17
17
16
16
17
17
17
Standard deviation
Placebo (N=17)
Active (N=17)
Week
1
2
6.0
7.7
10.4
10.1

FIGURE 5



1 represents MADRS score assessed prior to administration of open label dose

Figure 6

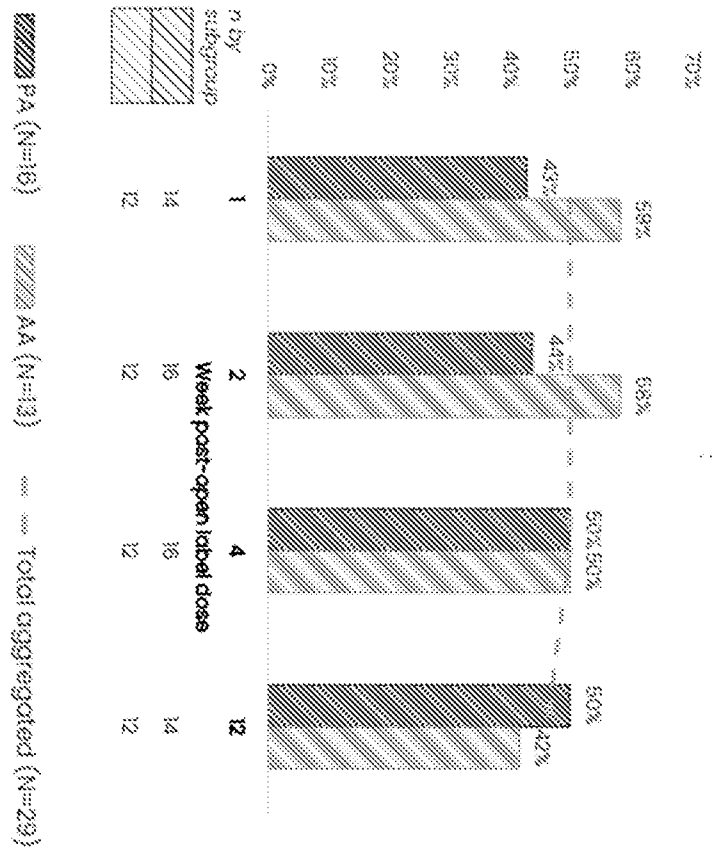
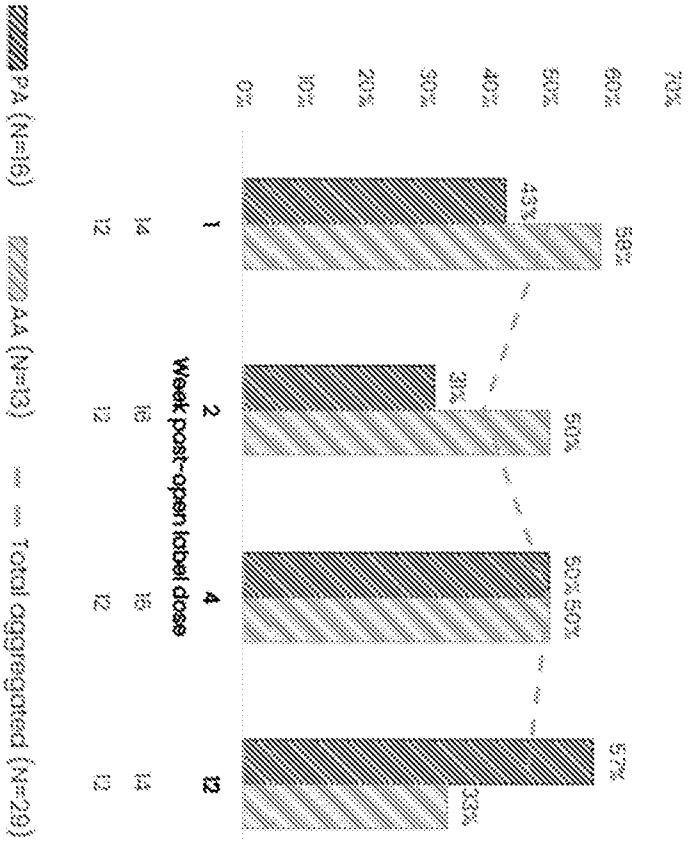


FIGURE 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/051569

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4045 A61P25/24
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, EMBL, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/082058 A1 (ELEUSIS THERAPEUTICS US INC [US]) 21 April 2022 (2022-04-21) page 1, line 12-28; page 2, line 7; page 13, line 14-32; page 19, line 13-31 ----- -/--	1,2,5,6, 9,10, 13-20, 22, 34-38, 41-47, 54-62, 65-69, 72,73, 76-83, 85, 97-101, 103-110, 116-120

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2024	25/04/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Borst, Markus

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 11 000 534 B1 (SIPPY BRADFORD [US]) 11 May 2021 (2021-05-11) column 2, line 1-31; column 18, line 48 - column 19, line 47; column 23, line 45-58; column 30, line 30-62; column 32, line 16-25	1-8,13, 19,20, 22,25, 34-43, 45-47, 54, 58-71, 76,77, 82,83, 85,88, 97-106, 108-110, 116-118
Y	D'SOUZA DEEPAK CYRIL ET AL: "Exploratory study of the dose-related safety, tolerability, and efficacy of dimethyltryptamine (DMT) in healthy volunteers and major depressive disorder", NEUROPSYCHOPHARMACOLOGY, vol. 47, no. 10, 3 June 2022 (2022-06-03), pages 1854-1862, XP93151441, Cham ISSN: 0893-133X, DOI: 10.1038/s41386-022-01344-y Retrieved from the Internet: URL:https://www.nature.com/articles/s41386-022-01344-y> abstract; sections "General study design", "Drugs", "Test sessions" on page 1855; section "Subjective effects" on page 1156-7; figure 2	1-120
Y	KRISTOFFER A. A. ANDERSEN: "Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies", ACTA PSYCHIATRICA SCANDINAVICA., vol. 143, no. 2, 1 December 2020 (2020-12-01), pages 101-118, XP93152649, DE ISSN: 0001-690X, DOI: 10.1111/acps.13249 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1111/acps.13249> abstract; Box: "Summations" on page 102; section "4.2 Long-lasting therapeutic effects" on page 111; figure 1	1-120

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2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARKER STEVEN A ED - SPOOREN WILL ET AL: "Administration of N,N-dimethyltryptamine (DMT) in psychedelic therapeutics and research and the study of endogenous DMT", PSYCHOPHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 239, no. 6, 22 January 2022 (2022-01-22), pages 1749-1763, XP037860918, ISSN: 0033-3158, DOI: 10.1007/S00213-022-06065-0 [retrieved on 2022-01-22] section "2. Administration of DMT with and without a MAOI: doses, routes, and effects" on page 1751-2; section "How do we best administer therapeutic or research doses of DMT?" on page 1753-4;	1-120
A	Anonymous: "Record History ¦ ver. 4: 2023-01-18 ¦ NCT05553691 ¦ ClinicalTrials.gov", , 18 January 2023 (2023-01-18), pages 1-11, XP093152700, Retrieved from the Internet: URL:https://clinicaltrials.gov/study/NCT05553691?tab=history&a=4 the whole document	1-120
A	Anonymous: "Record History ¦ ver. 4: 2023-01-18 ¦ NCT05553691 ¦ ClinicalTrials.gov", , 18 January 2023 (2023-01-18), pages 1-11, XP93152700, Retrieved from the Internet: URL:https://clinicaltrials.gov/study/NCT05553691?tab=history&a=4 the whole document	1-120
X,P	Anonymous: "Small Pharma Reports Positive Top-line Results from Phase", Globe Newswire, 25 January 2023 (2023-01-25), pages 1-10, XP93151567, Retrieved from the Internet: URL:https://www.globenewswire.com/en/news-release/2023/01/25/2594976/0/en/Small-Pharma-Reports-Positive-Top-line-Results-from-Phase-IIa-Trial-of-SPL026-in-Major-Depressive-Disorder.html [retrieved on 2024-04-15] section "Durability of antidepressant effect" on page 2	1-120

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/051569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022082058 A1	21-04-2022	NONE	
US 11000534 B1	11-05-2021	US 11000534 B1	11-05-2021
		US 2022110955 A1	14-04-2022
		US 2024000815 A1	04-01-2024