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(54) Title: 5-METHOXY-N,N-DIMETHYLTRYPTAMINE FOR THE TREATMENT OF SOCIAL/EMOTIONAL WITHDRAWAL OR DETACHMENT

(57) Abstract: 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or a pharmaceutically acceptable salt thereof is used in treating a patient who is suffering from social/emotional withdrawal or detachment.

5-METHOXY-N,N-DIMETHYLTRYPTAMINE FOR THE TREATMENT OF SOCIAL/EMOTIONAL WITHDRAWAL OR DETACHMENT

Technical Field

The present invention is directed to improved methods for the treatment of social/emotional withdrawal or detachment, in particular social/emotional withdrawal or detachment in a patient suffering from a mental or nervous system disorders, such as disorders characterized by depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorders due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disorders, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorders; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); and Personality Disorders, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD).

The social/emotional withdrawal or detachment can also occur in a patient suffering from sleep disturbance, for instance, insomnia.

The social/emotional withdrawal or detachment may also occur in a patient suffering from a medical health condition leading to an associated mental or nervous system condition including Traumatic Brain Injury (TBI).

The treatment comprises administering to a patient in need thereof a therapeutically effective amount of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or of a pharmaceutically acceptable salt thereof.

Background of the Invention

Symptoms such as anhedonia, emotional withdrawal and affective flattening are clustered together here as social/emotional withdrawal or detachment. Reduced social engagement is a further aspect associated with social/emotional withdrawal or detachment.

Anhedonia is the inability to experience pleasure. A patient suffers from anhedonia if there is subjectively a reduced ability to experience pleasure in usual activities. Anhedonia comprises consummatory (or liking) and anticipatory (or wanting) components. Consummatory pleasure refers to the “in the moment” pleasure experienced by the subject directly engaged in an enjoyable activity, whereas anticipatory pleasure refers to the experience of pleasure related to future activities.

Emotional withdrawal or detachment is an inability or unwillingness to connect with other people on an emotional level.

Affective flattening characterises the subjective sense of reduced intensity or range of feelings or emotions.

Reduced social engagement characterises subjective reports of reduced social and interpersonal engagement or interactions.

Social/emotional withdrawal or detachment can not only have a severe impact on the quality of life but can also lead to various secondary health problems.

Thus, there is a need for improved methods for the treatment of social/emotional withdrawal or detachment, in particular social/emotional withdrawal or detachment associated with a mental disorder or a nervous system disorder.

Summary of the Invention

An aim of the invention is in particular the provision of improved therapies which are more effective (i.e., a) a larger percentage of patients experiencing a clinical response, b) a larger average clinical response, c) an earlier onset of the clinical response, and/or d) a more durable clinical response) than previously described therapies.

A further aim of the current invention is to provide a compound for improved psychoactive therapies and dosing regimens for said therapies which have a better safety profile and/or are better tolerated than previously described therapies. Another aim of the current invention is to provide a compound for improved psychoactive therapies and dosing regimens for said therapies which are more convenient than previously described therapies. Another aim of the current invention is to provide a compound for improved psychoactive therapies and dosing regimens for said therapies which are associated with higher rates of patient compliance (including higher rates of treatment initiation) than previously described therapies. A still further aim of the current invention is to identify specific disease aspects and specific subgroups of disease aspects which benefit from such improved psychoactive therapies.

The present invention provides 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or a pharmaceutically acceptable salt thereof for use in treating a patient suffering from social/emotional withdrawal or detachment, in particular symptoms such as anhedonia, emotional withdrawal, affective flattening and/or reduced social engagement.

The present invention provides improved methods for the treatment of social/emotional withdrawal or detachment, in particular social/emotional withdrawal or detachment in a patient suffering from a mental or nervous system disorder, such as disorders characterized by depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorders due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disorders, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorders; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); and Personality Disorders, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD).

The invention also provides improved methods for the treatment of social/emotional withdrawal or detachment in a patient suffering from sleep disturbance, for instance, insomnia.

The invention also provides improved methods for the treatment of social/emotional withdrawal or detachment in a patient suffering from a medical health condition leading to an associated mental or nervous system condition including Traumatic Brain Injury (TBI).

The present invention also provides dose ranges and dosing regimen useful for the treatment of social/emotional withdrawal or detachment, in particular anhedonia, emotional withdrawal, affective flattening and/or reduced social engagement.

Detailed Description of the Invention

Definitions

As used in the context of the present invention, unless otherwise noted, the term "5-MeO-DMT" refers to the free base 5-MeO-DMT. It is contemplated that pharmaceutically acceptable salts of 5-MeO-DMT may also be used. Such salts are in particular acid addition salts, wherein the acid may be selected from, for instance, acetic acid, benzoic acid, citric acid, fumaric acid, hydrobromic acid, hydrochloric acid, hydrofluoric acid, hydroiodic acid, oxalic acid, succinic acid and triflic acid. A preferred example is the hydrobromide salt. The appropriate weight amount of a salt to be administered can be calculated from the weight amount of the free base, assuming that equimolar amounts are used.

As used in the context of the present invention, a "patient" to be treated is a human subject who is suffering from social/emotional withdrawal or detachment by a licensed professional in accordance with accepted medical practice or who is diagnosed by a licensed professional in accordance with accepted medical practice with a mental disorder or a nervous system disorder associated with social/emotional withdrawal or detachment. In the latter case, assessing social/emotional withdrawal or detachment may or may not be part of the diagnosis.

Diagnosis of a mental disorder or a nervous system disorder can, for instance, be in accordance with the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edi-

tion (DSM-5) published by the American Psychiatric Association. In some instances, as is apparent from the discussion of specific conditions below, the criteria may be modified or supplemented to better define patients or patient groups particularly benefiting from a treatment according to the invention. The diagnosis will in any event be by a physician or a psychologist. It is not sufficient that the human subject himself/herself considers that he/she is suffering from the disorder.

As used in the context of the present invention, unless otherwise noted, the terms "treating" and "treatment" shall include the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of compounds and methods according to the present invention to alleviate the signs and/or symptoms of the disease or eliminate the disease, condition, or disorder.

"Treatment of social/emotional withdrawal or detachment" shall include the management and care of a patient for the purpose of combating social/emotional withdrawal or detachment and includes the administration of compounds and methods according to the present invention to alleviate the signs and/or symptoms of social/emotional withdrawal or detachment or eliminate social/emotional withdrawal or detachment.

Social/emotional withdrawal or detachment may be associated with sleep disturbance, for instance, insomnia, a mental disorder or a nervous system disorder or another medical condition.

The patient may suffer from treatment resistant disease. Treatment resistance means that the patient had no adequate improvement after at least two adequate courses of therapy. The patient in particular had no adequate improvement after at least two adequate courses of therapy, wherein at least one of the two courses was a pharmacotherapy; for instance, the patient had no adequate improvement after at least two adequate courses of pharmacotherapy. The at least two prior courses of treatment were in particular administered in the current episode of the disease, for instance, if the patient suffers from a disorder characterized by depressive episodes, in the current episode of depression.

As used in the context of the present invention, unless otherwise noted, the term "therapeutically effective amount" shall mean the amount of active compound or pharmaceutical ingredient that elicits the biological or clinical response in a human that is being

sought by a researcher, medical doctor or other clinician, which includes alleviation of the signs and/or symptoms of the disease, condition or disorder being treated.

"Clinical response" includes, but is not limited to, improvements on rating scales. These scales assess (i) social/emotional withdrawal or detachment or aspects of social/emotional withdrawal or detachment and/or (ii) a mental disorder or nervous system disorder or aspects of such a disorder (iii) a medical health condition leading to an associated mental or nervous system condition and/or (iv) sleep.

The severity of a condition as well as changes of the severity can be assessed by the Clinical Global Impression (CGI) rating scales which are measures of symptom severity, treatment response and the efficacy of treatments.

The CGI rating scales were developed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after a treatment (Busner, J. and Tagrum, S. D., 2007. The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry 2007, 29-37).

The CGI-Severity (CGI-S) is based on one question the clinician has to answer: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" This is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

The CGI-S can be used to assess treatment success by comparing scores before and after treatment.

A clinical response may be reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score. According to the invention, a reduction in the CGI-S score means that the CGI-S is reduced by at least 1. Preferably, the CGI-S is reduced by at least 2 and/or to a score of 0. It is especially preferred if the CGI-S is reduced by at least 3 and/or to a score of 0.

Alternatively, treatment success can be assessed using the CGI-Improvement (CGI-I), which is similarly simple in its format. After the treatment, the clinician compares the patient's overall clinical condition to the one prior to the treatment (the so-called baseline value). Again, only one query is rated on a seven-point scale: "Compared to the patient's condition at admission to the project [prior to medication initiation], this pa-

tient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment."

The Patient Global Impression scale (PGI), also known as Subject Global Impression (SGI), is the counterpart to the Clinical Global Impressions scale (CGI). It consists of one item based on the CGI and adapted to the patient. It can measure disease severity (PGI-S) or disease improvement (PGI-I).

Individual items of scales as described herein as well as sub-combinations of individual items may be used to assess specific disease aspects.

As used in the context of the present invention, unless otherwise noted, the term "administration" (or "application") shall mean the introduction of an amount, which may be a predetermined amount, of active compound or pharmaceutical ingredient into a patient via any route. Preferably, the active compound is administered by inhalation, nasally, by buccal administration or by sublingual administration.

As used in the context of the present invention, unless otherwise noted, the terms "dose" and "dosage" and "dosage amount" shall mean the amount of active compound or pharmaceutical ingredient which is administered to a patient in an individual administration. The term "dosage regimen" (or "dosing regimen") shall mean a defined sequence of one or more individual administrations.

As used herein, "aerosol" means a stable system consisting of a gaseous medium (a pharmaceutically acceptable gas, such as air) and miniscule suspended solid and/or liquid particles. The term "degradation product" refers to a compound resulting from a chemical modification of 5-MeO-DMT as a result of a chemical reaction during aerosol formation. Such reaction includes, without limitation, oxidation. When a percentage of a "degradation product" is described in the context of the present invention, then this refers to the quantity of 5-MeO-DMT degradation products present in a sample divided by the quantity of 5-MeO-DMT plus 5-MeO-DMT degradation products present in the sample multiplied by 100%, i.e., (Sum of quantities of all 5-MeO-DMT degradation products present in the sample) / ((Quantity of 5-MeO-DMT present in the sample) + (Sum of quantities of all 5-MeO-DMT degradation products present in the sample)) x 100%. As used herein, the term "impurity" refers to unwanted compounds contaminat-

ing a sample of 5-MeO-DMT (or of a pharmaceutically acceptable salt thereof). Impurities may be contained in the starting material before aerosol formation or may be degradation products.

The term "purity" refers to 100% minus the percent of all 5-MeO-DMT degradation products and all other impurities present, i.e., 100% - (Sum of quantities of all 5-MeO-DMT degradation products present + Sum of quantities of all other impurities present) / (Quantity of 5-MeO-DMT present + Sum of quantities of all 5-MeO-DMT degradation products present + Sum of quantities of all other impurities present) x 100%.

The term "mass median aerodynamic diameter" (MMAD), is the diameter at which 50% of the particles present in an aerosol are larger than this calculated diameter, and 50% are smaller. The term "aerosol particle mass density" refers to the mass of aerosol particles per unit volume of aerosol. The term "aerosol particle formation rate" refers to the aerosolized mass of 5-MeO-DMT per unit of aerosolization time.

Social/Emotional Withdrawal or Detachment

Symptoms such as anhedonia; emotional withdrawal and affective flattening are clustered together here as social/emotional withdrawal or detachment. Reduced social engagement is a further aspect associated with social/emotional withdrawal or detachment.

Anhedonia is the inability to experience pleasure. The patient does not suffer from anhedonia if there is subjectively no reduced ability to experience pleasure in usual activities. Anhedonia is mild in the case of slight reduction in pleasure from usually pleasurable activities; moderate in the case of significant reduction in pleasure from usually pleasurable activities or some pleasure from isolated activities retained; or severe in the case of complete inability to experience pleasure.

Anhedonia comprises consummatory (or liking) and anticipatory (or wanting) components. Consummatory pleasure refers to the “in the moment” pleasure experienced by the subject directly engaged in an enjoyable activity, whereas anticipatory pleasure refers to the experience of pleasure related to future activities.

Affective flattening characterises the subjective sense of reduced intensity or range of feelings or emotions. The subject does not show affective flattening if there is no sense of reduced intensity or range of feeling or emotions. It is mild in the case of slight constriction of range of affect, or transient reduction in range or intensity of feelings; moderate in the case of significant constriction of range or intensity of feelings with preservation of some emotions, *e.g.*, inability to cry; and severe in the case of marked and pervasive constriction of range of affect or inability to experience usual emotions.

Emotional withdrawal or detachment is an inability or unwillingness to connect with other people on an emotional level. For example, the BPRS contains an item relating to emotional withdrawal, which is characterised as the deficiency in the subject's ability to relate emotionally during the interview situation. According to the description of this BPRS item, there is no emotional withdrawal if there is no lack of emotional involvement shown by occasional failure to make reciprocal comments, occasionally appearing preoccupied, or smiling in a stilted manner, but spontaneously engages the interviewer most of the time. There is a mild form of emotional withdrawal if there is a lack of emotional involvement shown by noticeable failure to make reciprocal comments, appearing preoccupied, or lacking in warmth, but responds to the interviewer when approached. It is moderate if the emotional contact is not present much of the interview because the subject does not elaborate responses, fails to make eye contact, does not seem to care if the interviewer is listening, or may be preoccupied with psychotic material. It is moderately severe if, in addition, emotional contact is not present most of the interview. Severe forms are present if emotional participation is actively avoided by the subject or if the subject is frequently unresponsive or responds with yes/no answers or responds with only minimal affect. It is extremely severe if the subject consistently avoids emotional participation, is unresponsive or responds with yes/no answers or may leave during the interview or just not respond at all.

Reduced social engagement characterises subjective reports of reduced social and interpersonal engagement or interactions. There is no reduced social engagement if there are no reports of reduced social and interpersonal engagement or interactions. It is mild in the case of slight reduction in social engagement with no impairment in social or interpersonal function; moderate in the case of clear reduction in social engagement with some functional sequelae, *e.g.*, avoiding some social engagements or conversations; and severe in the case of marked reduction in social interaction or avoidance of

almost all forms of social contact, *e.g.*, refusing to answer the phone or see friends or family.

Social/emotional withdrawal or detachment can be associated with a mental disorder or a nervous system disorder or some other medical conditions.

Mental or nervous system disorders which lead to, or are associated with, social/emotional withdrawal or detachment include disorders characterized by depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorders due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disorders, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorders; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); and Personality Disorders, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD).

The social/emotional withdrawal or detachment can also occur in a patient suffering from sleep disturbance, for instance, insomnia.

The social/emotional withdrawal or detachment can also occur in a patient suffering from medical health conditions leading to an associated mental or nervous system condition include Traumatic Brain Injury (TBI).

Measuring Social/Emotional Withdrawal or Detachment

Social/emotional withdrawal or detachment or individual aspects thereof, such as anhedonia, emotional withdrawal and affective flattening, can be evaluated by different instruments, such as questionnaires or scales.

Questionnaires assess the mental status of a patient based on observations made by the patient himself/herself, caregivers or the clinician administering the questionnaire. Questionnaires used to assess whether a patient suffers from a particular mental or nervous system disorder may comprise items related to social/emotional withdrawal or detachment.

The Snaith-Hamilton Pleasure Scale (SHAPS) is a 14-item scale that measures anhedonia, i.e., the inability to experience pleasure. The items cover the domains of: social interaction, food and drink, sensory experience, and interest/pastimes. A score of 2 or less constitutes a “normal” score, while an “abnormal” score is defined as 3 or more. Each item has four possible responses: strongly disagree, disagree, agree, or strongly agree. Either of the “disagree” responses score one point, and either of the “agree” responses score 0 points. Thus, the final score ranges from 0 to 14. The SHAPS has adequate construct validity and satisfactory test-retest reliability. High internal consistency has also been reported. The SHAPS has been used for measuring anhedonia in depression, but it is also frequently used to assess anhedonia in other patient groups.

In principle, the SHAPS measures hedonic tone during the last few days with 14 hypothetically formulated items. However, due to the hypothetical nature of the items an appropriate shorter recall period can also be applied for an earlier assessment time point.

Alternatively or additionally, the Dimensional Anhedonia Rating Scale (DARS) measuring interest, motivation, effort and consummatory pleasure across four domains: hobbies, food/drink, social activities and sensory experience can be used for the assessment of anhedonia. It comprises 17 items assessing state anhedonia right now. The DARS is rated on a five-point Likert scale from 0 (not at all) to 4 (very much), higher values indicating less anhedonia. All items are summed up to a total score in the range of 0 to 68. For each of the four hedonic domains, hobbies (four items, sum score 0–16), food/drink (four items, sum score 0–16), social activities (four items, sum score 0–16) and sensory experiences (5 items, sum score 0–20), participants are asked to provide two or three of their own favourite examples.

The Personality Inventory for DSM-5 (PID-5) – Adult is a 220 item self-rated personality trait assessment scale for adults age 18 and older. It assesses 25 personality trait facets including Anhedonia, Anxiousness, Attention Seeking, Callousness, Deceitfulness,

Depressivity, Distractibility, Eccentricity, Emotional Lability, Grandiosity, Hostility, Impulsivity, Intimacy Avoidance, Irresponsibility, Manipulativeness, Perceptual Dysregulation, Perseveration, Restricted Affectivity, Rigid Perfectionism, Risk Taking, Separation Insecurity, Submissiveness, Suspiciousness, Unusual Beliefs and Experiences, and Withdrawal, with each trait facet consisting of 4 to 14 items.

The trait facet Anhedonia contains the items 1, 23, 26, 30R, 124, 155R, 157, 189 (reverse scored items are marked with the letter “R”), the trait facet Withdrawal contains the items 10, 20, 75, 82, 136, 146, 147, 161, 182, 186 and the trait facet Intimacy Avoidance contains the items 89, 97R, 108, 120, 145, 203. These three trait facets can be combined to yield the broader trait domain designated Detachment.

The measure is completed by the individual prior to a visit with the clinician. Each item asks the individual to rate how well the item describes him or her generally.

Each item on the measure is rated on a 4-point scale. The response categories for the items are 0=very false or often false; 1=sometimes or somewhat false; 2=sometimes or somewhat true; 3=very true or often true. For items 7, 30, 35, 58, 87, 90, 96, 97, 98, 131, 142, 155, 164, 177, 210, and 215, the items are reverse-coded prior to entering into scale score computations.

The scores on the items within each trait facet should be summed and entered in the appropriate raw facet score box. In addition, the clinician is asked to calculate and use average scores for each facet and domain. The average scores reduce the overall score as well as the scores for each domain to a 4-point scale, which allows the clinician to think of the individual’s personality dysfunction relative to observed norms. The average facet score is calculated by dividing the raw facet score by the number of items in the facet (e.g., if all the items within the “Anhedonia” facet are rated as being “sometimes or somewhat true,” then the average facet score would be 16/8 = 2, indicating moderate anhedonia). An average domain score is calculated by summing and then averaging the 3 facet scores contributing primarily to the specific domain. For example, if the average facet scores on Anhedonia, Intimacy Avoidance and Withdrawal (scales primarily indexing Detachment) are all 2, then the sum of these scores would be 6, and the average domain score would be 6/3 = 2. Higher average scores indicate greater dysfunction in a specific personality trait facet or domain.

High scores on a facet or domain may indicate significant and problematic areas for the individual receiving care that might warrant further assessment, treatment, and follow-up.

Scales to Assess Mental and Nervous System Disorders

Numerous scales have been suggested to assess severity of a mental disorder or a nervous system disorder. Such scales are based on tests which can be self-administered or administered by a clinician.

Scales which may be used according to the invention include those known in the art for diagnosis and/or monitoring the mental or nervous system disorders discussed in more detail below.

Treatment outcome is assessed by using one or more indices or scales at one or more time points after completion of a treatment course.

The assessment can be carried out after the acute psychedelic experience has subsided. An appropriate point in time for an early assessment is generally about 2 to 3 hours after the last administration. An early assessment can generally be carried out, for instance, about 2 hours or about 3 hours after the last administration.

An assessment of an effect on sleep disturbance can, however, be carried out at the earliest on the day after the treatment (i.e., on day 1) so that the treated patient had the opportunity to sleep for at least one night.

Thus, an assessment at day 1 or on day 1 means an assessment on the day following the administration. The assessment will be carried out not earlier than 12 hours after the last administration and in any event not earlier than one night after the last administration and not later than 36 hours after the last administration. The assessment can be carried out after about 24 hours.

An assessment at day 7 or on day 7 means an assessment on the seventh day following the administration (the day of administration is day 0). Analogous definitions apply for other assessment timings measured in days.

When assessing a clinical response, for instance, using one of the scales to assess severity of a mental disorder or a nervous system disorder, at an early timepoint after

drug administration (e.g. at 2 hours) based on endpoints which have been developed for a longer recall period (e.g. normally 7 days for the MADRS), a rational modification of such endpoint (e.g. changing the MADRS recall period to 2 hours and carrying forward the sleep item recorded at baseline before drug administration) may be applied. The same applies with respect to any other scale applied herein, unless a recall period is specifically indicated.

The considerations outlined apply for early timepoints because, on the one hand, in order to assess a clinical response, the influence of the patient's status before the treatment on any score recorded after treatment should be kept as low as possible, whereas on the other hand the sleep item cannot be assessed 2 hours after drug administration.

At later timepoints, for instance, on day 1 or later, typically all items of the relevant scales to assess a clinical response can be assessed, using, if necessary, an adapted recall period, so that it is not necessary to carry forward any pre-treatment score.

Resting State Networks and Social/Emotional Withdrawal or Detachment

Brain processes can be studied by functional magnetic resonance imaging (fMRI). Brain activity is associated with blood flow, and temporal correlations of spontaneous blood oxygen level dependent (BOLD) signal fluctuations between different brain areas can be measured.

Functional images of the brain are acquired over the course of several minutes. Patterns of low-frequency BOLD signal oscillation are observed across the brain. The decomposition of this spontaneous signal reveals distributed areas with correlated and anti-correlated fluctuations.

In this way, resting-state fMRI can be used to characterize large-scale functional networks, so-called resting-state networks (RSN), which are a set of spatially distinct brain regions that show coordinated activity in the absence of any explicit cognitive task (i.e., at rest). The observed patterns, characterizing a network of brain regions with coherent patterns of signal variation, are called resting-state networks (RSN).

Different resting state networks have been identified and named mostly on the basis of spatial similarity between the resting state networks and activation patterns seen in task fMRI experiments.

Resting-state fMRI can therefore be used to assess the intrinsic functional organization of the brain. Resting-state networks have been characterized for aspects of attention, memory, cognitive control, default mode, motor, and sensory system.

RSNs have been shown to be responsible for various aspects of complex brain function, and it has been found that these connectivity networks are compromised in various disease states. Such disease states, which include certain forms of social/emotional withdrawal or detachment, are associated with altered functional connectivity within a specific resting state network and/or between one or more regions in one or more additional resting state networks.

Alterations in RSNs are also involved in anhedonia, which is one key aspect of social/emotional withdrawal or detachment. More specifically, anhedonia is associated with visual network hyperconnectivity and expansion of the visual network, dorsal attention network (DAN), and default mode network (DMN). Anhedonia also involves decreased between-network connectivity among the DMN, salience, DAN, somatomotor, and visual networks.

In addition, emotional detachment in adult psychopathy has been associated with structural abnormalities in the dorsal DMN. The dorsal DMN is of particular interest in the development of psychopathy due to the functions associated with it. Specifically, the dorsal DMN, and the regions it connects (the medial prefrontal cortex and posterior cingulate cortex (PCC)), underpin affective, social and moral processing. In adult psychopathy, microstructural abnormalities within the dorsal DMN are linked to the affective and interpersonal differences that define the disorder.

Thus, patients suffering from social/emotional withdrawal or detachment show altered functional connectivity within and/or between RSNs when compared to healthy, age-matched controls. Alterations are observed within and/or between the DMN, the salience, DAN, somatomotor, and visual networks.

In many instances, RSNs involved in social/emotional withdrawal or detachment are affected by mental or nervous system disorders, such as disorders characterized by

depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorders due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disorders, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorders; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); and Personality Disorders, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD).

Resting state networks involved in social/emotional withdrawal or detachment are also affected by mental or nervous system conditions which are a consequence of certain medical health conditions, such as Traumatic Brain Injury (TBI).

Resting state networks involved in social/emotional withdrawal or detachment are also affected by sleep disturbance, for instance, insomnia. In fact, social/emotional withdrawal or detachment and impairment of sleep are correlated.

Treatment of Social/Emotional Withdrawal or Detachment and Mental or Nervous System Disorders

According to the invention, social/emotional withdrawal or detachment occurring in a patient suffering from a mental disorder or a nervous system disorder can be treated. Moreover, social/emotional withdrawal or detachment occurring in a patient suffering from sleep disturbance, for instance, insomnia, can be treated.

In patients suffering from social/emotional withdrawal or detachment in association with another condition as detailed above, a treatment of social/emotional withdrawal or detachment according to the invention leads to an improvement of the condition with which the social/emotional withdrawal or detachment is associated.

Treatment according to the invention is by administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

5-MeO-DMT administered to a patient disrupts established functional connectivity patterns within and/or between resting state networks. This disruption leads to a reset of the pathological ill-connected connections as the networks reconnect. New, healthy functional connections are established with persistent effects.

Thus, according to the invention, influencing those networks by a therapy as described herein will lead to an improvement of the social/emotional withdrawal or detachment and, if the patient treated suffers from a mental disorder or a nervous system disorder, also of that disorder; if the patient treated suffers from sleep disturbance, for instance, insomnia, also of the sleep disturbance, for instance, insomnia.

To further support the clinical application of 5-MeO-DMT in patients suffering from social/emotional withdrawal or detachment, the inventors assessed clinical data relating to the use of 5-MeO-DMT in patients treated because of mental disease and noted particular improvements in social/emotional withdrawal or detachment which is typically also observed in patients with other disorders.

The data stem from a recently completed clinical trial investigating the use of 5-MeO-DMT in the treatment of patients diagnosed with Treatment Resistant Depression (TRD; see also the examples section below). While TRD is a specific condition, the inventors determined, as discussed in detail below, that certain clinical observations are made in the trial are relevant for devising a treatment for other conditions which are associated with social/emotional withdrawal or detachment.

In the clinical trial, 5-MeO-DMT was administered via inhalation (as described in more detail in the example section below). Patients were assigned to different groups. In the context of the present invention, the group who received a single, 12 mg dose and the group who underwent an intra-day individualized dosing regimen (IDR) that allowed for multiple, escalating doses (6 mg, 12 mg and 18 mg) within a single day, driven by the intensity of the patient-reported psychedelic experience are of interest.

The data gathered include the assessment of the treated patients against several scales including the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Brief Psychiatric Rating Scale (BPRS). While the focus of the trial was on demonstrat-

ing treatment efficacy through improvements in overall MADRS score, the inventors focused on the items comprising the various rating scales and noticed that particular subscore items, like items related to social/emotional withdrawal or detachment, are relevant for other conditions in which social/emotional withdrawal or detachment is based on similarly altered functional connectivity within and/or between the default mode network, the salience, dorsal attention, somatomotor, and visual networks.

Multiple patients within the recruited cohort displayed significant improvements, a result that confirms the inventors' finding that 5-MeO-DMT is a compound suitable for treating patients presenting with these symptoms.

More in particular, an aspect which can be treated by administration of 5-MeO-DMT, is social/emotional withdrawal or detachment, in particular anhedonia, emotional withdrawal and/or affective flattening. A further treated aspect is reduced social engagement. 5-MeO-DMT can be administered to patients to reduce or eliminate social/emotional withdrawal or detachment, in particular anhedonia, emotional withdrawal and/or affective flattening, in said patients. In addition, reduced social engagement is improved, i.e. it is reduced or eliminated.

The MADRS scale item "**inability to feel**", that is of particular relevance to social/emotional withdrawal or detachment, represents the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

A score of 0 indicates normal interest in the surroundings and in other people, a score of 2 indicates a reduced ability to enjoy usual interests. A score of 4 is assigned in case of a loss of interest in the surroundings and a loss of feelings for friends and acquaintances. A score of 6 reflects the experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

In the study group receiving the individualized dosing regimen, the aggregated score for the MADRS item "inability to feel" across all 8 patients was 36 at base line. After 2 hours, it was reduced to 12 which corresponds to an improvement of 24 points or 67%. At day 1 after treatment, it was reduced to 2 which corresponds to an improvement of 34 points or 94%. At day 7 after treatment, it was reduced to 6 which corresponds to an improvement of 30 points or 83%.

In the 12 mg group, the aggregated score for the MADRS item "inability to feel" across all 4 patients was 16 at base line. After 2 hours, it was reduced to 9 which corresponds to an improvement of 7 points or 44%. At day 1 after treatment, it was reduced to 1 which corresponds to an improvement of 15 points or 94%. At day 7 after treatment, it was reduced to 1 which corresponds to an improvement of 15 points or 94%.

The BPRS scale items which are of particular relevance to social/emotional withdrawal or detachment are "**inability to feel**" and "**blunted affect**".

The BPRS item "**emotional withdrawal**" relates to a deficiency in the patient's ability to relate emotionally during the interview situation. Possible scores are:

1 - No emotional withdrawal.

2 - Very Mild. Lack of emotional involvement shown by occasional failure to make reciprocal comments, occasionally appearing preoccupied, or smiling in a stilted manner, but spontaneously engages the interviewer most of the time.

3 - Mild. Lack of emotional involvement shown by noticeable failure to make reciprocal comments, appearing preoccupied, or lacking in warmth, but responds to interviewer when approached.

4 - Moderate. Emotional contact not present much of the interview because subject does not elaborate responses, fails to make eye contact, doesn't seem to care if interviewer is listening, or may be preoccupied with psychotic material.

5 - Moderately Severe. Same as "4" but emotional contact not present most of the interview.

6 - Severe. Actively avoids emotional participation. Frequently unresponsive or responds with yes/no answers (not solely due to persecutory delusions). Responds with only minimal affect.

7 - Extremely Severe. Consistently avoids emotional participation. Unresponsive or responds with yes/no answers (not solely due to persecutory delusions). May leave during interview or just not respond at all.

The aggregated score for the BPRS item "emotional withdrawal" was 13 at base line. After 3 hours, it was reduced to 8 which corresponds to an improvement of 5 points or

38%. At day 1 after treatment, it was reduced to 8 which corresponds to an improvement of 5 points or 38%. At day 7 after treatment, it was reduced to 8 which corresponds to an improvement of 5 points or 38%.

In the 12 mg group, the aggregated score for the BPRS item "emotional withdrawal" was 13 at base line. After 3 hours, it was reduced to 11 which corresponds to an improvement of 2 points or 15%. At day 1 after treatment, it was reduced to 8 which corresponds to an improvement of 5 points or 38%. At day 7 after treatment, it was reduced to 6 which corresponds to an improvement of 7 points or 54%.

The BPRS item "**blunted affect**" relates to a restricted range in emotional expressiveness of face, voice, and gestures as well as a marked indifference or flatness even when discussing distressing topics. Possible scores are:

1 - No blunted affect.

2 - Very Mild. Emotional range is slightly subdued or reserved but displays appropriate facial expressions and tone of voice that are within normal limits.

3 - Mild. Emotional range overall is diminished, subdued, or reserved, without many spontaneous and appropriate emotional responses. Voice tone is slightly monotonous.

4 - Moderate. Emotional range is noticeably diminished, patient doesn't show emotion, smile, or react to distressing topics except infrequently. Voice tone is monotonous or there is noticeable decrease in spontaneous movements. Displays of emotion or gestures are usually followed by a return to flattened affect.

5 - Moderately Severe. Emotional range very diminished, patient doesn't show emotion, smile or react to distressing topics except minimally, few gestures, facial expression does not change very often. Voice tone is monotonous much of the time.

6 - Severe. Very little emotional range or expression. Mechanical in speech and gestures most of the time. Unchanging facial expression. Voice tone is monotonous most of the time.

7 - Extremely Severe. Virtually no emotional range or expressiveness, stiff movements. Voice tone is monotonous all of the time.

The aggregated score for the BPRS item "blunted affect" was 15 at base line. After 3 hours, it was reduced to 11 which corresponds to an improvement of 4 points or 27%. At day 1 after treatment, it was reduced to 8 which corresponds to an improvement of 7 points or 47%. At day 7 after treatment, it was reduced to 8 which corresponds to an improvement of 7 points or 47%.

In the 12 mg group, the aggregated score for the BPRS item "blunted affect" was 11 at base line. After 3 hours, it was reduced to 8 which corresponds to an improvement of 3 points or 27%. At day 1 after treatment, it was reduced to 6 which corresponds to an improvement of 5 points or 45%. At day 7 after treatment, it was reduced to 5 which corresponds to an improvement of 6 points or 55%.

Thus, the scores of the scale items that are of particular relevance to social/emotional withdrawal or detachment, i.e., "inability to feel" (MADRS), “emotional withdrawal” (BPRS) and “blunted affect” (BPRS), are markedly improved. The inventors conclude that 5-MeO-DMT can be used to treat social/emotional withdrawal or detachment in patients, in particular in patients also suffering from a mental disorder or a nervous system disorder or a sleep disturbance, for instance insomnia.

Consequently, according to the invention, the treatment of a patient suffering from social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates social/emotional withdrawal or detachment.

The Active Agent

The above discussion shows that social/emotional withdrawal or detachment as such present a significant disease burden and deserve appropriate treatment.

The inventors considered that a carefully chosen hallucinogen may lead to an improved treatment of important aspects of social/emotional withdrawal or detachment and may lead to overall improvements of the condition.

One group of hallucinogens entails compounds which bind to the 5-hydroxytryptamine (5-HT) receptors, which are also referred to as serotonin receptors (described are 7 families 5-HT1 to 5-HT7 with several subtypes). Examples are lysergic acid diethylamide (LSD), psilocybin, and N,N-dimethyltryptamine (DMT). These serotonergic agents

are often referred to as "psychedelics", which emphasizes their predominant ability to induce qualitatively altered states of consciousness such as euphoria, trance, transcendence of time and space, spiritual experiences, dissolution of self-boundaries, or even near-death experiences, while other effects such as sedation, narcosis, or excessive stimulation are only minimal.

Chemically, serotonergic psychedelics are either phenylalkylamines or indoleamines, with the indoleamine class being divided into two subsets, ergolines and tryptamines, the latter being derived from tryptamine.

The various serotonergic psychedelics have different binding affinity and activation potency for various serotonin receptors, particularly 5-HT1A, 5-HT2A, and 5-HT2C, and their activity may also be modulated by interaction with other targets such as monoamine transporters and trace amine-associated receptors.

Recently published clinical studies which have used serotonergic psychedelic drugs such as LSD, psilocybin and DMT (using the shamanic brew Ayahuasca, which contains DMT) in certain mental disorders suggest that those compounds could provide an alternative to the currently available treatments for certain mental disorders. However, there are reports that these compounds can induce mania in patients suffering from depressive symptoms, and this may preclude their clinical use.

For instance, Lake et al. (Lake, C. R., Stirba, A. L., Kinneman, R. E. Jr, Carlson, B., Holloway, H. C., 1981. Mania associated with LSD ingestion. American Journal of Psychiatry. 138(11):1508-9) report about a patient who suffered a manic attack after ingesting LSD or an LSD analogue. The patient experienced acute symptoms of LSD intoxication, which resolved but were followed in about 3 weeks by a typical manic episode of psychotic magnitude. Hendin and Penn (Hendin, H.M., Penn, A. D., 2021. An episode of mania following self-reported ingestion of psilocybin mushrooms in a woman previously not diagnosed with bipolar disorder: A case report. Bipolar Disorders 23(4):1-3) report about an episode of mania following self- reported ingestion of psilocybin mushrooms. Szmulewicz et al. (Szmulewicz, A. G., Valerio, M. P., and Jose M Smith, J. M., 2015. Switch to mania after ayahuasca consumption in a man with bipolar disorder: a case report. International Journal of Bipolar Disorders (2015) 3:4) report on a switch to mania after consumption of ayahuasca, a DMT containing brew, in a man with bipolar disorder.

A further case report is found in Brown, T., Shao, W., Ayub, S., Chong, D., & Cornelius, C. (2017). A Physician's attempt to self-medicate bipolar depression with N, N-dimethyltryptamine (DMT). *Journal of Psychoactive Drugs*, *49*(4), 294-296.

The inventors considered that in order to avoid the induction of mania or hypomania or at least reduce the risk of induction of mania or hypomania, the compound administered must be appropriately chosen and preferably is administered in a particular dosing regimen.

The inventors identified 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) as a psychedelic of particular interest for use in therapy. 5-MeO-DMT has a distinct pharmacological profile which differs from that of other psychedelic compounds.

5-MeO-DMT is a potent, fast-acting, naturally occurring serotonin (5-HT) agonist, acting at both the 5-HT1A and the 5-HT2A receptor, with higher affinity for the 5-HT1A receptor subtype compared to other classical psychedelics.

Inhibition constants (K_i values) as further detailed on the example section below for psilocin (the dephosphorylated from of psilocybin which is formed after uptake of psilocybin), DMT and 5-MeO-DMT are 48, 38 and 1.80 nM, respectively, at 5-HT1A receptors located in the hippocampus of post-mortem human brain. Thus, 5-MeO-DMT exhibits high affinity and psilocin and DMT exhibit moderate affinity for 5-HT1A receptors. Inhibition constants (K_i values) for psilocin, DMT and 5-MeO-DMT are 37, 117 and 122 nM, respectively, at 5-HT2A receptors located in the frontal cortex of post-mortem human brain. Therefore, psilocin exhibits moderate/strong affinity and DMT and 5-MeO-DMT exhibit comparatively weak affinity for 5-HT2A receptors.

Relative to the other psychoactive compounds mentioned previously, 5-MeO-DMT displays an enhanced affinity for the 5-HT1A receptor, where it acts as a potent agonist. In the case of psilocin and DMT, there is an increased contribution of 5-HT2A binding, relative to 5-MeO-DMT, with the latter displaying the largest differential affinity for 5-HT1A over 5-HT2A of the three compounds. Therefore, 5-HT1A binding plays a much bigger role in the overall effect of 5-MeO-DMT relative to 5-HT2A binding compared to the other two compounds.

It has been reported that 5-HT1A agonism reduces impulsivity and aggression, whereas 5-HT2A agonism can result in short-term increases in these same traits. Further-

more, the dopamine system has been implicated in contributing to mania, with increased dopamine drive being linked to mania. LSD, psilocybin and DMT all display increased affinity for a variety of dopamine receptors relative to 5-MeO-DMT

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT can be administered to patients, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania in a patient suffering from a mental or nervous system disorder, including a disorder characterized by depressive episodes, for example, Major Depressive Disorder (MDD), Postpartum Depression (PPD), Persistent Depressive Disorder, Seasonal Affective Disorder and Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder; a Psychotic Disorder, such as Schizophrenia; or a personality disorder, such as Schizotypal Personality Disorder. The patient suffering from such a mental or nervous system disorder, treated according to the invention, does not experience treatment-emergent mania or hypomania.

It is also noted that reports of treatment-emergent mania or hypomania related to psychoactive substance use seem to indicate large quantities of the respective compounds (e.g., DMT/ayahuasca, psilocybin, LSD) were used.

The inventors' approach of sequential up-titration of 5-MeO-DMT significantly reduces the risk of excessive dose administration with its potential for attendant adverse events.

Still further, the induction by antidepressants of isolated events of hypomania has been reported in patients suffering from treatment resistant depression (TRD) (Bader, Cynthia D., and David L. Dunner. "Antidepressant-induced hypomania in treatment-resistant depression." Journal of Psychiatric Practice 13.4 (2007): 233-237). However, the recently concluded clinical trial of 5-MeO-DMT in TRD patients showed no evidence of hypomania induction.

5-MeO-DMT can induce peak experiences, i.e., experiences characterized by an emotional perspective shift, which is described as "loss of ego" which often culminates in an overwhelming sense of "oneness with the universe", more rapidly than other psychedelics and has a short duration of acute psychedelic effects (5 to 30 minutes after inhalation compared with several hours for e.g. oral psilocybin and oral LSD). These characteristics of 5-MeO-DMT are associated with an improved therapeutic profile which can be explained by specific alterations of Resting State Network (RSN) activity under 5-MeO-DMT treatment.

Furthermore, 5-MeO-DMT is a 5-HT7 receptor agonist showing high affinity towards the receptor. The inventors determined, using recombinant human 5-HT7 receptor, [^{3}H]LSD as a radio ligand and serotonin to estimate non-specific binding, a K_i of 2.3 nM.

Thus, besides the 5-HT1A and 5-HT2A receptors discussed above, 5-MeO-DMT also interacts with the 5-HT7 receptor. 5-MeO-DMT act as an agonist on this receptor and shows a high (nanomolar) binding affinity.

The 5-HT7 receptor has a role in neurogenesis, synaptogenesis and dendritic spine formation. It is, among other things, associated with central processes such as learning and memory, with sleep regulation and circadian rhythm and with nociception.

The 5-HT7 receptor is in particular expressed in the spinal cord, raphe nuclei, thalamus, hypothalamus including the suprachiasmatic nucleus, hippocampus, prefrontal cortex, striatal complex, amygdala and in the Purkinje neurons of the cerebellum.

The suprachiasmatic nucleus is the central pacemaker of the circadian timing system. It coordinates circadian rhythms in various brain regions. Disruption of this coordination will result in disease states, in particular disease states involving sleep disturbance. In patients suffering from sleep disturbance resting state functional connectivity analysis reveals alterations in functional connectivity between the suprachiasmatic nucleus and regions within the default mode network.

The expression of the 5-HT7 receptor in the suprachiasmatic nucleus corresponds to the function of the receptor in regulation of sleep/wake cycles. The inventors consider that this allows treatment of patients suffering from sleep disturbance by 5-MeO-DMT which acts on the receptor.

The inventors consider that binding of 5-MeO-DMT to the 5-HT7 receptor as one mediator of the pharmacological effects of 5-MeO-DMT, which involve functional connectivity "resets" of networks and neuroplasticity effects, contributes to the beneficial effects of 5-MeO-DMT in the treatment of patients suffering from sleep disturbance.

The inventors further consider that binding of 5-MeO-DMT to the 5-HT7 receptor as well as to the 5-HT1A receptor as two mediators of effects exerted by 5-MeO-DMT, which include functional connectivity "resets" of networks and neuroplasticity effects, allows achieving beneficial effects also in patients suffering from other symptoms or

conditions, such as cognitive dysfunction, anxiety, psychomotor retardation, negative thinking or sleep disturbance. This is supported by the clinical results demonstrated in studies referred to herein.

Another feature of 5-MeO-DMT is its short half-life.

5-MeO-DMT is mainly inactivated through a deamination pathway mediated by monoamine oxidase A, and it is O-demethylated by cytochrome P450 2D6 (CYP2D6) enzyme.

The inventors investigated pharmacokinetic properties of 5-MeO-DMT and observed rapid absorption and distribution of inhaled 5-MeO-DMT, with maximum concentrations and pharmacological effects observed during and immediately after dosing.

An analysis of the pharmacokinetic properties of 5-MeO-DMT after inhalation shows a very rapid decline of the plasma concentration. Already 10 minutes after administration, the concentration drops to 10 % of Cmax or below; after 2 hours, it is 1 % of Cmax or below; after 3 hours, 5-MeO-DMT is no longer detectable in the plasma. This applies over the whole dose range tested (6 mg, 12 mg, 18 mg). No accumulation is observed upon repeated administration within a time frame of 1 to 4 hours. Uptitration as disclosed herein will not lead to accumulation and thus not to higher plasma concentrations, for instance, 10 minutes, 2 hours, or 3 hours after administration.

The properties of 5-MeO-DMT make the compound especially suitable for the treatment of social/emotional withdrawal or detachment, in particular for patients suffering from a mental disorder or a nervous system disorder.

The properties of 5-MeO-DMT also allow specific dosage regimens, as discussed in more detail below.

According to the invention, isotopic variants of 5-MeO-DMT and pharmaceutically acceptable salts thereof can also be used. When reference is made to the use of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, the use of isotopic variants is also contemplated.

These variants are in particular deuterated forms of 5-MeO-DMT and pharmaceutically acceptable salts of such forms.

Deuterated forms of 5-MeO-DMT are forms having a higher deuterium content than expected based on the natural abundance of this isotope.

Deuterated forms of 5-MeO-DMT are in particular forms wherein deuterium has been introduced at one or more defined hydrogen positions.

Examples of deuterated forms of 5-MeO-DMT include, without limitation, 1-deuterio-2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, 1,1-dideuterio-2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, 1,1,2,2-tetradeuterio-2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, and N,N-dimethyl-2-[5-(trideuteriomethoxy)-1H-indol-3-yl]ethanamine.

Further examples include forms of 5-MeO-DMT wherein deuterium has been introduced at one or more hydrogen positions of the N-bound methyl groups. Still further examples include forms of 5-MeO-DMT wherein one or more deuterium atoms replace hydrogen atoms of the indole ring system. It is moreover noted that combinations of the above substitution patterns are also contemplated.

Preparation methods for these compounds are known in the art.

According to the invention, mixtures of deuterated forms of 5-MeO-DMT, mixtures of one or more deuterated form with non-deuterated 5-MeO-DMT, pharmaceutically acceptable salts of deuterated forms of 5-MeO-DMT, mixture of such salts as well as mixtures of salts of deuterated and non-deuterated 5-MeO-DMT can also be used.

Further according to the invention, deuterated 5-MeO-DMT and salts of deuterated 5-MeO-DMT are used in amounts that are equimolar to the amounts of the corresponding non-deuterated forms.

According to the invention, prodrugs of 5-MeO-DMT and pharmaceutically acceptable salts of such prodrugs can also be used. Such prodrugs of 5-MeO-DMT can be metabolically converted to 5-MeO-DMT. Thus, when reference is made to the use of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, this can be replaced by a 5-MeO-DMT prodrug or a salt thereof.

In suitable prodrugs, the hydrogen in position 1 of the indole moiety is substituted by an organic moiety which can be split off after administration.

Examples of suitable organic moieties are -C(O)OR^1, -C(O)R^2, -CH(R^3)OR^4, -C(O)OCH(R^3)OC(O)R^4, -C(O)OCH(R^3)OC(O)OR^4, -CH(R^3)C(O)R^4, -CH(R^3)OC(O)R^4, -CH(R^3)OC(O)OR^4, wherein each of R^1, R^2, R^3, and R^4 is independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each alkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, aryl, and heteroaryl is independently substituted or unsubstituted.

Preferred examples of organic moieties are -CH(R^3)OC(O)R^4 and -C(O)OR^1, wherein R^1, R^3, and R^4 are defined as above.

Prodrugs, especially those of the above structure, can also be used on the form of pharmaceutically acceptable salts.

Specific examples of prodrugs are 5-MeO-DMT carboxy-isopropyl valinate, preferably in salt form, in particular as ditrifluoroacetate (1-(((S)-2-amino-3-methylbutanoyl)oxy)-2-methylpropyl 3-(2-(dimethylamino)ethyl)-5-methoxy-1H-indole-1-carboxylate ditrifluoroacetate) and 5-MeO-DMT methyl pivalate (3-(2-(dimethylamino)ethyl)-5-rnethoxy-1H-indol-1-yl)methyl pivalate).

Preparation methods for prodrugs as discussed herein are known in the art.

According to the invention, the T_{max} value of the metabolite 5-MeO-DMT as measured in male Sprague-Dawley (SD) rats following oral dosing of the prodrug at 10 mg/kg is preferably 1 hour or less, more preferably 0.7 hours or less and in particular 0.5 hours or less.

Further according to the invention, prodrugs of 5-MeO-DMT and salts of prodrugs of 5-MeO-DMT are used in amounts that are equimolar to the amounts of the corresponding non-prodrug forms.

Modes of Administration

The therapeutically effective amount of 5-MeO-DMT is administered by inhalation, by nasal administration, by buccal administration or by sublingual administration. Administration via these routes can assure a rapid onset of action. A most preferred route of

administration is administration by inhalation. Preferably, the inhalation of the therapeutically effective amount of 5-MeO-DMT occurs within a single breath.

For nasal administration, 5-MeO-DMT can be employed as a neat substance or in the form of a formulation for nasal administration, examples of which are known in the art. For nasal administration, 5-MeO-DMT can be employed as a pharmaceutically acceptable salt, preferably the hydrobromide salt, or in the form of a formulation of a pharmaceutically acceptable salt, preferable the hydrobromide salt. Examples of appropriate devices are known in the art.

Buccal administration or sublingual administration can also rely on a pharmaceutically acceptable salt of 5-MeO-DMT, preferable the hydrobromide salt, as such or in the form of formulations, for instance, tablets, films, sprays, creams, as generally known in the art.

Administration is in particular by inhalation of an aerosol. Such an aerosol comprises (a) a pharmaceutically acceptable gas; (b) aerosol particles of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or a pharmaceutically acceptable salt thereof, wherein the aerosol has an aerosol particle mass density of about 0.5 mg/l to about 18 mg/l, such as about 0.5 mg/l to about 12.5 mg/l, preferably of about 1.3 mg/l to about 10 mg/l, in particular of about 2 mg/l to about 9 mg/l. The pharmaceutically acceptable gas is preferably air.

The aerosol particles preferably contain less than 1 wt% impurities, in particular less than 0.5 wt% impurities. They furthermore preferably contain less than 0.5 wt% 5-MeO-DMT degradation products, in particular less than 0.2 wt% 5-MeO-DMT degradation products resulting from a chemical modification of 5-MeO-DMT as a result of a chemical reaction during aerosol formation.

In a further preferred aspect, the aerosol essentially consists of (a) air; (b) aerosol particles of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The aerosol particles preferably contain 5-MeO-DMT in the form of the free base.

The aerosol is preferably characterized by a mass median aerodynamic diameter of less than 3 µm and more than 0.1 µm, in particular by a mass median aerodynamic diameter of less than 2 µm and more than 0.1 µm.

The aerosol may be formed by a) exposing a thin layer of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, configured on a solid support, to thermal energy, and b) passing air over the thin layer of 5-MeO-DMT to produce aerosol particles. The thin layer may have a thickness of less than about 10 µm, in particular less than about 7.5 µm. It may have a thickness in the range of about 0.1 µm to about 10 µm, in particular in the range of about 0.3 µm to about 7.5 µm.

The thin layer of 5-MeO-DMT, configured on a solid support, may be exposed to thermal energy via the air passing over the thin layer. Alternatively, the thin layer of 5-MeO-DMT, configured on a solid support, may be exposed to thermal energy via the solid support.

The air passing over the thin layer may have a temperature in the range of about 180°C to about 260°C. The air passing over the thin layer may in particular have a temperature of about 210°C and pass over the thin layer at a rate of about 12 l/min for a duration of about 15 seconds.

The aerosol particles may be contained in a volume of equal or less than about 3 liters, in particular in a volume of about 1 to about 3 liters, such as about 2 to about 3 liters. It is preferably delivered to a patient via a single inhalation.

5-MeO-DMT or a pharmaceutically acceptable salt thereof is provided in a form suitable for inhalation in a medical context. 5-MeO-DMT and pharmaceutically acceptable salts are provided thereof in the form of aerosols. These aerosols have a suitable aerosol particle mass density so that a therapeutically effective dose of the aerosol can be administered to a patient via a single inhalation.

Aerosols useful in the present invention can be formed using thermal energy. When using thermal energy to form an aerosol of a compound, it is very difficult to predict which conditions are suitable for safe, efficient and predictable aerosolization, in particular if the aerosol is to be used for systemic delivery of that compound to a patient via the lungs. Relevant variables in this context include a) the dose of the compound, b) the morphological state in which that compound is made available for aerosolization (e.g. in crystal form, or in form as a thin layer), c) the amount of thermal energy to which the compound is exposed (defined by temperature and duration of exposure), and d) the volume of air introduced to create the aerosol (defined by flow rate and duration of air flow).

The compositions and methods described herein are for safe, efficient and predictable systemic delivery of 5-MeO-DMT or a pharmaceutically acceptable salt thereof to a patient through inhalation. "Safe" means that the aerosol particles should contain only a very small amount of impurities and 5-MeO-DMT degradation products, "efficient" means that the dosage is aerosolized to a defined extent and preferably almost completely or completely, that the aerosol has desirable physical properties for delivery of the 5-MeO-DMT or a pharmaceutically acceptable salt thereof systemically via the lungs mainly via absorption in the pulmonary alveoli, and that the aerosol can be inhaled by the patient in a single inhalation (i.e., within one deep breath), and "predictable" means that there should be almost no or no variability in the amount of degradation products, in the extent of aerosolization, and in the physical properties of the aerosol.

A suitable aerosol can be achieved by a) providing the therapeutically effective amounts of 5-MeO-DMT as a thin layer, on a solid support, b) exposing the thin 5-MeO-DMT layer to elevated controlled temperatures for a short duration of time, and c) providing a controlled amount of air so that an aerosol is formed.

A composition for delivery of a therapeutically effective amount of 5-MeO-DMT may comprise an aerosol, wherein the aerosol is formed by a) exposing a thin layer of 5-MeO-DMT, configured on a solid support, to thermal energy, and b) passing air over the thin layer of 5-MeO-DMT; wherein said aerosol has one or more of the following features: 1) it contains aerosol particles which are characterized by a mass median aerodynamic diameter of less than 3 micron, 2) it contains aerosol particles which are characterized by less than 1% wt impurities and less than 0.5% 5-MeO-DMT degradation products, 3) it can be delivered to a patient via a single inhalation.

The generation of aerosol particles characterized by a mass median aerodynamic diameter of less than 3 microns, with less than 1% wt impurities and less than 0.5% wt 5-MeO-DMT drug degradation products, in an aerosol volume which can be delivered to a patient via a single inhalation, is achieved by defining a) the dosage amount of 5-MeO-DMT contained in the thin layer of 5-MeO-DMT, b) the thickness of the thin layer of the 5-MeO-DMT, c) the thermal energy to which the thin layer of 5-MeO-DMT is exposed (defined by temperature and duration of exposure), and d) the total amount of the air which passes over the thin layer of 5-MeO-DMT (defined by airflow rate and duration of airflow).

Preferably the thin layer of 5-MeO-DMT is exposed to thermal energy via the air passing over the thin layer, in which case that air is heated. The heated air passing over the thin layer may have a temperature in the range of about 180°C to about 260°C. The air passing over the thin layer may in particular have a temperature of about 210°C.

Alternatively, the thin layer of 5-MeO-DMT is exposed to thermal energy via the solid support, in which case the air passing over the thin layer is not heated, but the solid support is heated. The heated solid support may have a temperature in the range of about 180°C to about 420°C.

Preferably the 5-MeO-DMT used for formation of the thin layer, on the solid support, is highly pure, with a purity of at least 99%, preferably at least 99.5%.

Preferably the dosage amount of 5-MeO-DMT contained in the thin layer of 5-MeO-DMT, configured on the solid support, is from about 1 mg to about 25 mg, preferably from about 2 mg to about 20 mg, more preferably from about 4 mg to about 20 mg. Useful specific amounts are, e.g., about 4 mg, about 6 mg, about 8 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, and about 20 mg. Preferred specific amounts are e.g. about 6 mg, about 12 mg, and about 18 mg.

Solid supports, on which 5-MeO-DMT or a pharmaceutically acceptable salt thereof is provided, can have a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (e.g., less than 1.0 mm-sized) pores. Preferably, solid supports provide a large surface to volume ratio (e.g., greater than 100 per meter) and a large surface to mass ratio (e.g., greater than 1 cm^2 per gram).

A solid support of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

A number of different materials are used to construct the solid supports. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina;

graphite, porous carbons, carbon yarns and carbon felts; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amphorous silica S-5631 (Sigma, St. Louis, Mo.), BCR171 (an alumina of defined surface area greater than 2 m^2/g from Aldrich, St. Louis, Mo.) and a silicon wafer as used in the semiconductor industry. Carbon yams and felts are available from American Kynol, Inc., New York, N.Y.

Preferably the thickness of the thin layer of the 5-MeO-DMT, configured on the solid support, is less than about 10 µm, in particular less than about 7.5 µm. It may have a thickness in the range of about 0.1 µm to about 10 µm, in particular in the range of 0.3 µm to 7.5 µm.

Preferably the total amount of the air passing over the thin layer of 5-MeO-DMT is defined by a flow rate of between about 6 liters per minute and about 40 liters per minute, preferable between about 8 liters per minute and about 16 liters per minute and the duration of airflow is chosen so that the total volume of aerosol does not exceed about 3 liters, preferably is between about 1 liter and 3 liters, such as between 2 liters and 3 liters. E.g., at an airflow rate of about 6 liters per minute, the duration of airflow should be less than about 30 seconds. A useful specific airflow rate and duration is about 12 liters per minute and about 15 seconds, leading to an aerosol volume of about 3 liters. Another useful specific airflow rate and duration is 10 liters per minute and about 15 seconds, leading to leading to an aerosol volume of about 2.5 liters. Another useful specific airflow rate and duration is 8 liters per minute and about 15 seconds, leading to leading to an aerosol volume of about 2 liters. Another useful specific airflow rate and duration is 10 liters per minute and about 12 seconds, leading to leading to an aerosol volume of about 2 liters.

The aerosol formation rate is greater than 0.1 mg/sec.

The aerosol has an aerosol particle mass density of about 0.5 mg/l to about 18 mg/l, such as of about 0.5 mg/l to about 12.5 mg/l, preferably of about 1.3 mg/l to about 10 mg/l, in particular of about 2 mg/l to about 9 mg/l.

The 5-MeO-DMT aerosol particles are characterized by a mass median aerodynamic diameter of less than 3 micron and more than 0.1 micron, preferably of less than 2.5 micron and more than 0.1 micron, most preferably of less than 2 micron and more than 0.1 micron. The 5-MeO-DMT aerosol particles are characterized by less than 1% wt impurities, preferably by less than 0.5% wt impurities.

The 5-MeO-DMT aerosol particles are characterized by less than 0.5% wt 5-MeO-DMT degradation products, preferably by less than 0.2% wt 5-MeO-DMT degradation products.

A composition for delivery of a therapeutically effective amount of 5-MeO-DMT may comprise an aerosol, wherein the aerosol is formed by a) exposing a dosage amount of 12 mg 5-MeO-DMT, configured as a thin layer of less than 5 micron thickness on a solid support, to a temperature of 210° C via passing heated air over the thin layer for a duration of 15 seconds; wherein said aerosol has one or more of the following features: 1) it contains aerosol particles which are characterized by a mass median aerodynamic diameter of less than 3 micron, 2) it contains aerosol particles which are characterized by less than 1% impurities and less than 0.5% wt 5-MeO-DMT degradation products, 3) it can be delivered to a patient via a single inhalation.

A skilled person, knowing the aerosol characteristics and the aerosolization conditions defined in the present invention, can identify suitable vaporization devices or systems, which lead to the required aerosol characteristics. Examples of such suitable vaporization devices or systems include e.g. the Volcano Medic Vaporization System with the associated dosing capsules with drip pad (Storz & Bickel, Germany; as disclosed in e.g. EP 0 933 093 B1, and EP 1 884 254 B1 and Registered Community Design 003387299-0001) and the Staccato device (Alexza Pharmaceuticals, Mountain View, USA; as disclosed e.g. in US 7,458,374 B2, US 9,370,629 B2 and US 9,687,487 B2). The aerosol generated may be collected in a balloon and inhaled by the patient from the balloon.

Dosing Regimen

The present invention also provides dose ranges, particular doses as well as dosing regimens (administration schemes).

The invention is in part based on the inventors' conclusion that the occurrence of a peak psychedelic experience during the acute phase after administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof is driving its therapeutic benefit in patients suffering from social/emotional withdrawal or detachment, in particular one or more of the aspects defined above, either in a causal relationship or at least as a surrogate behavioural marker for the underlying unknown therapeutic mechanism.

Consequently, achieving peak experiences more rapidly, in a larger proportion of patients and with better reproducibility in an individual patient, compared with previously tested psychedelic agents and dosing regimens, will lead to a better therapeutic profile.

Further, the present invention also relies on the short duration of action of 5-MeO-DMT and the absence of relevant tolerance (i.e., the absence of diminished or no psychedelic effects after re-administration), as a basis for enabling a dosing regimen with frequent re-administrations (such as more than once daily, or daily), which are designed to increase the rate of occurrence of peak experiences, thereby increasing the therapeutic benefit. Such repeat administrations within short time also allow an intraindividual dose-optimization which reduces the risk of overdosing, which may otherwise lead to somatic side effects, such as the serotonin syndrome, negative psychic reactions, such as flashbacks of the experience at later timepoints, induction of mania or hypomania or to less meaningful psychedelic experiences with few or no memories of the altered state (so-called "white-outs"). Further, starting with a low dose allows familiarization of the patient with the psychedelic experience in general, and allows preparation for the more intense symptoms to occur at the higher doses, which will positively influence the experience at those higher doses. Also, the prospect of being able to initiate treatment with a low dose will increase patient acceptance of the therapeutic approach and improve overall compliance rates on the patient population level.

Frequent re-administrations of a serotonergic psychedelic with the aim to increase the rate and tailor the reproducibility of peak experiences and to improve the therapeutic effect, reduce the side effects and improve the compliance rates may not be possible with other psychedelics, due to the late onset and long duration of psychedelic effects and due to the rapid development of tolerance (i.e. diminished or no psychedelic effects after re-administration) which can last for several days.

A patient as defined herein who suffers from social/emotional withdrawal or detachment is treated by administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the 5-MeO-DMT is administered as a monotherapy, i.e., the patient does not receive any other treatment for social/emotional withdrawal or detachment.

The dosage amount of 5-MeO-DMT administered to a patient, as defined herein, suffering from social/emotional withdrawal or detachment, is in the range of about 1 mg to about 25 mg, or any amount of range therein, preferably from about 2 mg to about 20 mg, more preferably from about 4 mg to about 20 mg. Useful specific amounts are e.g. about 4 mg, about 6 mg, about 8 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, and about 20 mg. Patients may also be treated with an equimolar dose of a pharmaceutically acceptable salt of 5-MeO-DMT, such as the hydrobromide salt. Note that in this specification, when ranges are set forth, such as "about 1 mg to about 25 mg," the inventor contemplates all discrete values within that range, some of which are specifically mentioned, but all of which are not - simply for the purpose of brevity.

In preferred embodiments the improved methods for the treatment of a patient, as defined herein, suffering from social/emotional withdrawal or detachment, with a therapeutically effective amount of 5-MeO-DMT, comprise the occurrence of a clinical response not later than about 2 hours after administration of 5-MeO-DMT.

In preferred embodiments the improved methods for the treatment of a patient, as defined herein, suffering from social/emotional withdrawal or detachment, with a therapeutically effective amount of 5-MeO-DMT, comprise the persistence of a clinical response, including a clinical response which occurred not later than about 2 hours after administration of 5-MeO-DMT, until at least about 6 days after the last administration of 5-MeO-DMT, preferably until at least about 14 days after the last administration of 5-MeO-DMT, more preferably until at least about 28 days after the last administration of 5-MeO-DMT.

In preferred embodiments the improved methods for the treatment of a patient, as defined herein, suffering from social/emotional withdrawal or detachment, with a thera-

peutically effective amount of 5-MeO-DMT comprise the administration of more than a single dose of 5-MeO-DMT.

In a preferred embodiment this more than a single dose of 5-MeO-DMT is administered to a patient in one or more treatment blocks, each block consisting of 2 to 7 administrations, with not less than about 1 hour and not more than about 24 hours between each administration within each treatment block, and not less than about 6 days between the end of one treatment block and the start of the next treatment block.

In an even more preferred embodiment this more than a single dose of 5-MeO-DMT is administered to a patient in one or more treatment blocks, each block consisting of 1 to 3 administrations, with about 24 hours between each administration within each treatment block, and not less than about 6 days between the end of one treatment block and the start of the next treatment block.

In a most preferred embodiment this more than a single dose of 5-MeO-DMT is administered to a patient in one or more treatment blocks, each block consisting of 1 to 3 administrations, with about 1 to 4 hours, preferably 1 to 2 hours, between each administration within each treatment block, and not less than about 6 days between the end of one treatment block and the start of the next treatment block.

In an embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient in each of the administrations and in each of the treatment blocks is constant for that individual patient and is selected from about 1 mg to about 25 mg, preferably from about 2 mg to about 20 mg, more preferably from about 4 mg to about 20 mg. Useful specific amounts are e.g. about 4 mg, about 6 mg, about 8 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, and about 20 mg.

In a preferred embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient is selected from about 2 mg to about 8 mg for the first administration within each treatment block, and then increases with each subsequent administration within each treatment block until the earlier of 20 mg being reached or all administrations within that treatment block being administered.

In an even more preferred embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient is selected from about 2 mg to about 8 mg for the first administration within each treatment block, and then increases with each subsequent

administration within each treatment block until the earlier of 20 mg being reached or all administrations within that treatment block being administered or the patient having experienced a peak psychedelic experience or the supervising physician having decided that further dose increases are inappropriate based on observed side effects.

For embodiments where the dosage amount increases for subsequent administrations, the dosage amount for the next administration is determined by adding about 2 mg to about 10 mg, preferably about 4 mg to about 8 mg, most preferably about 6 mg, to the dosage amount of the prior administration. For example, if the dosage amount of the first administration was 6 mg and the dosage amount increase is 6 mg, unless one of the previously mentioned stopping criteria has been reached, then the dosage amount of the second administration will be 12 mg. Preferably, the dosage amount for the third administration will be 18 mg.

In a preferred embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient in each treatment block is selected from about 2 mg to about 8 mg for the first administration, and then increased, unless the patient has already experienced a peak psychedelic experience within that treatment block or the supervising physician has decided that further dose increases are inappropriate based on observed side effects, to a dosage selected from about 8 mg to about 14 mg for the second administration, and from about 14 mg to about 20 mg for the third administration. Useful specific amounts for the first, second and third administration are e.g. about 6 mg, about 12 mg, and about 18 mg.

In a further preferred embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient is selected from about 2 mg to about 8 mg for the first administration of the first treatment block, and then increases with each subsequent administration within that first treatment block until the earlier of 20 mg being reached or all administrations within that treatment block being administered or the patient having experienced a peak psychedelic experience or the supervising physician having decided that further dose increases are inappropriate based on observed side effects, with that highest dosage in that first treatment block being used as the dosage for all subsequent treatment blocks and administrations within those subsequent treatment blocks. For example, if the highest dosage in the first treatment block was 18 mg because the patient experienced a peak psychedelic experience at that dose, then the

dosage for all subsequent treatment blocks and administrations within those subsequent treatment blocks will be 18 mg.

In a most preferred embodiment the dosage amount of the 5-MeO-DMT administered to an individual patient is selected from about 2 mg to about 8 mg for the first administration of the first treatment block, and then increased, unless the patient has already experienced a peak psychedelic experience within that treatment block or the supervising physician has decided that further dose increases are inappropriate based on observed side effects, to a dosage selected from about 8 mg to about 14 mg for the second administration of the first treatment block, and from about 14 mg to about 20 mg for the third administration of the first treatment block, with the highest dosage in that first treatment block being used as the dosage for all subsequent treatment blocks and administrations within those subsequent treatment blocks. Useful specific amounts for the first, second and third administration in the first treatment block are e.g. about 6 mg, about 12 mg, and about 18 mg.

It is understood that a pharmaceutically acceptable salt of 5-MeO-DMT can also be used in all of the above dosing regimen, and that the appropriate weight amounts of a salt to be administered can be calculated from the stated weight amounts of the free base, assuming that equimolar amounts are used.

According to the invention, 5-MeO-DMT is preferably not administered together with a MAO inhibitor.

The occurrence of a "peak psychedelic experience" in a patient can be identified through achievement of at least 60% of the maximum possible score in each of the four subscales (mystical, positive mood, transcendence of time and space, and ineffability) of the 30-item revised Mystical Experience Questionnaire (MEQ-30) (as described in Barrett FS, J Psychopharmacol. 2015;29(11):1182-90).

The occurrence of a "peak psychedelic experience" in a patient can also be identified through achievement of at least 60% of the maximum possible score of the Oceanic Boundlessness (OBN) dimension of the Altered States of Consciousness (ASC) questionnaire (as described in Roseman L et al., Front Pharmacol. 2018; 8:974).

In accordance with the invention, the occurrence of a "peak psychedelic experience" in a patient is preferably identified through achievement of a score of at least 75 in the

Peak Experience Scale (PES) Total Score, also referred to as the Peak Psychedelic Experience Questionnaire (PPEQ), which averages answers scored by the patient from 0 to 100 for the following three questions: 1. How intense was the experience; 2. To what extent did you lose control; 3. How profound (i.e. deep and significant) was the experience?

Treatment of Social/Emotional Withdrawal or Detachment and Sleep Disturbance

Sleep disturbance refers to conditions, whether idiopathic or occurring in the context of a medical condition such as for example a mental disorder or a nervous system disorder, that affect sleep quality, timing, or duration. It impacts a person's ability to properly function while the person is awake and is linked to a pattern of high negative emotions and low positive emotions.

There are two fundamental types of sleep: rapid eye movement (REM) sleep and non-REM sleep. Non-REM sleep can be divided into four stages (I-IV). These non-REM stages correspond to an increasing depth of sleep. Non-REM and REM sleep alternate during each of the four to five cycles of normal human sleep each night. During the earlier proportion of the night, non-REM sleep is deeper and occupies a disproportionately large amount of time, particularly within the first cycle of sleep. As the night progresses, non-REM sleep becomes shallow and more of each cycle is allocated to REM sleep.

Normal healthy sleep consists of different phases as outlined above that proceed in successive, tightly regulated order through the night.

Disruption of this tight regulation results in sleep disturbances.

Common forms of sleep disturbances encompass disorders of initiating and maintaining sleep (insomnia), disorders of excessive somnolence (hypersomnia), disorders of sleep–wake schedule (circadian rhythm disorders), dysfunctions associated with sleep, sleep stages, or partial arousals (parasomnia), disorders characterized by respiratory disturbance during sleep (sleep-related breathing disorders) and disorders characterized by abnormal movements during sleep (sleep-related movement disorders). In a broad sense, fatigue can also be considered a sleep disturbance.

Insomnia is a sleep disturbance where people have difficulty falling or staying asleep. People with insomnia have difficulty falling asleep; wake up often during the night and have trouble going back to sleep; wake up too early in the morning; have unrefreshing sleep; and/or have at least one daytime problem such as fatigue, sleepiness, problems with mood, concentration, accidents at work or while driving, etc. due to poor sleep.

Hypersomnia is characterized by excessive daytime sleepiness, and/or prolonged night-time sleep. Sleep drunkenness is also a symptom found in hypersomnia patients. It is a difficulty transitioning from sleep to wake. Individuals experiencing sleep drunkenness report waking with confusion, disorientation, slowness and repeated returns to sleep.

Circadian rhythm disorders are characterized by chronic or recurring sleep disturbances due to alterations of the individual's internal circadian rhythm or due to misalignments between their circadian rhythm and their desired or required work or social schedule. This dyssynchrony may be transient or persistent. The ensuing clinical picture combines elements of both insomnia and hypersomnia. Sleep periods are usually shortened and disrupted, performance during the desired waking state is impaired, and temporary opportunities to revert to a regular sleep schedule are unsuccessful.

Parasomnia designates various forms of sleep disturbance characterized by abnormal behavioural or physiological activity (such as sleepwalking or nightmares) that people experience prior to falling asleep, while asleep, or during the arousal period between sleep and wakefulness. There are considerable variations in terms of characteristics, severity, and frequency. Parasomnia may compromise the quality of sleep.

Sleep-related breathing disorders are characterized by abnormal and difficult respiration during sleep. Respiration is a complex process that relies heavily on the coordinated action of the muscles of respiration and the brain. With a potentially serious impact on sleep and the balance of oxygen and carbon dioxide in the blood, these sleep disturbances appear as chronic snoring, sleep apnoea, sleep related hypoventilation and/or hypoxemia. In some of these disorders, respiration is also abnormal during wakefulness. The reduction of airflow leads to intermittent hypoxia, with microarousals or awakenings, causing sleep fragmentation and excessive daytime sleepiness. Inflammation and endothelial dysfunction may ensue and reduce vascular elasticity and increase coagulation predisposing individuals to atherosclerosis, which, along with reduced oxygenation, may cause heart and brain damage.

In sleep-related movement disorders repetitive, relatively simple, usually stereotyped, movements interfere with sleep or its onset. The most common of these are restless leg syndrome (RLS) and periodic limb movement disorder (PLMD).

Fatigue describes a state of tiredness that does not resolve with rest or sleep. It is a feeling of exhaustion, lethargy, or decreased energy, usually experienced as a weakening or depletion of one's physical or mental resource and characterised by a decreased capacity for work and reduced efficiency in responding to stimuli. Fatigue is normal following a period of exertion, mental or physical, but sometimes may occur in the absence of such exertion as a symptom of health conditions.

Not getting the proper amount or quality of sleep may lead to personality changes and may not only exacerbate existing mental illness, but also be a trigger for the development of mental illness. Sleep disturbance may also lead to social withdrawal, as sleep deprivation leads to an increased feeling of loneliness and reduced desire to socially interact. A short sleep duration increases the odds of mood deficits by 55%. Anhedonia is a key symptom and mechanism by which lack of sleep affects mood. Moreover, sleep loss can also adversely affect life by contributing to the development of obesity, diabetes and heart disease.

Treatment of sleep disturbance varies depending on the type and underlying cause. Maintenance of good sleep hygiene, a healthy sleep environment, and a consistent sleep-wake schedule are often considered as first-line treatment. If not successful, treatment also involves pharmacotherapy or psychotherapy.

Available treatments are not successful in all patients, may be associated with side effects and/or require treatment over a long period of time to achieve a relevant treatment effect.

In patients suffering from sleep disturbance in association with a mental disorder or a nervous system disorder known treatments of the mental or nervous system disorder do not necessarily improve the sleep disturbance.

For instance, sleep disturbance is frequently associated with mental disorders, such as depression. However, treatment of depression does not necessarily lead to an improvement of the concomitant sleep disturbances. While most antidepressants have been proven to influence the sleep architecture, some classes of antidepressants im-

prove sleep, but others may cause sleep impairment (Hutka et al. Association of Sleep Architecture and Physiology with Depressive Disorder and Antidepressants Treatment. Int J Mol Sci. 2021 Jan 29;22(3):1333., Abstract).

To assess sleep, parameters such as sleep duration, sleep architecture, sleep latency, and the frequency and duration of awakenings throughout the night can be measured. The quantitative metrics may be measured using objective methods, including polysomnography, actigraphy, and the determination of sleep latency, or by way of self-reported measures (questionnaires).

Polysomnography is a technique requiring that a patient is monitored overnight at a specialized clinic. A variety of functions are measured throughout the night, including eye movements, brain and muscle activity, respiratory effort and airflow, blood oxygen levels, body positioning and movements, snoring, and heart rate.

Sleep latency can be measured by the multiple sleep latency test (MSLT). This test provides an objective measure to determine how long it takes a person to fall asleep across a multiplicity of test naps. An average sleep latency of approximately 10 minutes is considered to be normal; less than eight minutes is indicative of sleep disturbance. Accompanying analysis of brain activity can assist in the further diagnose of the sleep disturbance.

Sleep-rating questionnaires capture ratings of components of sleep quality, such as perceptions of sleep depth, rousing difficulties, and restfulness after sleep, in addition to other factors that could affect sleep quality, such as comorbid conditions and medication use.

The evaluation of the qualitative aspects of sleep experience is important, as sleep complaints can often persist despite normal values for quantitative measures of sleep.

Questionnaires not only facilitate a quick and accurate assessment of a complex clinical problem, but they are potentially also helpful for tracking a patient's progress. Thus, self-reported sleep questionnaires completed by patients are an important mainstay for the assessment of sleep disturbance in clinical practice.

Various sleep quality indexes are known. The following indexes include examples of questionnaires to assess sleep in general and questionnaires to assess in particular

insomnia, hypersomnia, circadian rhythm disorders and parasomnia, respectively. The invention is, however, not limited to the use of a particular index or questionnaire.

Sleep quality in general can be assessed, for instance, with Sleep Quality Scale (SQS) and the Sleep-50 questionnaire.

The Sleep Quality Scale (SQS) is an all-inclusive assessment tool to achieve a general, efficient measure suitable for evaluating sleep quality in a variety of patient and research populations. Individual questions on daytime symptoms, such as attention, concentration difficulties or memory problems (Item 15, “Poor sleep makes hard for me to think”, item 19 “Poor sleep causes me to make mistakes at work”, item 21 “Poor sleep makes me forget things more easily”, item 22 “Poor sleep makes it hard to concentrate at work”), restoration after sleep, problems initiating and maintaining sleep, difficulty waking, and sleep satisfaction can be scored from 0 ("rarely") -3 ("almost always"), with higher scores being indicative for more acute sleep problems.

The SLEEP-50 questionnaire consists of 50 items designed to screen for various kinds of sleep disturbance in the general population. The scale consists of nine subscales, reflecting some of the most common disorders and complaints related to sleep and the factors required for diagnosis such as sleep apnoea, insomnia, narcolepsy, restless legs/periodic leg movement disorder, circadian rhythm sleep disorder, sleepwalking, nightmares, factors influencing sleep, and the impact of sleep complaints on daily functioning. For each item, respondents are provided with a scale ranging from 1 ("not at all") to 4 ("very much") and are asked to indicate the extent to which the statement has matched their experience over the previous month or another appropriate recall window.

The questionnaire requires that for diagnosing a sleep disturbance not only the specific subscale (e.g., insomnia) exceeds a certain cut-off point, but also the impact subscale (Spoormaker et al. Initial validation of the SLEEP-50 questionnaire. Behav Sleep Med. 2005;3(4):227-46., table 4 for optimal cut-off values and scoring procedures).

Treatment success is indicated (i) by a decrease of the score, preferably (ii) by a decrease to below the cut-off value.

A common questionnaire assessing sleep disturbance is the Pittsburgh Sleep Quality Index. Other instruments are the insomnia severity index and the Espie sleep disturbance questionnaire.

The Pittsburgh Sleep Quality Index (PSQI) assesses overall sleep quality and disturbances. The PSQI is a self-rated questionnaire comprising 19 questions. Respondents are asked to indicate how frequently they have experienced certain sleep difficulties over the past month or another appropriate recall window.

The 19 self-rated questions assess a wide variety of factors relating to sleep quality, including estimates of sleep duration and latency and of the frequency and severity of specific sleep-related problems. These 19 items are grouped into seven component scores: (1) subjective sleep quality; (2) sleep latency; (3) sleep duration; (4) habitual sleep efficiency; (5) sleep disturbances; (6) use of sleeping medication; (7) daytime dysfunction.

Each component is assigned a score of 0 to 3. Higher scores indicate more acute sleep disturbances. Detailed Scoring Instructions for the Pittsburgh Sleep Quality Index can be found in the Appendix of Buysse et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213.

The seven component scores are then summed to yield one global score, with a range of 0-21 points, "0" indicating no difficulty and "21" indicating severe difficulties in all areas. A global score cut-off of 5 distinguishes poor from good sleepers. A global score > 5 indicates that a patient is having severe difficulties in at least two areas, or moderate difficulties in more than three areas.

If treatment outcome is assessed using the PSQI, treatment success is indicated (i) by a decrease of the score, preferably (ii) by a decrease to 5 or below.

The Insomnia Severity Index (ISI) is a 5-item questionnaire relating to subjective sleep quality, severity of symptoms, subjective satisfaction with sleep, the degree to which insomnia interferes with daily functioning (Item 3, “To what extent do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc).”), how noticeable the respondent feels his or her insomnia is compared to others, and the overall level of

distress created by the sleep problem. Individual responses can be scored from 0 (=none) to 4 (=very); a higher total score corresponds to more severe insomnia. A total score of 0–7 indicates "no clinically significant insomnia," 8–14 means "subthreshold insomnia," 15–21 is "clinical insomnia (moderate severity)," and 22–28 means "clinical insomnia (severe)" (A. Shahid et al. (eds.), STOP, THAT and One Hundred Other Sleep Scales, Springer Science+Business Media, LLC 2012; Bastien et al. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001 Jul;2(4):297-307).

The usual recall window for the ISI is two weeks, but other appropriate recall windows can also be used herein.

Treatment success is indicated (i) by a decrease of the score, for instance, by > 7 points, in particular > 8 point; preferably (ii) by a decrease to below the cut-off value for clinically significant insomnia.

The Sleep Preoccupation Scale (SPS) is a 22-item, self-report scale, designed to assess daytime cognitions in patients with insomnia. Though researchers have frequently focused on nighttime thoughts and preoccupations when attempting to treat disordered sleep, a growing body of research suggests that daytime beliefs about sleep may be just as significant in the experience of insomnia. SPS items evaluate two distinct domains: the cognitive and behavioural consequences of poor sleep (e.g., negative thoughts and perceptions), and the affective consequences (e.g., worry and distress). The tool may be particularly useful for clinicians attempting to identify and treat the origins of sleep issues in their patients.

The Espie sleep disturbance questionnaire (SDQ) evaluates subjective experiences of insomnia. With ratings on restlessness/agitation, mental overactivity, consequences of insomnia, and lack of sleep readiness, the SDQ is concerned specifically with beliefs about the sources of sleep issues. Respondents use a five-point scale to indicate how often certain statements about insomnia are representative of their experience. 1 means "never true," while 5 means "very often true." Higher scores are indicative of more dysfunctional beliefs about the causes and correlates of insomnia (A. Shahid et al., loc. cit.; Espie et al. Insomniacs' attributions. psychometric properties of the Dysfunctional Beliefs and Attitudes about Sleep Scale and the Sleep Disturbance Questionnaire. J Psychosom Res. 2000 Feb;48(2):141-8).

Treatment success is indicated by a decrease of the score.

Hypersomnia or hypersomnolence can be assessed by the Epworth sleepiness scale, the Stanford sleepiness scale, or the idiopathic hypersomnia severity scale.

The Epworth sleepiness scale (ESS) evaluates overall daytime sleepiness. The questionnaire asks respondents to rate how likely they are to fall asleep in eight different situations representing a moment of relative inactivity, such as a nap in the afternoon or sitting in a car stopped in traffic. Using a scale of 0–3 (with 0 meaning "would never doze" and 3 meaning "high chance of dozing"), respondents rate their likelihood of falling asleep. Scoring ranges from 0-24; the higher the score, the higher the severity of daytime sleepiness. A cut-off score of 10 identifies daytime sleepiness at a potentially clinical level (A. Shahid et al., loc. cit. Johns et al., A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep, 1991 Dec;14(6):540-5).

Treatment success is indicated (i) by a decrease of the score, preferably (ii) by a decrease to 10 or below.

The Stanford sleepiness scale is a subjective measure of sleepiness, evaluating sleepiness at specific moments in time. Consisting of only one item, the scale requires respondents to select one of seven statements best representing their current level of perceived sleepiness. A scale from 1 (=Feeling active and vital; alert; wide awake) to 7 (=Almost in reverie; sleep onset soon; lost struggle to remain awake) is used to assess the level of sleepiness (A. Shahid et al., loc. cit.; Hoddes et al. The development and use of the Stanford sleepiness scale (SSS). Psychophysiology, 1972, 9, 150).

Treatment success is indicated by a decrease of the score.

Parasomnias can be evaluated by the Paris Arousal Disorders Severity Scale (PADSS).

The Paris Arousal Disorders Severity Scale (PADSS) is a self-rating scale listing parasomniac behaviours, assessing their frequency and includes an evaluation of consequences (Arnulf et al. A scale for assessing the severity of arousal disorders. Sleep. 2014 Jan 1;37(1):127-36).

Treatment success is indicated (i) by a decrease of the score, preferably (ii) by a decrease to below the cut-off value.

A common questionnaire that assesses sleep-related breathing disorders is the Berlin Questionnaire (A. Shahid et al., loc. cit.; Netzer et al., Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999 Oct 5;131(7):485-91). An appropriate recall period can also be chosen.

Treatment success is indicated by a decrease of the score.

A common questionnaire that assesses sleep-related movement disorders is the International Restless Legs Syndrome Study Group Rating Scale (A. Shahid et al., loc. cit.; Walters et al.; International Restless Legs Syndrome Study Group 2003. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Medicine 4(2), pp. 121–132).

Treatment response can be assessed by a decrease of the score.

Fatigue is commonly assessed by for example the FACES (Fatigue, Anergy, Consciousness, Energy, Sleepiness).

The FACES (Fatigue, Anergy, Consciousness, Energy, Sleepiness) rating scale is a 50 items checklist to distinguish between tiredness, sleepiness, and fatigue. Respondents use a scale ranging from 0 ("not at all") to 3 ("strongly") to indicate the degree to which they have experienced each feeling or energy state over the course of the previous week or another appropriate recall period. Higher scores indicate more acute states of tiredness or fatigue, except for those items belonging to the energy subscale (A. Shahid et al., loc. cit.; Shapiro et al., Development of an adjective checklist to measure five FACES of fatigue and sleepiness. Data from a national survey of insomniacs. J Psychopomp Res. 2002 Jun;52(6):467-73).

Effective treatment reduces scoring in tiredness and/or fatigue and/or increases scoring on the energy subscale.

Treatment response can be evaluated by above-mentioned quantitative measurements such as polysomnography or actigraphy and/or the use of the above-mentioned questionnaires. Depending on the respective sleep scale, a significant reduction or increment, respectively, in total score, or significant reduction of prevalence, frequency and impact on daily-functioning, respectively is indicative for treatment-induced improvement of the sleep disturbance.

Common tests that assess social/emotional withdrawal or detachment or aspects thereof that can be used are, for example, the Snaith-Hamilton Pleasure Scale (SHAPS), the Dimensional Anhedonia Rating Scale (DARS) and the Personality Inventory for DSM-5 (PID-5) – Adult.

To enhance the understanding of the pathophysiology and potential compensatory mechanisms at play, resting-state fMRI has been widely applied in patients with sleep disturbances.

Altered resting state networks can be found in insomnia, hypersomnia, circadian rhythm disorders, parasomnias, sleep-related breathing disorders and sleep-related movement disorders.

In insomnia patients, dysfunctional connectivity is observed within the default mode network (DMN) and within the salience network, which is implicated in the detection and integration of emotional and sensory stimuli. Studies have suggested that these networks contain critical regions integrating emotional and bodily states, and the dysfunctional connectivity with other brain areas may underlie the vigilance, subjective distress, and poor sleep continuity of patients.

For instance, sleep deprivation in healthy subjects leads to functional connectivity alterations within and/or between the default mode network, dorsal attention network and salience network and these brain functional connectivity changes somewhat resemble the vulnerability patterns of patients with Alzheimer's disease.

In hypersomnia patients, the default mode network is affected. For instance, in idiopathic hypersomnia, distinct DMN hubs - the precuneus and medial prefrontal cortex - demonstrate significant changes, and functional connectivity in the DMN correlates with self- reported sleepiness severity.

A study investigating differences between night shift nurses and day work nurses revealed that dysrhythmia of circadian rhythms contributes to resting-state functional changes in the cerebellum, involved in sleep regulation, and cognitive functions such as responsiveness and alertness. Moreover, the functional connectivity of the DMN is fundamentally different in early and late circadian phenotypes. Like other forms of sleep disturbance, circadian rhythm disorders can lead to changes in brain functional

connectivity. Changes in resting state brain functional connectivity have been reported in various diseases with circadian rhythm disorders.

While functional brain imaging is technically difficult to perform during a parasomnia event, differences in the precuneus have been observed in disorders of arousal representing a non-REM parasomnia.

The precuneus is involved in the analysis and integration of visual, audio, and somesthetic information and the monitoring of movements. The precuneus is a subregion of the DMN. Thus, in patients with parasomnias the default mode network is affected.

Resting-state fMRI studies in patients suffering from sleep-related breathing disorders, such as obstructive sleep apnoea (OSA), have demonstrated that long-term exposure to oxidative stress, intermittent hypoxia, hypo- and hypercapnia and sleep fragmentation, some of the major causes of OSA brain injury, may lead to significant global and regional connectivity deficits, especially in the default mode network (DMN) and regions involved in the arousal and sensorimotor systems.

Sleep-related movement disorders, such as for example periodic limb movements during sleep are reflected by alterations in the prefrontal motor control pathway, a subregion of the default mode network. Also, activity in the cerebellum and thalamus, with additional activation in the red nuclei and brainstem can be observed.

In many instances, resting state networks involved in sleep regulation are also involved in social/emotional withdrawal or detachment. Thus, according to the invention, influencing those networks by a therapy according to the invention will lead to an improvement of the sleep disturbance and, if the patient treated suffers from social/emotional withdrawal or detachment, also of the social/emotional withdrawal or detachment.

Clinical data from studies of patients suffering from TRD or Postpartum Depression (PPD) confirm that sleep disturbance can successfully be treated.

In the studies, which involved the administration of 5-MeO-DMT, among others the MADRS item "reduced sleep", which reflects insomnia, was assessed.

The MADRS item "reduced sleep" represents the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well. A score of 0 is assigned when the subject sleeps as usual. A score of 2 reflects slight difficulty drop-

ping off to sleep or slightly reduced, light or fitful sleep. A score of 4 means that sleep is reduced or broken by at least two hours. A score of 6 means less than two or three hours sleep.

In the study group receiving the individualized dosing regimen, the aggregated score for the MADRS item "reduced sleep" across all 8 patients was 25 at base line. At day 1 after treatment, the earliest timepoint for assessing an impact of the treatment on sleep, it was reduced to 12 which corresponds to an improvement of 13 points or 52%. At day 7 after treatment, it was reduced to 9 which corresponds to an improvement of 16 points or 64%.

In the 12 mg group, the aggregated score for the MADRS item "reduced sleep" across all 4 patients was 12 at base line. At day 1 after treatment, it was reduced to 10 which corresponds to an improvement of 2 points or 17%. At day 7 after treatment, it was reduced to 6 which corresponds to an improvement of 6 points or 50%.

Thus, the score of the scale item that is of particular relevance to sleep disturbance, "reduced sleep", is markedly improved. The inventors conclude that 5-MeO-DMT can be used to treat sleep disturbance, in particular patients suffering from a mental disorder or a nervous system disorder.

Treating a patient suffering from sleep disturbance, in particular insomnia, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the sleep disturbance, in particular the insomnia.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from sleep disturbance, in particular insomnia, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from sleep disturbance, in particular insomnia, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment, in

particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance

after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment, in particular of anhedonia, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists

until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment, in particular of social withdrawal, in a patient suffering from sleep disturbance, in particular insomnia, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment, in particular of social withdrawal, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment, in particular of social withdrawal, in a patient suffering from sleep disturbance, in particular insomnia, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from a sleep disturbance, in particular insomnia. An improvement

in social/emotional withdrawal or detachment will therefore also lead to an improvement of the sleep disturbance, in particular insomnia. Since social/emotional withdrawal or detachment furthermore also affects other aspects of the sleep disturbance, the inventors conclude that the improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the sleep disturbance, in particular insomnia.

In cases of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, a clinical response may be reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score. According to the invention, a reduction in the CGI-S score means that the CGI-S is reduced by at least 1. Preferably, the CGI-S is reduced by at least 2 and/or to a score of 0. It is especially preferred if the CGI-S is reduced by at least 3 and/or to a score of 0.

An improvement of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score in a patient also suffering from associated social/emotional withdrawal or detachment, occurs not later than about 24 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement in idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

In an embodiment, an improvement in idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed on day 7 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof and preferably persists until at least 14 days, more preferably until at least 28 days.

In cases of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, an improvement in sleep disturbance, as reflected by at least a score of "much improved" in the Clinical Global Impression - Improvement (CGI-I) score or the Patient Global Impression - Improvement (PGI-I) score, preferably occurs not later than about 24 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

In cases of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, an improvement in sleep disturbance, as reflected by a reduction by at least a score of "much improved" in the CGI-I score or the PGI-I score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Improvements in cases of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment may also be assessed by any other scale reflecting changes in sleep quality or quantity, as indicated above, for instance the Pittsburgh Sleep Quality Index (PSQI).

If treatment outcome is assessed using the PSQI, treatment success is indicated (i) by a decrease of the score, preferably (ii) by a decrease to 5 or below.

An improvement in idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a decrease of the PSQI global score, in particular by a decrease to 5 or below, preferably occurs not later than about 24 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period spans from the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. Such an improvement in idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a decrease of the PSQI global score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period spans from the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

An improvement of idiopathic sleep disturbance in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the PSQI global score, is observed on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period spans from the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Social/emotional withdrawal or detachment and sleep disturbance, in particular insomnia, are closely linked to mental and nervous system disorders. Both, social/emotional withdrawal or detachment and sleep disturbance, in particular insomnia, occur in mental or nervous system disorders, such as disorders characterized by depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorders due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disorders, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorders; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); Personality Disorders, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD).

Social/emotional withdrawal or and sleep disturbance, in particular insomnia, also both occur in medical health conditions leading to an associated mental or nervous system condition, such as Traumatic Brain Injury (TBI).

A treatment according to the invention will lead to improvements in both social/emotional withdrawal or detachment and sleep disturbance, in particular insomnia, and furthermore to an improvement in the associated mental or nervous system disorder, examples of which are listed above.

Treatment of Social/Emotional Withdrawal or Detachment and Mental and Nervous System Disorders

In patients suffering from social/emotional withdrawal or detachment in association with a mental disorder or a nervous system disorder a treatment of social/emotional withdrawal or detachment according to the invention leads to an improvement of the condition with which the social/emotional withdrawal or detachment is associated.

While social/emotional withdrawal or detachment may be considered a condition deserving treatment independent of any other conditions, disorders or symptoms an individual may suffer from, several mental disorders and disorders of the nervous system are associated with social/emotional withdrawal or detachment. Notably, the relationship between social/emotional withdrawal or detachment and mental disorder is bidirectional. Not only can mental disorders have a social/emotional withdrawal or detachment on the emotional state of the patient, but social/emotional withdrawal or detachment can also be a contributing factor to the onset, progression and prognosis of mental or nervous system disorders.

In many instances, resting state networks involved in social/emotional withdrawal or detachment are also involved in the conditions listed above.

5-MeO-DMT has the ability to disrupt established functional connectivity patterns of resting state networks. This disruption leads to a reset of the pathological ill-connected brain connections as the networks reconnect. New, healthy functional connections are established with persistent effects.

Disorders Characterized by Depressive Episodes

There are several disorders which are characterized by depressive episodes.

A depressive episode is a period of depressed mood and/or loss of pleasure in most activities.

For instance, according to DSM-V, a Major Depressive Episode is characterized by five or more symptoms that have been present during the same 2-week period and repre-

sent a change from previous functioning; at least one of the symptoms being either (1) depressed mood or (2) loss of interest or pleasure.

The patient suffering from a disorder characterized by depressive episodes may suffer from a treatment resistant form of the disorder.

A patient suffering from disorders characterised by depressive episodes often also suffers from social/emotional withdrawal or detachment.

Social/emotional withdrawal or detachment is included as a diagnostic criterion for disorders characterized by depressive episodes. It may be assessed as part of the determination of the MADRS or the BPRS.

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a ten-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders. Higher MADRS scores indicate more severe depression.

Items are apparent sadness; reported sadness; inner tension; reduced sleep; reduced appetite; concentration difficulties; lassitude; inability to feel; pessimistic thoughts; and suicidal thoughts and each item yields a score of 0 to 6. The overall score ranges from 0 to 60.

The MADRS item “inability to feel” represents the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced. It is rated 0 if there is a normal interest in the surroundings and in other people. It is rated 1, 2 or 3 if there is a reduced ability to enjoy usual interests; 3, 4 or 5 if there is a loss of interest in the surroundings, of feelings or friends and acquaintances; and 6 if there is the experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

The item “emotional withdrawal” of the Brief Psychiatric Rating Scale (BPRS) represents the deficiency in relating to the interviewer and to the interviewer situation. The interviewer rates only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.

The BPRS item “blunted affect” represents the reduced emotional tone, apparent lack of normal feeling or involvement.

Social/emotional withdrawal or detachment or aspects thereof, such as anhedonia, in patients suffering from a disorder characterized by depressive episodes can, for instance, be assessed using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from a disorder characterized by depressive episodes altered functional connectivity is observed within and/or between several brain regions implicated in processing, regulation, emotional memory; cognitive processes related to rumination; impaired concentration and physiological arousal.

Treating a patient suffering from a disorder characterized by depressive episodes, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the disorder characterized by depressive episodes.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically

acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of emotional withdrawal, is reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by an improvement in the score of the BPRS item “emotional withdrawal” preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of blunted affect, is reflected by at least an improvement in the

score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at

least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhe-

donia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of social withdrawal, as reflected by at least an im-

provement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a disorder characterized by depressive episodes, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to a disorder characterized by depressive episodes. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the disorder characterized by depressive episodes. Since social/emotional withdrawal or detachment furthermore also affects other aspects of a disorder characterized by depressive episodes, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the disorder characterized by depressive episodes.

An improvement of the disorder characterized by depressive episodes in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the disorder characterized by depressive episodes in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the disorder characterized by depressive episodes in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Major Depressive Disorder (MDD) is a mood disorder that causes a persistent feeling of sadness and loss of interest. It affects how a person feels, thinks and behaves and can lead to a variety of emotional and physical problems.

The patient suffering from MDD may suffer from a treatment resistant form of the disorder.

The patient may suffer from treatment resistant disease. Treatment resistance means that the patient had no adequate improvement after at least two adequate courses of therapy. The patient in particular had no adequate improvement after at least two adequate courses of therapy, wherein at least one of the two courses was a pharmacotherapy; for instance, the patient had no adequate improvement after at least two adequate courses of pharmacotherapy. The at least two prior courses of treatment were in particular administered in the current episode of depression.

Anhedonia is a core symptom and key feature of MDD, as outlined in the DSM-5.

Depressive symptoms are also associated with spending less time in social interactions. Social withdrawal was prevalent and links to suicidal ideation in patients with MDD.

Social/emotional withdrawal or detachment in a patient suffering from MDD may be assessed as part of the determination of the MADRS or the BPRS. Social/emotional withdrawal or detachment or at least aspects thereof may furthermore be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS), the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from MDD dysfunctional connectivity and regulation within and/or between multiple resting-state networks including the DMN, salience network, executive control network and limbic network is observed. Functional connectivity differs significantly from that observed in healthy controls.

Treating a patient suffering from MDD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of MDD.

The patient may suffer from moderate or severe MDD as indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or more or by a Hamilton Depression Rating Scale (HAM-D) score of 17 or more. It is further considered that the patient may suffers from severe major depressive disorder as indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 35 or more or by a Hamilton Depression Rating Scale (HAM-D) score of 25 or more.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, is reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of blunted affect, is reflected by at least an improvement in the score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, as reflected by at least an improvement in

the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5

(PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earli-

er than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on

day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from MDD, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to MDD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of MDD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of MDD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of MDD.

An improvement of the MDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the MDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT

or a pharmaceutically acceptable salt thereof. An improvement of the MDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

A further aspect of MDD in a patient also suffering from associated social/emotional withdrawal or detachment which can be treated by administration of 5-MeO-DMT, is suicidal ideation. 5-MeO-DMT can be administered to MDD patients also suffering from associated social/emotional withdrawal or detachment to reduce or eliminate suicidal ideation in said patients.

In the above-mentioned clinical studies relating to patients suffering from TRD involving the administration of 5-MeO-DMT, among others the MADRS item “suicidal thoughts” was assessed.

“Suicidal thoughts” represents a feeling that life is not worth living, that a natural death would be welcome, having suicidal thoughts, and/or making the preparations for suicide. Suicidal attempts should not in themselves influence the rating for this MADRS item.

A score of 0 means that the patient enjoys life. A score of 2 is assigned if the PPD patient is weary of life, and/or has only fleeting suicidal thoughts. A score of 4 means the patient feels they would be better off dead, suicidal thoughts are common and suicide is considered as a possible solution but the patient has no specific plans or intention. A score of 6 is assigned in case the patient has explicit plans for suicide and/or is making active preparations.

This MADRS scale item is of particular relevance to suicidal ideation.

In the study group receiving the individualized dosing regimen, the aggregated score for the MADRS item “suicidal thoughts” across all 8 patients was 11 at base line. After 2 hours, it was reduced to 3 which corresponds to an improvement of 8 points or 73%. At day 1 after treatment, it was reduced to 1 which corresponds to an improvement of 10 points or 91%. At day 7 after treatment, it was reduced to 3 which corresponds to an improvement of 8 points or 73%.

In the 12 mg group, the aggregated score for the MADRS item “suicidal thoughts” across all 4 patients was 8 at base line. After 2 hours, it was reduced to 3 which corresponds to an improvement of 5 points or 63%. At day 1 after treatment, it was reduced to 5 which corresponds to an improvement of 3 points or 38%. At day 7 after treatment, it was reduced to 7 which corresponds to an improvement of 1 point or 13%.

Thus, the score of the scale item that is of particular relevance to suicidal ideation, “suicidal thoughts”, is markedly improved, at least in the individualized dosing regimen patients. The inventors conclude that 5-MeO-DMT can be used to treat suicidal ideation in MDD patients.

Thus, according to the invention, the treatment of a patient suffering from MDD associated with social/emotional withdrawal or detachment reduces or eliminates the suicidal ideation.

The reduction or elimination of suicidal ideation in a patient suffering from MDD associated with social/emotional withdrawal or detachment is reflected by at least an improvement in the score of the MADRS item suicidal thoughts about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance, after about 24 hours, on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of suicidal ideation in a patient suffering from MDD associated with social/emotional withdrawal or detachment, as reflected by at least an improvement in the score of the MADRS item suicidal thoughts, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of suicidal ideation in a patient suffering from MDD associated with social/emotional withdrawal or detachment, as reflected by at least an improvement in the score of the MADRS item suicidal thoughts, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from MDD associated with social/emotional withdrawal or detachment, preferably using dosing

schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from MDD associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Bipolar Disorder (BD) is a mental health condition characterized by extreme mood swings that include emotional lows (major depressive episodes) and highs (manic or hypomanic episodes). BD is a recurrent chronic disorder that affects more than 1% of the world's population irrespective of ethnic origin or socioeconomic status.

BD is classified as Bipolar I Disorder if there has been at least one manic episode, with or without depressive episodes. It is classified as Bipolar II Disorder if there has been at least one hypomanic episode (but no full manic episodes) and one major depressive episode. If these symptoms are due to drugs or medical problems, they are not diagnosed as Bipolar Disorder.

The patient suffering from BD including Bipolar I Disorder and Bipolar II Disorder may suffer from a treatment resistant form of the disorder.

The patient may suffer from treatment resistant disease. Treatment resistance means that the patient had no adequate improvement after at least two adequate courses of therapy. The patient in particular had no adequate improvement after at least two adequate courses of therapy, wherein at least one of the two courses was a pharmacotherapy; for instance, the patient had no adequate improvement after at least two adequate courses of pharmacotherapy. The at least two prior courses of treatment were in particular administered in the current episode of depression.

Distinct brain regions of patients with Bipolar I Disorder and Bipolar II Disorder have been implicated in blunted affect and emotional withdrawal.

In a study of 197 adolescents with Bipolar Disorder, anhedonia was present amongst 90.9% of individuals during their severe depressive episode. The severity of the symptom was significantly associated with the severity of the disorder.

A single 0.5 $mg \cdot kg^{-1}$ ketamine infusion decreased levels of anhedonia rapidly in patients with treatment resistant bipolar depression. The single infusion took effect within 40 minutes and lasted up to 14 days. Positron emission tomography (PET) results of a

subgroup of these individuals found that the anti-anhedonic effect was in part increased by glucose metabolism in the dorsal anterior cingulate cortex (an element of the DAN) and putamen (part of the basal ganglia RSN) of the brain.

Social/emotional withdrawal or detachment in a patient suffering from BD may be assessed as part of the determination of the MADRS, the BPRS or the BDRS. Social/emotional withdrawal or detachment or at least aspects thereof may furthermore be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS), the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

The Bipolar Depression Rating Scale (BDRS) is designed to measure the severity of depressive symptoms in bipolar depression. The BDRS is validated for clinical use by trained raters. Based on a clinical interview, the BDRS items rate the severity of depressive and/or mixed symptoms expressed by patients currently and during the past few days. If there is a discordance between symptoms currently and the last few days, the rating should reflect current symptoms. The scale contains 20 questions and the maximum score possible is 60. Higher scores indicate greater severity.

The questions address depressed mood; sleep disturbance; appetite disturbance; reduced social engagement; reduced energy and activity; reduced motivation; impaired concentration and memory; anxiety; anhedonia; affective flattening; feelings of worthlessness; feelings of helplessness and hopelessness; suicidal ideation; feelings of guilt; psychotic symptoms; irritability; lability; increased motor drive; increased speech; agitation.

Each of these aspects is assessed and assigned a score of 0, 1, 2 or 3.

The BDRS item “reduced social engagement” reports reduced social and interpersonal engagement or interactions. It is scored as 0 if it is normal; 1 (mild) in case of slight reduction in social engagement with no impairment in social or interpersonal function; 2 (moderate) in case of a clear reduction in social engagement with some functional sequelae, e.g., avoidance of some social engagements or conversations; 3 (severe) in case of a marked reduction in social interaction or avoidance of almost all forms of social contact, e.g., the patient refuses to answer the phone or see friends or family.

The BPRS item “anhedonia” relates to the subjectively reduced ability to experience pleasure in usual activities. It is scored as 0 in case of no subjectively reduced ability to experience pleasure in usual activities; 1 (mild) in case of a slight reduction in pleasure from usually pleasurable activities; 2 (moderate) in case of a significant reduction in pleasure from usually pleasurable activities; some pleasure from isolated activities retained; 3 (severe) in case of a complete inability to experience pleasure.

The BDRS item “affective flattening” is the subjective sense of reduced intensity or range of feelings or emotions. It is score with 0 in case of no subjective sense of reduced intensity or range of feelings or emotions; 1 (mild) in case of a slight constriction of range of affect, or transient reduction in range or intensity of feelings; 2 (moderate) in case of a significant constriction of range or intensity of feelings with preservation of some emotions, e.g., unable to cry; 3 (severe) in case of a marked and pervasive constriction of range of affect or inability to experience usual emotions.

Patients suffering from Bipolar Disorder show characteristic aberrant intrinsic organization and interconnectivity of resting state networks. In comparison with healthy controls, resting state functional magnetic resonance imaging studies demonstrated functional connectivity alterations of specific regions within and/or between the default mode network, the salience network, and the central executive network. In particular functional connectivity alterations within the default mode network are also observed in patients suffering from sleep disturbance.

Treating a patient suffering from BD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of BD.

Typically, the patient suffering from BD, whether diagnosed with bipolar II disorder or with bipolar I disorder, suffers from a current major depressive episode.

The severity of a current major depressive episode may be assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). The patient may have a total score of equal to or greater than 19, such as greater or equal than 24, in particular greater or equal than 37.

Alternatively or in addition, the patient may have a Bipolar Depression Rating Scale (BDRS) total score of 19, such as greater or equal than 24, in particular greater or equal than 37.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Bipolar Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, is

reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of blunted affect, is reflected by at least an improvement in the score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of reduced social engage-

ment, is reflected by at least an improvement in the score of the BDRS item “reduced social engagement” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of reduced social engagement, as reflected by an improvement in the score of the BDRS item “reduced social engagement”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of reduced social engagement, as reflected by an improvement in the score of the BDRS item “reduced social engagement”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, is reflected by at least an improvement in the score of the BDRS item “anhedonia” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by an improvement in the score of the BDRS item “anhedonia”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by an improvement in the score of the BDRS item “anhedonia”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of affective flattening, is reflected by at least an improvement in the score of the BDRS item “affective flattening”

about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of affective flattening, as reflected by an improvement in the score of the BDRS item “affective flattening”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of affective flattening, as reflected by an improvement in the score of the BDRS item “affective flattening”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-

MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BD, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to BD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of BD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of BD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of BD.

An improvement of the BD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the BD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Bipolar Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until

at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from Bipolar Disorder, such as Bipolar I Disorder and Bipolar II Disorder, associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from Bipolar Disorder, such as Bipolar I Disorder and Bipolar II Disorder, associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Postpartum Depression (PPD) is a debilitating mood disorder occurring during pregnancy or within 4 weeks following delivery. While over 50% of women may experience short-lasting low mood or tearfulness after childbirth, a subset of women may develop PPD. Epidemiological studies estimate that the prevalence rate of PPD is about 15%.

The patient suffering from PPD may suffer from a treatment resistant form of the disorder.

Analysis of data from 663 women with perinatal depression found that the anhedonia and anxiety were prominent symptoms 8 weeks post-partum.

Social isolation is one of five identified dimensions that correlate with and predict maternal depressive symptoms.

PPD is also known as major depressive disorder with peripartum onset. According to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria, PPD is diagnosed when major depressive disorder (MDD) symptoms begin during pregnancy or within four weeks of delivery. Accordingly, PPD patients also suffer from social/emotional withdrawal or detachment, in particular anhedonia.

Social/emotional withdrawal or detachment in a patient suffering from PPD may be assessed as part of the determination of the MADRS or the BPRS. Social/emotional withdrawal or detachment or at least aspects thereof may furthermore be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional

Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients with PPD, significant changes in neural activity in brain regions important for self-regulation, empathy, emotion, and cognition are observed. PPD is associated with dysfunctional connectivity of resting state networks, for instance, within and/or between the default mode network and frontoparietal network.

Treating a patient suffering from PPD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of PPD.

A patient may suffer from moderate or severe PPD as indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or more or by a Hamilton Depression Rating Scale (HAM-D) score of 16 or more. It is further considered that the patient may suffer from severe PPD as indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 35 or more or by a Hamilton Depression Rating Scale (HAM-D) score of 27 or more.

A patient treated according to the invention may have a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or more or a 17-item Hamilton Depression Rating Scale (HAM-D) score of 16 or more.

Further, a patient treated according to the invention may have a MADRS score of 28 or more or a HAM-D score of 22 or more.

Still further, a patient treated according to the invention may have a MADRS score of 35 or more or a HAM-D score of 25 or more.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD occurs not later than about 2 hours after the last administration of

5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, is reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, as reflected by an

improvement in the score of the BPRS item “emotional withdrawal”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of blunted affect, is reflected by at least an improvement in the score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically ac-

ceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction

or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PPD, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to PPD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of PPD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of PPD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of PPD.

An improvement of the PPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14;

and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the PPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the PPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Social/emotional withdrawal or detachment moreover compromises maternal functioning.

Maternal functioning can, for instance, be assessed using the Barkin Index of Maternal Functioning (BIMF). This index was designed to measure functioning in the year after childbirth. The BIMF is a 20-item self-report measure of functioning. Each item is assigned a score between 0 and 6 so that the maximum total score is 120. The higher the score, the better maternal functioning is rated.

The BIMF identifies the key functional domains of a mother during the postnatal period as: self-care, infant care, mother-child interaction, psychological wellbeing of the mother, social support, management, and adjustment.

A BIMF score of 95 or below is considered herein as representing slightly compromised maternal functioning, a score of 80 or below is considered herein as representing compromised maternal functioning, a score of 65 or below is considered herein as representing severely compromised maternal functioning.

The inventors have determined that increases in the score of the MADRS item "inability to feel" and/or the BPRS items “emotional withdrawal” and “blunted affect” have negative impacts on maternal functioning (maternal competence relating to interactions with the infant(s) as well as maternal self-care).

Increased scores in the MADRS item inability to feel and/or the BPRS items emotional withdrawal and/or blunted affect impair psychological wellbeing, social support and management. Conversely, improvements regarding the MADRS item "inability to feel"

and/or the BPRS items “emotional withdrawal” and “blunted affect” lead to improvements in maternal functioning, in particular in the BIMF functional domains psychological wellbeing, social support and/or management.

The inventors conclude that 5-MeO-DMT can be used to treat PPD patients to achieve an improvement of social/emotional withdrawal or detachment, in particular a reduction or elimination of inability to feel, emotional withdrawal and/or blunted affect.

The inventors furthermore conclude that a reduction or elimination of inability to feel, emotional withdrawal and/or blunted affect by treating a PPD patient does not only lead to a reduction in the MADRS or BPRS total score, but also to an improvement in maternal functioning, as reflected by an increase in the BIMF score.

The BIMF total score is improved by 10 % or more, preferably by 20 % or more.

The improvement of maternal functioning in a patient suffering from PPD is reflected by at least an improvement in the BIMF total score on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The improvement of maternal functioning in a patient suffering from PPD, as reflected by at least an improvement in the BIMF total score, occurs not later than about 6 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The improvement of maternal functioning, as reflected by at least an improvement in the BIMF total score, preferably persists until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from PPD associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from PPD associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Seasonal Affective Disorder is a mood disorder with seasonal pattern, with symptoms often beginning in autumn and remitting in spring. Many people experience sadness, hopelessness, a loss of interest in activities, fatigue, and social withdrawal.

The patient suffering from Seasonal Affective Disorder may suffer from a treatment resistant form of the disorder.

Seasonal Affective Disorder is associated with social/emotional withdrawal or detachment, including social withdrawal and anhedonia. Seasonal Affective Disorder is characterised according to the DSM-V by depressive episodes that meet the criteria for major depressive episode including anhedonia.

Social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder may be assessed as part of the determination of the MADRS or the BPRS. Social/emotional withdrawal or detachment or at least aspects thereof may furthermore be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Resting state activity involved in sensorimotor, attention, and visual processing is altered in patients with Seasonal Affective Disorder compared to healthy controls.

In patients suffering from Seasonal Affective Disorder altered functional connectivity is observed within and/or between several brain regions implicated in processing, regulation, emotional memory; cognitive processes related to rumination; impaired concentration and physiological arousal. Dysfunctional connectivity is observed within and/or between the DMN, salience network, executive control network and limbic network. Functional connectivity differs significantly from that observed in healthy controls.

Treating a patient suffering from Seasonal Affective Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Seasonal Affective Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for

instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, is reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of blunted affect, is reflected by at least an improvement in the score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a

pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at

least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt

thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, as

reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Seasonal Affective Disorder, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more

preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to Seasonal Affective Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of Seasonal Affective Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Seasonal Affective Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Seasonal Affective Disorder.

An improvement of the Seasonal Affective Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Seasonal Affective Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Seasonal Affective Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from Seasonal Affective Disorder associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from Seasonal Affective Disorder associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Persistent Depressive Disorder

Persistent Depressive Disorder, also referred to as dysthymia, is a chronic form of depression. It is diagnosed if depression is present for most of the day for the majority of days over at least a two-year period. Any symptom-free period is less than 2 months.

While depressed, two or more of the following must be present: 1. Hopelessness; 2. Energy low or fatigue; 3. Self-esteem is low; 4. Sleep decreased (insomnia) or increased (hypersomnia): 5. Appetite poor, or overeating; 6. Difficulty making decisions or poor concentration.

The patient suffering from Persistent Depressive Disorder may suffer from a treatment resistant form of the disorder.

According to the DSM-V, Persistent Depressive Disorder can is characterized by the criteria for a major depressive disorder which may be continuously present for 2 years, which include anhedonia. Social withdrawal is also a prevalent symptom in patients suffering from Persistent Depressive Disorder.

Social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder may be assessed as part of the determination of the MADRS or the BPRS. Social/emotional withdrawal or detachment or at least aspects thereof may furthermore be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from Persistent Depressive Disorder altered functional connectivity is observed within and/or between several brain regions implicated in processing, regulation, emotional memory; cognitive processes related to rumination; impaired concentration and physiological arousal. Dysfunctional connectivity is observed within and/or between the DMN, salience network, executive control network and limbic network. Functional connectivity differs significantly from that observed in healthy controls.

In patients suffering from Persistent Depressive Disorder dysfunctional connectivity and regulation among multiple resting-state networks including the DMN, salience network, executive control network and limbic network is observed. Functional connectivity differs significantly from that observed in healthy controls.

Treating a patient suffering from Persistent Depressive Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Persistent Depressive Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of inability to feel, is reflected by at least an improvement in the score of the MADRS item “inability to feel” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceuti-

cally acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of inability to feel, as reflected by an improvement in the score of the MADRS item “inability to feel”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, is reflected by at least an improvement in the score of the BPRS item “emotional withdrawal” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, as reflected by an improvement in the score of the BPRS item “emotional withdrawal”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of blunted affect, is reflected by at least an improvement in the score of the BPRS item “blunted affect” about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, occurs not later

than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of blunted affect, as reflected by an improvement in the score of the BPRS item “blunted affect”, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional

Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of anhedonia, as

reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Persistent Depressive Disorder, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is closely linked to Persistent Depressive Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of Persistent Depressive Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Persistent Depressive Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Persistent Depressive Disorder.

An improvement of the Persistent Depressive Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Persistent Depressive Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of

5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Persistent Depressive Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from Persistent Depressive Disorder associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from Persistent Depressive Disorder associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Anxiety Disorder

An **Anxiety Disorder** is a type of mental health condition. Symptoms include feelings of nervousness, panic and fear as well as sweating and a rapid heartbeat. Anxiety is linked to fear and manifests as a future-oriented mood state that consists of a complex cognitive, affective, physiological, and behavioural response system associated with preparation for the anticipated events or circumstances perceived as threatening.

The patient suffering from Anxiety Disorder may suffer from a treatment resistant form of the disorder.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Anxiety Disorders are associated with alterations in the functional connectivity of resting state networks. Anxiety Disorders show abnormalities in the default mode network (DMN) affecting the sense of self, the salience network (SN) controlling emotion/anxiety and the somatomotor network (SMN) responsible for bodily awareness.

The resting state balance within and/or between each of these networks, e.g., SMN and SN, relative to the DMN may be abnormal in the different anxiety disorders.

Treating a patient suffering from an Anxiety Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Anxiety Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharma-

ceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Anxiety Disorder, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after

the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Anxiety Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Anxiety Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Anxiety Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the

last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Anxiety Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment occurs in patients with an Anxiety Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of Anxiety Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Anxiety Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Anxiety Disorder.

An improvement of the Anxiety Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Anxiety Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Anxiety Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Generalised Anxiety Disorder (GAD) is characterized by persistent and excessive, difficult to control worry about a wide range of situations and issues. Patients suffering from GAD may anticipate disaster and may be overly concerned about money, health, family, work, or other issues.

Generalized anxiety disorder is diagnosed when an individual experiences persistent worry about everyday challenges out of proportion to the perceived threat. Patients with GAD usually experience excessive fear that can last months to years.

GAD interferes with social, occupational, or other important areas of functioning.

The patient suffering from GAD may suffer from a treatment resistant form of the disorder.

In a study of 224 individuals primarily diagnosed with GAD, anhedonia was found to be the crucial element for association between quality of life (QoL), sleep problems and negative cognitions.

A large longitudinal study of older adults found that social isolation is associated with higher anxiety as well as depressive symptoms.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Patients with GAD show altered functional connectivity, especially within the default mode network.

Treating a patient suffering from GAD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of GAD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about

24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, is reflected

by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) –

Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment occurs in patients with GAD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of GAD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of GAD, the inventors conclude that the observed

improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of GAD.

An improvement of the GAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the GAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the GAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Social Anxiety Disorder (SAD), also called social phobia, is one of the most common types of anxiety. SAD is characterized by intense anxiety or fear of being judged, negatively evaluated, or rejected in a social or performance situation. This often leads to avoidance of the social situation and can cause impairments in school, work, or relationships.

SAD is characterized by intense anxiety or fear of being judged, negatively evaluated, or rejected in a social or performance situation.

The patient suffering from SAD may suffer from a treatment resistant form of the disorder.

Social withdrawal is a core feature of SAD, characterised by fear and avoidance of social interactions. Social avoidance is also seen in SAD, and patients who suffer with concomitant major depression show higher social avoidance scores than SAD alone.

Avoidance of social situations and more time spent alone could reflect a behavioural outcome from anhedonia; however, less time in social contexts also increases anhe-

donia. This establishes a spiral of withdrawal and exacerbation which escalates social disconnect.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from SAD, altered functional connectivity is observed in the default mode network and the salience network.

Treating a patient suffering from SAD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of SAD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psyche-

delic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, is reflected

by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of social withdrawal, as reflected by at least an im-

provement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SAD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment occurs in patients with SAD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of SAD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of SAD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of SAD.

An improvement of the SAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the SAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the SAD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Obsessive Compulsive and Related Disorders

Obsessive Compulsive Disorder (OCD) is a mental illness that causes repeated unwanted thoughts or sensations (obsessions) or the urge to do something over and over again (compulsions). Patients may suffer from both obsessions and compulsions.

The patient suffering from OCD may suffer from a treatment resistant form of the disorder.

Anhedonia is suggested to be a mechanism mediating the comorbid relationship between OCD and MDD symptoms in adolescents.

A relationship between OCD symptoms and anhedonia independent of depression has also been found.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Neuroimaging studies using functional magnetic resonance imaging of patients suffering from OCD show functional connectivity alterations within and/or between frontoparietal network, salience network, and default mode network.

Treating a patient suffering from OCD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of OCD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination

of social/emotional withdrawal or detachment in a patient suffering from OCD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from OCD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is common in patients with OCD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of OCD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of OCD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of OCD.

An improvement of the OCD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the OCD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the OCD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Body Dysmorphic Disorder (BDD) patients misperceive defects in their appearance, disrupting their ability to function in their daily lives, with disturbing preoccupations, ritualistic behaviours, and emotional distress**.**

The patient suffering from BDD may suffer from a treatment resistant form of the disorder.

Social isolation is extremely common in patients with BDD, showing high levels of impairment in social functioning.

The total score on the Social Adjustment Scale is lower for individuals with BDD than the published US norm.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Personality Inventory for DSM-5 (PID-5) – Adult.

Functional magnetic resonance imaging of patients suffering from BDD reveals alterations within and/or between certain brain areas located in the default mode network, the dorsal attention network and the salience network.

Treating a patient suffering from BDD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the BDD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BDD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from BDD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the BDD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of BDD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the BDD.

An improvement of the BDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the BDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the BDD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14

days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Post-Traumatic Stress Disorder (PTSD)

Post-Traumatic Stress Disorder (PTSD) is a mental health condition that can develop based on a terrifying event - either experienced or witnessed by the patient. Symptoms may include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event.

A patient suffering from PTSD may suffer from a treatment resistant form of the disorder.

The DSM-5 indicates that anhedonia is one of the most important symptoms associated with PTSD.

Emotional numbing is a known symptom in PTSD. A study of 310 veterans with PTSD found that anhedonia had a positive relationship with emotional numbing in PTSD, which increased risk for comorbid major depressive disorder.

Social withdrawal has been identified as an avoidant coping strategy used by individuals with PTSD. A positive correlation was found between social withdrawal and future PTSD symptoms, recognising social withdrawal as a possible therapeutic target.

Social/emotional withdrawal or detachment is an important aspect in patients suffering from PTSD. This is supported by different items of the PTSD checklist for DSM-5 (PCL-5), such as “Loss of interest in activities that you used to enjoy”, Feeling distant or cut off from other people” and “Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)”.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Analysis of resting state functional magnetic resonance imaging in patients suffering from PTSD reveals alterations within and/or between regions located in the default mode network and salience network.

Treating a patient suffering from PTSD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of PTSD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, as reflected by at least an im-

provement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for

DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PTSD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earli-

er than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is a very important aspect in patients suffering from PTSD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of PTSD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of PTSD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of PTSD.

An improvement of the PTSD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the PTSD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the PTSD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Pain Disorders

Chronic Pain, also referred to as persistent pain, is long standing pain that persists beyond the usual recovery period, for instance, after an injury or operation, despite medication or treatment. Patients may also suffer from Chronic Pain without any apparent cause, such as a history of an injury or operation.

Chronic Pain interferes with quality of life, mental and emotional health. Social/emotional withdrawal or detachment occurs in patients suffering from pain and has been associated with Chronic Pain.

A patient suffering from Chronic Pain may suffer from a treatment resistant form of the disorder.

A large study of chronic pain patients found that individuals with Chronic Pain reported higher levels of anhedonia than healthy controls.

Chronic Pain individuals who misuse prescribed opioids had higher anhedonia scores than those who didn't misuse opioids.

Social isolation is an important factor in pain-related appraisal and coping. The impact of pain is reduced in individuals who perceive a greater sense of inclusion from and engagement with others.

The Snaith-Hamilton Pleasure Scale (SHAPS), an instrument developed for assessing anhedonia, has been already used in studies with patients suffering from Chronic Pain. The Brief Pain Inventory (BPI-sf) also assesses the interference of pain with the enjoyment of life and relations with other people. This shows that social/emotional withdrawal or detachment is associated with Chronic Pain.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Chronic Pain patients display brain alterations regarding brain function and structure. These changes are related to the persistence of pain, long after the initial nociceptive input has disappeared. Resting state functional magnetic resonance imaging reveals alterations in distinct regions within and/or between the default mode network, the somatomotor/sensorimotor network, and the salience network.

Treating a patient suffering from Chronic Pain, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of Chronic Pain.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after

about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from

Chronic Pain, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Chronic Pain, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients with Chronic Pain. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of Chronic Pain. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Chronic Pain, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Chronic Pain.

An improvement of the Chronic Pain in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Chronic Pain in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Chronic Pain in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Fibromyalgia is a chronic disorder that is characterized by widespread musculoskeletal pain throughout the body or at multiple sites, accompanied by fatigue, sleep disturbances, memory and mood issues. Patients may also encounter muscle and joint stiffness, tenderness to touch, numbness or tingling in the arms and legs, problems with concentrating, thinking clearly, and memory (sometimes called “fibro fog”), heightened sensitivity to light, noise, odors, and temperature, or digestive issues, such as bloating or constipation.

Studies show that Fibromyalgia patients have a heightened sensitivity to pain, so they feel pain when others do not.

Anhedonia is a common phenomenon in Fibromyalgia. Interventions which also target patients' anhedonia may be superior over interventions which only targets somatic symptoms (e.g., poor appetite or fatigue).

Patients suffering from Fibromyalgia commonly experienced loss of intimacy with partners and social isolation.

Previous treatment of fibromyalgia is symptomatic.

Brain imaging studies and other research have uncovered evidence of altered signaling in neural pathways that transmit and receive pain in people with Fibromyalgia.

Resting-state functional magnetic resonance imaging of patients with Fibromyalgia shows altered functional connectivity within and/or between the DMN and executive attention network and between the DMN and the insular cortex, a brain region known to process evoked pain.

Treating a patient suffering from Fibromyalgia and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Fibromyalgia.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, is reflected by at least an im-

provement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdraw-

al or detachment in a patient suffering from Fibromyalgia, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on

day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Fibromyalgia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients with Fibromyalgia. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of Fibromyalgia. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Fibromyalgia, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Fibromyalgia.

An improvement of the Fibromyalgia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Fibromyalgia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Fibromyalgia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Mental and Behavioural Disorders due to Psychoactive Substance Use

Substance Use Disorder (SUD) is a mental disorder that affects a person's behaviour, leading to a person's inability to control their use of substances such as legal or illegal drugs, alcohol, or medications. Symptoms can range from moderate to severe, with addiction being the most severe form of SUD.

A patient suffering from SUD may suffer from a treatment resistant form of the disorder.

Social isolation plays a key role in the development and maintenance of SUD, particularly opioid use disorder.

It can also lead to an increase in drug taking behaviour due to a lack of protective social interactions. Taking drugs alone increases risk of opiate overdose and isolation from one's social network increases risk of withdrawal.

Anhedonia also plays an important role in the pathogenesis of SUD and is associated with poorer treatment outcomes in patients with cocaine-use disorder.

The Snaith-Hamilton Pleasure Scale is a 14-item scale that measures anhedonia and has been used in a study with patients diagnosed with stimulant abuse or dependence. This shows that social/emotional withdrawal or detachment is associated with SUD.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from SUD, deficits in cognitive control are associated with altered connectivity within and/or between resting state networks, such as the default mode network, the salience network, the central executive network, the limbic network and the reward network.

Treating a patient suffering from SUD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of SUD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than

about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction

or elimination of social/emotional withdrawal or detachment in a patient suffering from SUD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from SUD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of SUD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of SUD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of SUD.

An improvement of the SUD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the SUD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the SUD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Psychotic Disorders

Psychotic Disorders are severe mental disorders that cause abnormal thinking and perceptions. Psychotic disorders are characterised by significant impairments in reality testing and alterations in behaviour manifest in positive symptoms such as persistent

delusions, persistent hallucinations, disorganised thinking (typically manifest as disorganised speech), grossly disorganised behaviour, and experiences of passivity and control, negative symptoms such as blunted or flat affect and avolition, and psychomotor disturbances.

A patient suffering from a Psychotic Disorder may suffer from a treatment resistant form of the disorder.

The DSM-5 describes anhedonia as an example of 'negative symptoms' that define psychotic disorders.

Emotional and cognitive deficits associated with social anhedonia may be caused by underlying neural deficits in the ventrolateral prefrontal cortex (VLPFC).

It has been suggested that reduced opportunity for structured social events and workplace interactions in part explain social and emotional withdrawal in patients with psychosis.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Brain imaging of patients suffering from psychosis by functional magnetic resonance imaging of brain resting state networks, reveals profound alterations in distinct regions within and/or between the central executive network, the default mode network and the salience network. Even in patient populations at risk for psychosis, alterations in resting state networks can be identified.

Treating a patient suffering from a Psychotic Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Psychotic Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for in-

stance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Psychotic Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The

reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not

start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from a Psychotic Disorder, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, the occurrence of social/emotional withdrawal or detachment is an important disease aspect in patients suffering from a Psychotic Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Psychotic Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of a Psychotic Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the Psychotic Disorder.

An improvement of a Psychotic Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of a Psychotic Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT

or a pharmaceutically acceptable salt thereof. An improvement of the Psychotic Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from a Psychotic Disorder characterised by mania or hypomania and associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from a Psychotic Disorder characterised by mania or hypomania and associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Schizophrenia is a severe mental health condition characterised by disturbances in multiple mental modalities, including thinking, perception, self-experience, cognition, volition, affect and behaviour. Psychomotor disturbances, including catatonia, may be present.

A patient suffering from Schizophrenia may suffer from a treatment resistant form of the disorder.

Social withdrawal and anhedonia are core features of Schizophrenia, described as classical ‘negative’ symptoms of the disease. They can be explained by a common driving factor which is diminished motivation and pleasure seen in patients with Schizophrenia.

Evidence from clinical interview studies reveals that the majority of patients diagnosed with Schizophrenia displays anhedonia.

Emotional and cognitive deficits associated with social anhedonia may be caused by underlying neural deficits in the ventrolateral prefrontal cortex (VLPFC).

It has been alternatively suggested that reduced opportunity for structured social events and workplace interactions in part explain social and emotional withdrawal in this patient group.

The Brief Clinical Assessment Scale for Schizophrenia (BCASS) contains a separate item relating to “blunted affect”. In addition, the Brief Negative Symptom Scale (BNSS) also contains relevant items, such as, for example “anhedonia” and “blunted affect”. Moreover, the Snaith-Hamilton Pleasure Scale (SHAPS), relating to the measurement of anhedonia, has been already used for measuring anhedonia in Schizophrenia patients. This shows that social/emotional withdrawal or detachment is an important aspect of Schizophrenia.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Abnormal resting state functional connectivity, particularly within and/or between the default mode network, the frontoparietal network and the salience network, is reported in individuals with Schizophrenia. In individuals at high risk for psychosis and in those diagnosed with schizophrenia, several studies have found associations between sleep disturbances and symptom severity.

Treating a patient suffering from Schizophrenia, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of Schizophrenia.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia is observed about 2 hours; on day 1, for instance after about 24 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia preferably persists until at least 6 days; in particular until at least 14

days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of emotional withdrawal, is reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute

psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, in particular of emotional withdrawal, as reflected by at least an improvement in the average score of the trait facet intimacy avoidance of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia is reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, as reflected by at least an improvement in the average score of the trait domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the

last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizophrenia, as reflected by at least an improvement in the average score of the domain detachment of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an integral aspect in patients suffering from Schizophrenia. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Schizophrenia. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Schizophrenia, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of Schizophrenia.

An improvement of Schizophrenia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of Schizophrenia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of Schizophrenia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from Schizophrenia associated with social/emotional withdrawal or detachment, preferably

using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from Schizophrenia associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Dementia

Dementia is generally characterized by a loss of memory, language, problem-solving and other thinking abilities that are severe enough to interfere with daily life.

Dementia is caused by brain changes which trigger a decline in cognitive abilities and also affect behaviour, feelings and relationships.

Studies suggest that profound anhedonia is a key feature in early-onset dementia.

In consequence, social/emotional withdrawal or detachment is common in individuals with dementia, having negative impact on the quality of life of both patients and their families.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Dementia affects various functional and structural connectivity networks in the brain, as can be shown by magnetic resonance imaging studies. Alterations within and/or between the default mode network (DMN), the salience network, and the central executive network (CEN) are observed.

Treating a patient suffering from Dementia and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of Dementia.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia is observed about 2 hours after the last administration of 5-

MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Dementia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from

Dementia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment occurs in patients suffering from Dementia. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Dementia. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Dementia, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the Dementia.

An improvement of the Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alzheimer's Dementia (AD) is a highly prevalent neurodegenerative disorder with an insidious onset and gradual progression of cognitive deficits. Apathy is a very common symptom in neurocognitive disorders such as AD. Prevalence estimates range between 51-72% based on severity of AD, with greater disease severity associated with greater risk of apathy.

In a study of 100 patients with autopsy-confirmed AD, social withdrawal was found to be the earliest recognisable symptom of the disorder, which occurred on average 33 months prior to AD diagnosis.

Social isolation is associated with an elevated risk of all-cause dementia. The relationship between cognitive function and social isolation may be mediated by reduced grey matter volumes in areas that are related to memory and learning.

Anhedonia is frequently observed in AD patients.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

AD affects various functional and structural connectivity networks in the brain which are associated with the topography, clinical phenotype, and severity of the disease. Magnetic resonance imaging studies have demonstrated successive structural and functional disconnection among brain regions supporting the idea that AD is a disconnection syndrome. Alterations within and/or between the default mode network (DMN), salience network, and central executive network (CEN) are observed both in patients with AD and individuals who were at high risk for developing AD.

Therefore, influencing those networks by a therapy according to the invention will lead to an improvement of the social/emotional withdrawal or detachment, and also to an improvement of the symptoms of AD.

Treating a patient suffering from AD and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of AD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD,

in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from AD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from AD. An improvement in social/emotional withdrawal or de-

tachment will therefore also lead to an improvement of the AD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of AD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the AD.

An improvement of the AD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the AD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the AD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Dementia with Lewy Bodies (DLB) is a type of dementia characterized by changes in sleep, behaviour, cognition, movement, and regulation of automatic bodily functions.

Anhedonia is a common symptom in Dementia with Lewy Bodies (DLB). In a study of 312 patients, anhedonia was more frequently seen in individuals with Lewy Bodies dementia than in Alzheimer's disease.

Social isolation is associated with an elevated risk of all-cause dementia. The relationship between cognitive function and social isolation may be mediated by reduced grey matter volumes in areas that are related to memory and learning.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from DLB, resting state network (RSN) alterations can be identified. Functional MRI studies show changes in functional connectivity within and/or between the default mode network, salience network, executive network and basal ganglia/limbic network.

Treating a patient suffering from DLB and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of DLB.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than

about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction

or elimination of social/emotional withdrawal or detachment in a patient suffering from DLB, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from DLB. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the DLB. Since social/emotional withdrawal or detachment furthermore also affects other aspects of DLB, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the DLB.

An improvement of the DLB in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the DLB in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the DLB in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Vascular Dementia is a common type of dementia characterized by problems with reasoning, planning, judgment, memory and other thought processes. Vascular Dementia is due to brain parenchyma injury resulting from one or more cerebrovascular

event (ischemic or haemorrhagic). The vascular aetiology is very varied, ranging from microvascular disease to large vessel stroke.

Social withdrawal is amongst the foremost behavioural alteration seen in patients with Vascular Dementia. Specific alterations may change over time based on neural regions affected by vascular insult in Vascular Dementia.

When compared to Alzheimer's disease, decreased affect/withdrawal was found to be more severe in patients with ischaemic Vascular Dementia.

Patients suffering from severe Vascular Dementia show higher levels of anhedonia than patients suffering from mild/moderate Vascular Dementia.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Functional magnetic resonance imaging reveals altered functional connectivity of resting state networks after a cerebrovascular insult. Patients show an abnormal functional connectivity within and/or between the DMN and other resting state networks.

Treating a patient suffering from Vascular Dementia and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of Vascular Dementia.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia preferably persists until at least 6 days; in particular until at

least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Vascular Dementia, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from Vascular Dementia. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Vascular Dementia. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Vascular Dementia, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the Vascular Dementia.

An improvement of the Vascular Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Vascular Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Vascular Dementia in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

A Fronto-Temporal Dementia (FTD) is a neurodegenerative disorder caused by progressive nerve cell loss in the brain's frontal or temporal lobes that constitutes a leading cause of younger onset dementia.

Patients present with heterogeneous constellations of behavioural and psychological symptoms among which progressive changes in social conduct, lack of empathy, apathy, disinhibited behaviours, and cognitive impairments are frequently observed.

The behavioural variant is characterized by at least three symptoms such as disinhibition; apathy or inertia, which leads to inactivity and lack of effort; loss of sympathy or empathy; perseverative, compulsive, ritualistic behaviours or stereotypies; and hyperorality and dietary changes, associated with a prominent decline in social cognition and/or executive abilities.

Anhedonia is a primary stand-alone symptom of FTD comparing FTD to healthy old-aged controls. Anhedonia is present early in the disease course.

Social withdrawal is common in FTD.

Anhedonia has been measured in patients suffering from FTD with the Snaith-Hamilton Pleasure Scale (SHAPS), indicating the relevance of social/emotional withdrawal or detachment in these patients.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Resting state-functional magnetic resonance imaging (Rs-fMRI) analysis of individuals suffering from a FTD reveals global functional deterioration and a loss of network integration. Altered functional connectivity was mainly identified within and/or between the attention network, the default mode network and in particular the salience network.

Treating a patient suffering from FTD and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of FTD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on

day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at

least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the

recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from FTD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from FTD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the FTD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of FTD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the FTD.

An improvement of the FTD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the FTD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the FTD in a patient also suffering

from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Parkinson's Disease (PD)

Parkinson's Disease (PD) is an illness characterized by gradually progressive problems with movement, most commonly involving slowing of movements, a tremor present at rest, and walking instability which can cause falls.

Anhedonia is one of the most frequent psychiatric symptoms in PD. Overall anhedonia scores are significantly higher in PD than in healthy controls.

PD can interfere with individuals' social functioning and lead to social withdrawal. Social withdrawal may result in negative outcomes for persons with PD, such as decreased quality of life.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In PD patients, a functional reorganization of resting state networks, critical to generate and maintain an efficient behavioral and cognitive performance, is observed.

Levodopa, which improves the clinical status of Parkinson patients, has the potential to influence functional connectivity of resting state networks in Parkinson patients.

Treating a patient suffering from PD and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of PD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about

24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale

(DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more prefer-

ably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from PD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from PD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the PD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of PD, the inventors

conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the PD.

An improvement of the PD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the PD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the PD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Eating Disorders

An **Eating Disorder** is a mental disorder characterised by abnormal eating behaviours that negatively affect a person's physical or mental health.

A patient suffering from an Eating Disorder may suffer from a treatment resistant form of the disorder.

A meta-analysis of 10 studies found that anhedonia was significantly higher in groups with Eating Disorders than healthy control groups. There are also suggestions that anhedonia may be correlated with increased symptom severity.

Social withdrawal is particularly prevalent in individuals with Eating Disorders, with higher levels of self-criticism seen compared to other mental disorders.

The relevance of social/emotional withdrawal or detachment in patients suffering from Eating Disorders is reflected in, for example, the Clinical Impairment Assessment Questionnaire (CIA3.0), which is a 16-item, self-report instrument, which was designed to measure an impairment of Eating Disorders overall and in three specific domains

(personal, cognitive, social). Exemplary items of this questionnaire relate to the interference with doing things the patient used to enjoy or with the relationship to others.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients suffering from Eating Disorders, results from functional network connectivity studies indicate disrupted resting-state connectivity within and/or between executive networks, the default-mode network and the salience network.

Treating a patient suffering from an Eating Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the Eating Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day

28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6

days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt

thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an Eating Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from an Eating Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Eating Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of an Eating Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the Eating Disorder.

An improvement of the Eating Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Eating Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S

score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Eating Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Autism Spectrum Disorder (ASD)

Patients suffering from an **Autism Spectrum Disorder (ASD)**, including autism, Asperger's syndrome and atypical autism, have persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication. The condition is moreover characterized by a range of restricted, repetitive, and inflexible patterns of behaviour, interests or activities that are clearly atypical or excessive for the individual's age and sociocultural context.

Anhedonia may serve as a common underlying transdiagnostic psychopathology feature, predictive of the severity of ASD. It may be recommended for clinicians to screen for anhedonia severity in individuals diagnosed with an ASD.

ASD and depression have overlapping features in several key areas, including most notably social withdrawal.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

ASD is a disorder of brain network connectivity. Neuroimaging studies indicate that ASD is related to the anomalous responses in certain brain areas, significant alteration of brain networks, including altered functional connectivity within and/or between the default mode network (DMN) and the sensory processing network, and disturbed neural synchronization between brain areas.

Treating a patient suffering from an ASD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT

or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the ASD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last ad-

ministration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from an ASD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period

does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ASD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from an ASD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the ASD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of an ASD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the ASD.

An improvement of the ASD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the ASD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the ASD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Attention Deficit Hyperactivity Disorder (ADHD)

Attention Deficit Hyperactivity Disorder (ADHD) is a condition that affects a patient's behaviour. A patient suffering from ADHD can seem restless, may have trouble concentrating and may act on impulse.

Patients with ADHD may also have additional problems, such as sleep and anxiety disorders.

A patient suffering from ADHD may suffer from a treatment resistant form of the disorder.

Social isolation was found to be pervasive amongst school-aged boys with ADHD. Social isolation occurred as a result of peer rejection and could often result in bullying and

harassment by peer groups. ADHD symptoms in early childhood increase the risk of social isolation in later childhood.

In adults, anhedonia is also associated with ADHD.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Resting state network analysis in patients suffering from ADHD reveals dysfunctional connectivity across multiple brain resting state networks, in particular dysfunctional connectivity within and/or between distinct regions of the default mode network, the dorsal attention network and the salience network.

Treating a patient suffering from ADHD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the ADHD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on

day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at

least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the

recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from ADHD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment occurs in patients suffering from ADHD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the ADHD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of ADHD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the ADHD.

An improvement of the ADHD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the ADHD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the ADHD in a pa-

tient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Personality Disorders

Schizotypal Personality Disorder is a mental health condition marked by a consistent pattern of intense discomfort with relationships and social interactions. Patients suffering from Schizotypal Personality Disorder have unusual thoughts, speech and behaviours, which hinder their ability to form and maintain relationships.

A patient suffering from Schizotypal Personality Disorder may suffer from a treatment resistant form of the disorder.

Social anhedonia is a key facet of Schizotypal Personality Disorder.

The Brief Negative Symptom Scale (BNSS), which can also be applied for Schizotypal Personality Disorder, contains relevant items, such as, for example “anhedonia” and “blunted affect”. This shows that social/emotional withdrawal or detachment is an important aspect of a Schizotypal Personality Disorder.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

In patients with Schizotypal Personality Disorder, DMN functional connectivity, particularly that involving cognitive or emotional regulation, is altered. Neuroimaging analysis by fMRI further reveals alterations within and/or between frontoparietal network and dorsal attention network.

Treating a patient suffering from Schizotypal Personality Disorder, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of Schizotypal Personality Disorder.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of social anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), in particular in the score of the items relating to social anhedonia, about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of social anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), in particular in the score of the items relating to social anhedonia, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from GAD, as reflected by at least an improvement in the score of the DARS, in particular in the score of the items relating to social anhedonia, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular

of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from Schizotypal Personality Disorder, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from Schizotypal Personality Disorder. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the Schizotypal Personality Disorder. Since social/emotional withdrawal or detachment furthermore also affects other aspects of Schizotypal Personality Disorder, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the Schizotypal Personality Disorder.

An improvement of the Schizotypal Personality Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the Schizotypal Personality Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-

MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the Schizotypal Personality Disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Compared to other psychedelics, like LSD, psylocibin or DMT, 5-MeO-DMT or a pharmaceutical acceptable salt thereof can be administered to patients suffering from Schizotypal Personality Disorder associated with social/emotional withdrawal or detachment, preferably using dosing schemes as described herein, without a significant risk of inducing mania or hypomania.

Preferably, the patient suffering from Schizotypal Personality Disorder associated with social/emotional withdrawal or detachment does not experience treatment-emergent mania or hypomania.

Borderline Personality Disorder (BPD)

Persistent mood instability, impulsivity, identity disturbance and interpersonal dysfunction are characteristic traits for **Borderline Personality Disorder (BPD)**.

A patient suffering from BPD may suffer from a treatment resistant form of the disorder.

Anhedonia is an important feature of BPD and contributes to the severity of symptoms. Patients with BPD may suffer from social withdrawal.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Patients with BPD show abnormal connectivity patterns in resting-state networks. Analysis of functional connectivity of brain resting state networks using functional magnetic resonance imaging reveals alterations within and/or between various networks, such as for example the default mode network and salience network.

Treating a patient suffering from BPD, including a treatment resistant form of the disorder, and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of the BPD.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, as reflected by at least an improvement in

the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5

(PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from BPD, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earli-

er than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

As indicated above, social/emotional withdrawal or detachment is an important aspect in patients suffering from BPD. An improvement in social/emotional withdrawal or detachment will therefore also lead to an improvement of the BPD. Since social/emotional withdrawal or detachment furthermore also affects other aspects of BPD, the inventors conclude that the observed improvement in social/emotional withdrawal or detachment will additionally contribute to an overall improvement of the BPD.

An improvement of the BPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the BPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the BPD in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Medical Health Conditions Leading to an Associated Mental or Nervous System Condition

The social/emotional withdrawal or detachment may occur in a patient suffering from medical health condition leading to an associated mental or nervous system condition.

Social/Emotional Withdrawal or Detachment Due to Traumatic Brain Injury (TBI)

A traumatic brain injury (TBI) is an injury to the brain caused by an external force.

Traumatic brain injuries are characterized as primary or secondary brain injuries. A primary brain injury refers to the structural damage created during the time of impact from contact, acceleration–deceleration, and/or rotational forces. A secondary brain injury refers to the damage sustained from the subsequent cellular processes that occur from the primary injury (ie, hypoxia and/or raised intracranial pressure).

Anhedonia is a common symptom following Traumatic Brain Injury.

TBI can have wide-ranging physical and psychological effects, which may appear immediately after the traumatic event, while others may appear days or weeks later. The cognitive, behavioral, and sensorimotor disabilities that result from TBI often dramatically decrease quality of life. TBI can cause irritability, anxiety, insomnia, and depression. Depression after a TBI is characterized by decreased social contact.

Social/emotional withdrawal or detachment or at least aspects thereof may be assessed, for instance, by using the Snaith-Hamilton Pleasure Scale (SHAPS) or the Dimensional Anhedonia Rating Scale (DARS) or the Personality Inventory for DSM-5 (PID-5) – Adult.

Resting state functional connectivity analysis reveals alterations in overall functional connectivity within and/or between resting state networks, such as the DMN, the frontoparietal network, the executive network, and the sensory motor network. For instance, highly connected regions that can be found within the DMN are particularly susceptible to alterations in functional connectivity following traumatic brain injury.

Treating a patient suffering from TBI and associated social/emotional withdrawal or detachment with 5-MeO-DMT or a pharmaceutically acceptable salt thereof reduces or eliminates the social/emotional withdrawal or detachment and leads to an improvement of TBI.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI occurs not later than about 2 hours after the last administration of 5-

MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, is reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, as reflected by at least an improvement in the score of the Snaith-Hamilton Pleasure Scale (SHAPS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, as reflected by at least an improvement in the score of the SHAPS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, is reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS) about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, as reflected by at least an improvement in the score of the Dimensional Anhedonia Rating Scale (DARS), occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, as reflected by at least an improvement in the score of the DARS, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, is reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of anhedonia, as reflected by at least an improvement in the average score of the trait facet anhedonia of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Alternatively or additionally, the reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of social withdrawal, is reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point. The reduction or elimination of social/emotional withdrawal or detachment in a patient suffering from TBI, in particular of social withdrawal, as reflected by at least an improvement in the average score of the trait facet withdrawal of the Personality Inventory for DSM-5 (PID-5) – Adult, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, wherein the recall period does not start earlier than the time point when acute psychedelic experiences have subsided after the last administration to the assessment time point.

Social/emotional withdrawal or detachment due to TBI is related to other symptoms which develop as a consequence of TBI. An improvement in social/emotional withdrawal or detachment will also lead to an improvement of such other symptoms.

An improvement of the TBI in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

An improvement of the TBI in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof. An improvement of the TBI in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the CGI-S score, preferably persists until at least 6 days; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

Examples

The following Examples are listed to aid understanding of the invention and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1 - 5-MeO-DMT aerosol generation and administration

Step 1: A stock solution of 5-MeO-DMT free base in 100% ethanol is prepared in a volumetric flask, so that the target dosage of 5-MeO-DMT free base to be administered via inhalation to the volunteer or patient is contained in a solution volume of 200 µl. Typical target dosages are from 1 mg to 25 mg 5-MeO-DMT. E.g. for a target dosage of 18 mg 5-MeO-DMT, 90 mg of 5-MeO-DMT will be dissolved in 100% ethanol for a final solution volume of 1 ml. Aliquots of the stock solution can then be stored in vials until further use.

Step 2: 200 µl of the solution is transferred to a dosing capsule containing the drip pad (Storz & Bickel, Germany), and then the dosing capsule is closed with its lid.

Step 3: The dosing capsule filled with the 5-MeO-DMT ethanol solution is transferred to the filling chamber of a first Volcano Medic Vaporizer, which has been pre-heated with the temperature set at 55°C. Then the airflow of the vaporizer is switched on for 60 seconds at the pre-set rate of about 12 l/min. The heated air will flow through the dosing capsule, allowing the ethanol to evaporate, with the target dosage of 5-MeO-DMT

being left in the capsule, as a thin layer covering the stainless-steel wire mesh. Accurate preparation of the dosing capsule can be confirmed by demonstrating that the final weight increase of the capsule compared to the weight of the empty capsule is about equal to the target dosage of 5-MeO-DMT.

Step 4: The prepared dosing capsule is removed from the filling chamber. It is then transferred to the filling chamber of a second Volcano Medic Vaporizer, which has been pre-heated with the temperature set at 210°C and the airflow on for at least 5 minutes and then turned off immediately prior to transfer. An inhalation balloon with a valve (Storz & Bickel, Germany) is mounted on the socket of the filling chamber, the filling chamber is closed tightly and immediately afterwards the airflow is switched on for exactly 15 seconds at the pre-set flow rate of about 12 l/min, and then turned off. This will allow the full dose of 5-MeO-DMT to aerosolize and be distributed in approximately 3 liters of air in the inhalation balloon. Accurate aerosolization of the 5-MeO-DMT can be confirmed by demonstrating that the capsule weight has returned to about its initial weight.

Step 5: The balloon is then disconnected from the filling chamber, which automatically closes the valve. After attachment of the mouthpiece to the balloon, the aerosol is ready for immediate administration to the volunteer or patient.

Step 6: To prepare for the administration, the patient is asked to initially perform 1-2 deep inhalations with full exhalations, ending this sequence with a deep exhalation. Then, with the mouthpiece firmly held against the lips, the full and complete volume of the inhalation balloon is inhaled in one inhalation, holding the breath for 10 (±2.5) seconds, followed by a normal exhalation. After completing the inhalation procedure, the patient will be instructed to lie down.

Further details regarding the administration of 5-MeO-DMT by inhalation are disclosed in Example 1 of WO 2020/169850 A1, the contents of which is incorporated herein by reference.

Example 2 - Preparation of 5-MeO-DMT in high purity

5-MeO-DMT (2.0 g) was dissolved in MTBE (4 mL, 2.0 volumes) at 35 to 40°C before being cooled to room temperature over 30 minutes. After stirring at room temperature for 50 minutes no crystallisation was observed, therefore, the batch temperature was decreased to 7 to 12°C over 30 minutes. After stirring at 7 to 12°C for 10 minutes crystallisation occurred. The batch was subsequently filtered following a 1 hour stir out at 7 to 12°C. After washing with MTBE (1 mL, 0.5 volumes), at 7 to 12°C, the batch was pulled dry under vacuum for 3.5 hours to yield a pale orange solid in 1.02 g (50% recovery). The isolated solid was analysed for purity by HPLC as described in WO 2020/169850 A1. The purity was found to be 99.74 %area.

The results from the analysis further indicate that the level of individual impurities was below 0.10%area. Solvent analysis of sample indicated an MTBE level of 17 ppm.

Example 3 - Preparation of 5-MeO-DMT hydrobromide salt

5-MeO-DMT HBr was prepared on a 100mg scale.

5-MeO-DMT free base was combined with isopropyl acetate (10 vols), and the resulting solution of 5-MeO-DMT was heated to 50°C. HBr was charged (1M in ethanol, 1eq) in one single aliquot. The mixture was held at temperature and equilibrated for 3 hours.

After 1 hour, a suspension had formed. The suspension was finally cooled to room temperature and equilibrated for 18 hours. Solids were isolated by filtration and dried in vacuo at 40°C for 18 hours.

An off-white crystalline material was obtained.

The salt has a melting point of 174°C and is characterized by an X-ray diffraction pattern comprising peaks at 14.5°2• ±0.2°2• ; 16.7°2• ±0.2°2• ; 17.0°2• ±0.2°2• ; 20.6°2• ±0.2°2• ; 20.7°2• ±0.2°2• ; 21.4°2• ±0.2°2• ; 24.2°2• ±0.2°2• ; 24.8°2• ±0.2°2• ; 25.3°2• ±0.2°2• ; 27.4°2• ±0.2°2• ; measured using Cu K• radiation.

Example 4 - Determination of inhibition constants for central 5-HT1A and 5-HT2A receptors in post-mortem human brain membrane preparations

In this study, the affinity of three psychedelic test compounds (psilocin, DMT and 5-MeO-DMT) for 5-HT1A and 5-HT2A receptors in post-mortem human brain tissue from the hippocampus and frontal cortex, respectively, was determined using the technique of radioligand binding.

Human brain samples were obtained from the Edinburgh Sudden Death Brain Bank. All donors were sudden deaths with no prior history of coma, psychiatric or neurological disorders and under the age of 65 with a post-mortem interval of less than or equal to 72 hours.

Binding to 5-HT1A receptors in post-mortem human hippocampus

Hippocampus was homogenised in ice-cold 0.25 M sucrose (1:30 w/v) using a motor driven Teflon pestle (12 strokes at 120 rpm). Myelin and cell debris were removed by centrifugation at 1,000g for 10 minutes. The supernatant was stored on ice and the pellet re-homogenised in 0.25 M sucrose (1:15 w/v) and centrifuged at 750g for 10 minutes. The supernatants were combined and diluted in ice-cold membrane preparation buffer, (1:100 w/v) using a tight-fitting glass/Teflon homogeniser (12 strokes, 800 rpm) and centrifuged at 20,500 g for 10 minutes. The pellet was resuspended in ice-cold membrane preparation buffer and incubated at 37˚C for 10 minutes before being centrifuged at 20,500 g for 10 minutes. The pellet was resuspended and centrifuged a final time to wash the tissue (20,500 x g for 10 mins). The resulting pellet was then re-suspended in ice-cold assay buffer at a tissue concentration equivalent to 3.125 mg wet weight of tissue/ml. All centrifugations were carried out at 4°C. The membrane preparation buffer consisted of 50 mM Tris-HCl, pH 7.7, 4 mM $CaCl_2$ and 0.1% ascorbic acid. The assay buffer consisted of 50 mM Tris, pH 7.7, 4 mM $CaCl_2$, 0.1% ascorbic acid and 10 µM Pargyline.

For saturation binding analysis, hippocampal membranes (400 µl; equivalent 1.25 mg wet weight tissue/tube) was incubated with 50 µl of 0.075 – 9.6 nM [^{3}H]8-OH-DPAT and either 50 µl of assay buffer (total binding) or 50 µl of 1 µM WAY 100635 (non-specific binding) at 25°C for 30 minutes. The wash buffer consisted of 50 mM Tris, pH 7.7.

In a displacement assay, hippocampal membranes (400 µl; equivalent 1.25 mg wet weight tissue/tube) were incubated with 50 µl of 0.6 nM [^{3}H]8-OH-DPAT and either 50 µl of assay buffer (total binding) or 50 µl of 1 • M WAY 100635 (non-specific binding) or 50 µl of one of the test compounds in one of ten concentrations between 1 and 10000 nM at 25°C for 30 minutes.

Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11731 filters, pre-soaked in 0.5% polyethylenimine (PEI) using a Skatron cell harvester. Filters were rapidly washed with ice-cold wash buffer (wash setting 0,9,9) and radioactivity determined by liquid scintillation counting (1 ml Packard MV Gold scintillator).

The concentration of compound required to inhibit 50% of specific binding (IC_{50}) and the Hill Slope were calculated by using non-linear regression. The K_i was calculated using the one-site binding model allowing for ligand depletion.

Binding to 5-HT2A receptors in post-mortem human frontal cortex

Frontal cortex was homogenised in ice-cold 0.25 M sucrose (1:30 w/v) using a motor driven Teflon pestle (12 strokes at 120 rpm). Myelin and cell debris was removed by centrifugation at 1,000g for 10 minutes. The supernatant was stored on ice and the pellet re-homogenised in 0.25 M sucrose (1:15 w/v) and centrifuged at 750g for 10 minutes. The supernatants were combined and diluted in ice-cold 50 mM Tris-HCl assay buffer, pH 7.4 (1:100 w/v), homogenised using a tight-fitting glass/Teflon homogeniser (12 strokes, 800 rpm) and centrifuged at 20,500 g for 10 minutes. The pellet was centrifuged a further two times to wash the tissue (20,500 x g for 10 mins). The resulting pellet was then resuspended in ice-cold 50 mM Tris-HCl assay buffer, pH 7.4 at a tissue concentration equivalent to 10 mg wet weight of tissue/ml. All centrifugations were carried out at 4°C.

For saturation binding analysis, frontal cortical membranes (400 µl; equivalent to 4 mg wet weight of tissue/tube) were incubated with 50 µl of 0.00625 – 0.8 nM [^{3}H]MDL-100,907 and either 50 µl of assay buffer or 50 µl of 10 • M ketanserin (non-specific binding) at 25°C for 60 minutes. The assay and wash buffer consisted of 50 mM Tris-HCl buffer pH 7.4.

In a displacement assay, frontal cortical membranes (400 µl; equivalent 4 mg wet weight tissue/tube) was incubated with 50 µl of 0.1 nM [3H]MDL-100,907 and either 50 µl of assay buffer (total binding) or 50 µl of 10 • M ketanserin (non-specific binding) or 50 µl of one of the test compounds in one of ten concentrations between 1 and 10000 nM at 25°C for 60 minutes.

Membrane bound radioactivity was recovered and determined as above. Data analysis was also as above.

Results

The dissociation constant (K_d value) of [^{3}H]8-OH-DPAT for 5-HT1A receptors in hippocampal membranes from post-mortem human brain tissue was determined for each of the three donors. The dissociation constants (K_d values) obtained were 0.51, 0.28 and 0.52 nM, respectively.

Mean inhibition constants (K_i values) for psilocin, DMT and 5-MeO-DMT were 48, 38 and 1.80 nM (mean n=3), respectively. All compounds gave Hill slopes approximating to unity, suggesting a one-site binding model.

The dissociation constant (K_d values) of [^{3}H]MDL-100,907 for 5-HT2A receptors in frontal cortical membranes from post-mortem human brain tissue was determined for each of the three donors. The dissociation constants (K_d values) obtained were 0.11, 0.08 and 0.08 nM, respectively.

Mean inhibition constants (K_i values) for psilocin, DMT and 5-MeO-DMT were 37, 117 and 122 nM (mean n=3), respectively. All compounds gave Hill slopes approximating to unity, suggesting a one-site binding model.

The selectivity ratio of psilocin, DMT and 5-MeO-DMT for 5-HT2A over 5-HT1A receptors was 0.78, 3.1 and 68, respectively.

Example 5 - Toxicological testing of 5-MeO-DMT

5-MeO-DMT did not induce mutation in four histidine-requiring bacterial strains (TA98, TA100, TA1535 and TA1537) of Salmonella typhimurium, and one tryptophan-requiring

strain (WP2 uvrA pKM101) of Escherichia coli. These conditions included treatments at concentrations up to 5000 µg/plate (the maximum recommended concentration according to current regulatory guidelines), in the absence and in the presence of a rat liver metabolic activation system (S-9).

Example 6 - Assessment of the pharmacokinetics of 5-MeO-DMT and bufotenine

In order to investigate the pharmacokinetic properties of 5-MeO-DMT, three groups of 8 subjects each were formed. Subjects were administered a single dose of 6 mg; 12 mg or 18 mg 5-MeO-DMT via inhalation. Blood samples were obtained at 1; 2; 4; 7; 10; 15; 20; 30; 45 min and 1; 1.5; 2; 3; 4 hours after administration.

5-MeO-DMT concentrations were determined using LC-MS/MS. PK parameters were generated by algebraic analysis of the concentration versus time plots for each individual. The analysis was carried out using the software Phoenix WinNonlin 6.3.

Median Cmax values obtained for the three groups were 11.85 ng/ml (6 mg group), 22.90 ng/ml (12 mg group) and 38.45 ng/ml (18 mg group).

Table 1 below shows median percentage plasma concentrations relative to Cmax as determined for the time points indicated.

	Median percentage plasma concentration relative to Cmax													
time (min)	1	2	4	7	10	15	20	30	45	60	90	120	180	240
6 mg	96	98	83	56	40	22	16	10	8	4	2	1	0	N.A.
12 mg	100	79	59	30	22	12	8	5	3	2	0	0	0	0
18 mg	100	79	59	30	22	12	8	5	3	2	0	0	0	0

Pharmacokinetic measurements were also carried out for dosing schemes relying on uptitration. Substantially similar results were obtained.

Blood concentrations were also determined for the 5-MeO-DMT metabolite bufotenine. Only in few samples, concentrations were above the lower level of quantification (LLOQ) (25 pg/ml). From 15 min onwards, the bufotenine concentration was always below the LLOQ.

Substantially similar observations were made when subjects receiving an uptitration scheme were included.

Example 7 - Clinical trial in patients suffering from TRD

A Phase 1/2 clinical trial of 5-MeO-DMT, administered via inhalation as described herein, in patients with treatment-resistant major depressive disorder (TRD) has been completed. This trial was designed in two parts. Part A was an open-label, single-arm, single-dose Phase 1 trial with two dose levels (12 mg (n=4) and 18 mg (n=4)). Part B was an open-label, single-arm Phase 2 trial applying an individualized dosing regimen with intra-patient dose escalation with 5-MeO-DMT. Patients (n=8) received at least one and up to three doses of 5-MeO-DMT (6 mg, 12 mg and 18 mg) in a single day, with higher doses only being administered if a peak experience was not achieved at the previously administered dose. The primary endpoint of Part A was to assess the safety and tolerability of single dosing of 5-MeO-DMT in patients with TRD. The primary endpoint of Part B was to assess the effects on the severity of depression, as assessed by the proportion of patients in remission on day seven after dosing, defined as a MADRS total score of less than or equal to 10.

In Part A, 3 of 4 patients in both groups (12 mg and 18 mg) experienced at least one ADR, all of which were mild and resolved spontaneously. No SAEs were reported.

Two of four patients (50%) in the 12 mg group and one of four patients (25%) in the 18 mg group had a MADRS remission on day seven after dosing, and one further patient (25%) in the 18 mg group had a MADRS clinical response on day seven after dosing. The mean MADRS change from baseline at day seven was -21.0 (-65%) in the 12 mg group and -12.8 (-41%) in the 18 mg group.

In Part B, 7 of 8 patients (87.5%) experienced at least one ADR. All ADRs resolved spontaneously. No SAEs were reported.

The primary endpoint was met with seven of eight patients (87.5%) achieving a MADRS remission on day seven ($p<0.0001$). The mean MADRS change from baseline at day seven was 24.4 (76%).

No clinically significant changes were observed in either Part A or Part B in any of the safety laboratory analyses, vital signs, psychiatric safety assessments or measures of cognitive function.

Results are summarized in the tables below.

Scale item	Scale	Baseline IDR	2 / 3 hours	Improvement 2 / 3 hours	Percentage improvement
Concentration Difficulties	MADRS	30	11	19	63.33%
Lassitude	MADRS	27	10	17	62.96%
Inability to Feel	MADRS	36	12	24	66.67%
Inner Tension	MADRS	26	11	15	57.69%
Pessimistic Thoughts	MADRS	28	7	21	75.00%
Suicidal Thoughts	MADRS	11	3	8	72.72%
Guilt Feelings	BPRS	34	14	20	58.82%
Tension	BPRS	16	11	5	31.25%
Anxiety	BPRS	37	19	18	48.65%
Emotional Withdrawal	BPRS	13	8	5	38.46%
Blunted Affect	BPRS	15	11	4	26.67%

Table 2-A Scores recorded against relevant MADRS and BPRS items for patients assigned to intra-day individualised dosing regimen (IDR). The item scores represent the sum of the individual patient scores for all patients (n=8) in the IDR group. Assessment 2 hours (MADRS) or 3 hours (BPRS) after administration of the last dose.

Scale item	Scale	Baseline IDR	Day 1	Improvement at Day 1	Percentage improvement
Reduced Sleep	MADRS	25	12	13	52.00%
Concentration Difficulties	MADRS	30	1	29	96.67%
Lassitude	MADRS	27	5	22	81.48%
Inability to Feel	MADRS	36	2	34	94.44%

Inner Tension	MADRS	26	6	20	76.92%
Pessimistic Thoughts	MADRS	28	4	24	85.71%
Suicidal Thoughts	MADRS	11	1	10	90.91%
Guilt Feelings	BPRS	34	11	23	67.65%
Tension	BPRS	16	11	5	31.25%
Anxiety	BPRS	37	16	21	56.76%
Emotional Withdrawal	BPRS	13	8	5	38.46%
Blunted Affect	BPRS	15	8	7	46.67%

Table 2-B Scores recorded against relevant MADRS and BPRS items for patients assigned to intra-day individualised dosing regimen (IDR). The item scores represent the sum of the individual patient scores for all patients (n=8) in the IDR group. Assessment on day 1.

Scale item	Scale	Baseline IDR	Day 7	Improvement at Day 7	Percentage improvement
Reduced Sleep	MADRS	25	9	16	64.00%
Concentration Difficulties	MADRS	30	9	21	70.00%
Lassitude	MADRS	27	3	24	88.89%
Inability to Feel	MADRS	36	6	30	83.33%
Inner Tension	MADRS	26	12	14	53.85%
Pessimistic Thoughts	MADRS	28	3	25	89.29%
Suicidal Thoughts	MADRS	11	3	8	72.73%
Guilt Feelings	BPRS	34	10	24	70.59%
Tension	BPRS	16	10	6	37.50%
Anxiety	BPRS	37	17	20	54.05%
Emotional Withdrawal	BPRS	13	8	5	38.46%
Blunted Affect	BPRS	15	8	7	46.67%

Table 2-C Scores recorded against relevant MADRS and BPRS items for patients assigned to intra-day individualised dosing regimen (IDR). The item scores represent the sum of the individual patient scores for all patients (n=8) in the IDR group. Assessment on day 7.

Scale item	Scale	Baseline 12mg	2 / 3 hours	Improvement after 2 / 3 hours	Percentage improvement
Concentration Difficulties	MADRS	16	7	9	56.25%
Lassitude	MADRS	16	10	6	37.50%
Inability to Feel	MADRS	16	9	7	43.75%
Inner Tension	MADRS	13	2	11	84.62%
Pessimistic Thoughts	MADRS	16	8	8	50.00%
Suicidal Thoughts	MADRS	8	3	5	62.50%
Guilt Feelings	BPRS	18	9	9	50.00%
Tension	BPRS	14	9	5	35.71%
Anxiety	BPRS	25	11	14	56.00%
Emotional Withdrawal	BPRS	13	11	2	15.38%
Blunted Affect	BPRS	11	8	3	27.27%

Table 3-A Scores recorded against relevant MADRS and BPRS items for patients assigned to 12mg dosing regimen. The item scores represent the sum of the individual patient scores for all patients (n=4) in the 12mg group. Assessment 2 hours (MADRS) or 3 hours (BPRS) after administration of the dose.

Scale item	Scale	Baseline 12mg	Day 1	Improvement at Day 1	Percentage improvement
Reduced Sleep	MADRS	12	10	2	16.67%
Concentration Difficulties	MADRS	16	2	14	87.50%
Lassitude	MADRS	16	0	16	100.00%
Inability to Feel	MADRS	16	1	15	93.75%
Inner Tension	MADRS	13	3	10	76.92%
Pessimistic Thoughts	MADRS	16	7	9	56.25%
Suicidal Thoughts	MADRS	8	5	3	37.50%
Guilt Feelings	BPRS	18	5	13	72.22%
Tension	BPRS	14	6	8	57.14%
Anxiety	BPRS	25	6	19	76.00%
Emotional Withdrawal	BPRS	13	8	5	38.46%
Blunted Affect	BPRS	11	6	5	45.45%

Table 3-B Scores recorded against relevant MADRS and BPRS items for patients assigned to 12mg dosing regimen. The item scores represent the sum of the individual patient scores for all patients (n=4) in the 12mg group. Assessment on day 1.

Scale item	Scale	Baseline 12mg	Day 7	Improvement at Day 7	Percentage improvement
Reduced Sleep	MADRS	12	6	6	50.00%
Concentration Difficulties	MADRS	16	3	13	81.25%
Lassitude	MADRS	16	3	13	81.25%
Inability to Feel	MADRS	16	1	15	93.75%
Inner Tension	MADRS	13	5	8	61.54%
Pessimistic Thoughts	MADRS	16	8	8	50.00%
Suicidal Thoughts	MADRS	8	7	1	12.50%
Guilt Feelings	BPRS	18	5	13	72.22%
Tension	BPRS	14	6	8	57.14%
Anxiety	BPRS	25	6	19	76.00%
Emotional Withdrawal	BPRS	13	6	7	53.85%
Blunted Affect	BPRS	11	5	6	54.55%

Table 3-C Scores recorded against relevant MADRS and BPRS items for patients assigned to 12mg dosing regimen. The item scores represent the sum of the individual patient scores for all patients (n=4) in the 12mg group. Assessment on day 7.

Example 8 - Clinical trial of 5-MeO-DMT administered via inhalation to patients with postpartum depression

The single-arm, open-label clinical trial will involve 15 adult female patients with clinically diagnosed postpartum depression (PPD).

The patients will receive a single-day individualized 5-MeO-DMT dosing regimen via inhalation after vaporization.

More in particular, the patients will receive up to three doses of 5-MeO-DMT on Day 0: 6 mg, 12 mg, and 18 mg.

1. All patients will receive an initial dose of 6 mg 5-MeO-DMT.
2. The second dose (12 mg) will only be administered if:
    a. A peak experience (total score of • 75) has not been achieved following the 6 mg dose, and
    b. The 6 mg dose was safe and well-tolerated according to the investigator,
    c. Any psychoactive effects (PsE) of the prior dose have subsided, and
    d. Pre-dose vital parameters and forced expiratory volume in one second (FEV1) are in normal range, or if outside of the normal range, are not clinically significant according to the investigator.
3. Similarly, a third dose (18 mg) will only be administered if:
    a. A peak experience (total score of • 75) has not been achieved following the 12 mg dose, and
    b. The 12 mg dose was safe and well-tolerated according to the investigator, and
    c. Any PsE of the prior dose have subsided, and
    d. Pre-dose vital parameters and forced expiratory volume in one second (FEV1) are in normal range, or if outside of the normal range, are not clinically significant according to the investigator.

The patients will be assessed for a peak psychedelic experience (based on a patient-scored visual analogue scale, the PE scale), sedation, and other endpoints after dosing. Follow-up visits are planned for Day 1, and Day 7 after the dosing day.

The following criteria must be met by all patients considered for clinical trial participation:

1. Is female and in the age range between 18 and 45 years (inclusive) at screening.
2. Has a body mass index (BMI) in the range of 18.5 and 35 kg/m^2 (inclusive) at screening.
3. Meets the trial criteria for PPD as assessed by a trial psychiatrist or registered psychologist:

   a. Diagnosis of Major Depressive Disorder without psychotic features, confirmed by the Mini-International Neuropsychiatric Interview (MINI), with peri-partum onset that began no earlier than gestation and no later than the first 4 weeks postpartum.
   b. Has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of equal to or greater than 28 at screening and pre-dose on Day 0.
6. Must have either ceased lactating at screening; or, if still lactating or actively breast feeding at screening, must agree to temporarily cease breastfeeding from just prior to receiving study drug on Day 0 through 24 hours post last dose, and to pump and discard all breastmilk during those 24 hours as needed, but need to include a pump/discard at 2.5 hours post last dose and 24 hours post last dose prior to reinitiating breastfeeding.
4. Must agree to remain completely abstinent (complete avoidance of heterosexual intercourse) or use a highly effective (failure rate <1%), medically accepted contraceptive method for 30 days prior to dosing and for 90 days after 5-MeO-DMT dosing. Patients must have a negative pregnancy test at screening and on the pre-test day (Day -1).
5. Is willing to delay start of other antidepressant or anxiety medication until after the end of the trial at Day 7 and agrees to keep any psychotherapy unchanged during the trial.

A potential patient who meets any of the following key exclusion criteria will be excluded from participation in this trial:

1. Has, based on history, psychiatric assessment, and evaluation of the MINI, a current or prior diagnosis of bipolar disorder, a manic or hypomanic episode, a psychotic disorder, Major Depressive Disorder (MDD) or other mood disorder with psychotic features, obsessive compulsive disorder, post-traumatic stress disorder (PTSD), autism spectrum disorder, borderline personality disorder, schizophrenia, delusional disorder, paranoid personality disorder, schizoaffective disorder, clinically significant intellectual disability, or any other psychiatric comorbidity that renders the patient unsuitable for the trial according to the investigator's judgment.
2. Has one or more first or second degree relatives with a current or previously diagnosed bipolar disorder, psychotic disorder or other mood disorder (including MDD) with psychotic features.

3. Is in the judgement of a trial psychiatrist or registered psychologist, at significant risk for suicide based on history, psychiatric assessment, and evaluation of suicidal ideation and suicidal behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS).
4. Has taken anti-depressive medication within 14 days or 5 half-lives (whichever is longer) prior to dosing (exception: within the last 5 weeks in the case of fluoxetine).
5. Has taken any other medication with monoamine oxidase inhibitor (MAOI) activity within 14 days or 5 half-lives (whichever is longer) prior to dosing.
6. Has previously experienced a significant adverse reaction to a hallucinogenic or psychedelic drug (e.g., psilocybin, *Psilocybe* spp. mushrooms, 5-MeO-DMT, DMT, ayahuasca, LSD, mescaline) according to the investigator's judgment.
7. Has known allergies or hypersensitivity or any other contraindication to 5-MeO-DMT.
8. Has any current or past clinically significant condition (e.g., severe infection, pulmonary disease, uncontrolled hypertension, new onset of hypertensive disorders of pregnancy during pregnancy or in the postnatal period (e.g., gestational hypertension, pre-eclampsia-eclampsia, superimposed pre-eclampsia), uncontrolled diabetes, severe cardiovascular disease, severe hepatic or renal failure, severe brain disorder (including seizure disorder, stroke, dementia, degenerative neurologic diseases, meningitis, encephalitis, and head injury with loss of consciousness) that renders the patient unsuitable for the trial according to the investigator's judgment.
9. Takes any medication or other substance that renders the patient unsuitable for the trial according to the investigator's judgment.
10. Has a clinically significant abnormality in physical examination, vital signs, ECG, or clinical laboratory parameters which renders the patient unsuitable for the trial according to the investigator's judgment.
11. Patient who has a positive pregnancy test at screening or on the pre-test day (Day -1), is pregnant, or plans to become pregnant during the course of the trial and up to 90 days after 5-MeO-DMT dosing.
12. Patients with DSM-5 drug or alcohol use disorder within 6 months prior to screening.

The primary objective of the trial is to determine the onset and 7-day durability of anti-depressive effects of a single-day individualized dosing regimen of 6 mg, 12 mg and 18 mg of 5-MeO-DMT in adult, female patients with PPD.

Secondary objectives are to determine the anti-depressive effects; the anti-anxiety effects; the effects on maternal behavior; the safety and tolerability; the intensity and duration of psychoactive effects (PsE); the impact on cognitive outcome of a single-day individualized dosing regimen of 6 mg, 12 mg and 18 mg of 5-MeO-DMT in adult, female patients with PPD.

An exploratory objective is to determine in breastmilk, blood and urine the amount of 5-MeO-DMT and metabolites, bufotenine and 5-methoxyindole-3-acetic acid (5-MIAA), measured by LC/MS/MS (metabolite identification screening may be performed, as required), following dose administration of a single-day IDR of 6 mg, 12 mg and 18 mg of 5-MeO-DMT in adult, female patients with PPD.

The primary endpoint of the study is the evaluation of the anti-depressive effects of 5-MeO-DMT by the change from baseline in MADRS assessed at Day 7.

Secondary endpoints include the anti-depressive effects of 5-MeO-DMT evaluated by

- The anti-depressive effects of 5-MeO-DMT evaluated by:
    - The proportion of patients in remission (MADRS• 10) at 2 hours after the final study drug dosing on Day 0, and at Day 1 and Day 7;
    - Change from baseline in MADRS assessed at 2 hours after the final study drug dosing on Day 0, and at Day 1;
    - The proportion of responders (• 50% reduction from baseline in MADRS total score) at 2 hours after the final study drug dosing on Day 0, and at Day 1 and Day 7;
    - Change from baseline in Clinical Global Impression – Severity scale (CGI-S) 2 hours after final study drug dosing on Day 0, and at Day 1 and Day 7;
- Effects on maternal behaviour as assessed by the change from baseline in the Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores to Day 7;

- Exposure of 5-MeO-DMT and bufotenine in breastmilk obtained at the pre-test day (Day -1), 1 hour after last study drug dosing, at discharge, in the evening of Day 0, and on Day 1 and on Day 7;
- Exposure of 5-MeO-DMT and bufotenine in blood obtained at the pre-test day (Day -1), 1 hour after last study drug dosing, at discharge, on Day 1 and on Day 7;
- The safety and tolerability of 5-MeO-DMT evaluated by:
    - Reporting of treatment-emergent adverse events (TEAEs);
    - Clinically significant changes from baseline in ECG, vital signs, safety laboratory assessments, peak flow respirometry;
    - Assessment of sedation (Modified Observer's Assessment of Alertness and Sedation scale [MOAA/S]) following each dose (when the PsE has subsided and 60 minutes after each study drug dosing) and as part of the discharge evaluation on Day 0;
    - Change from baseline in Clinician Administered Dissociative States Scale (CADSS) assessed as part of the discharge evaluation on Day 0 and at Day 1 and Day 7;
    - Change from baseline in Brief Psychiatric Rating Scale (BPRS) assessed as part of the discharge evaluation on Day 0, and at Day 1 and Day 7;
    - Change from baseline in C-SSRS assessed as part of the discharge evaluation on Day 0, and at Day 1 and Day 7;
    - Change from baseline in YMRS assessed as part of the discharge evaluation on Day 0, and at Day 1 and Day 7;
- The PsE experienced by the patients as reported 30 to 60 minutes after each dosing, when the PsE has subsided:
    - PsE assessment using the peak experience (PE) scale to assess the achievement of a PE (PE scale total score • 75);
    - Challenging Experience Questionnaire (CEQ);
    - Mystical Experience Questionnaire (MEQ-30);
- Duration of the PsE defined as the time from study drug dosing to the time when the PsE have subsided (investigator- and patient-scored), completed 30 to 60 minutes after each dosing;

One patient with postpartum depression diagnosed by a psychiatrist has, so far, been recruited into the clinical trial. Diagnosis was Major Depressive Disorder without psychotic features, confirmed by the Mini-International Neuropsychiatric Interview (MINI) (v7.0.2), with peri-partum onset that began no earlier than gestation and no later than the first 4 weeks postpartum. The patient was diagnosed with postpartum depression after giving birth to her third child. The patient completed all planned visit days. The inhalation procedure was adequately performed by the patient and was well tolerated with no inhalation-related adverse events.

Results

Except for a temporary, clinically non-relevant increase in heart rate and blood pressure shortly after administration of 5-MeO-DMT, no other noteworthy changes in vital parameters occurred. Assessments of ECG (at 3 hours after administration) and safety laboratory analyses (at 7 days), CADSS (at 3 hours, 1 day and 7 days) were unremarkable. The few reported adverse events (cramping left abdominal pain and headache, both on Day 0) were mild, short-lasting and resolved spontaneously by the end of the study.

With regard to the intensity of the psychedelic experience, the recorded PES score achieved upon exposure to a nominal dose of 6mg was 17.3. This score indicated the need to proceed to the administration of a subsequent, higher dose of 12mg, per the design of the individualised dosing regimen. The PES score achieved for this dose was 85.7 and, being •75, indicated the occurrence of a peak psychedelic experience and the completion of the IDR for this patient.

Significantly, the patient reported a major improvement in her depressive symptoms as assessed by MADRS at the earliest assessment timepoint of 2 hours after drug administration, with the effect being maintained over time (Table 4). The patient also fulfilled standard criteria for MADRS response (at least 50% improvement from baseline) and MADRS remission (MADRS total score equal or less than 10).

Table 4 - MADRS/BPRS scores table

Scale item	Baseline	2hr (MADRS);	Day 1	Day 7	Improvement

		Discharge (BPRS)			2hr; Dis-charge	Day 1	Day 7
MADRS							
Reported sadness	4	0	0	0	4	4	4
Apparent sadness	5	0	0	0	5	5	5
Inner Tension	5	0	0	1	5	5	4
Reduced Sleep	5	5	0	0	0	5	5
Reduced appetite	0	0	0	0	0	0	0
Concentration Difficulties	0	0	0	0	0	0	0
Lassitude	3	0	0	0	3	3	3
Inability to Feel	3	0	0	0	3	3	3
Pessimistic Thoughts	4	0	0	0	4	4	4
Suicidal Thoughts	0	0	0	0	0	0	0
Total MADRS	**29**	**5**	**0**	**1**	**24**	**29**	**28**
BPRS							
Somatic Concern	6	1	1	1	5	5	5
Anxiety	7	1	1	1	6	6	6
Emotional withdrawal	5	1	1	1	4	4	4
Conceptual disorganiza-tion	1	1	1	1	0	0	0
Guilt feelings	6	1	1	1	5	5	5
Tension	6	1	1	1	5	5	5
Mannerisms and Postur-ing	1	1	1	1	0	0	0
Grandiosity	1	1	1	1	0	0	0
Depressive Mood	6	1	1	1	5	5	5
Hostility	1	1	1	1	0	0	0
Suspiciousness	1	1	1	1	0	0	0
Hallucinatory behaviour	1	1	1	1	0	0	0
Motor retardation	1	1	1	1	0	0	0
Uncooperativeness	1	1	1	1	0	0	0
Unusual Thought Content	1	1	1	1	0	0	0
Blunted affect	1	1	1	1	0	0	0
Excitement	2	1	1	1	1	1	1
Disorientation	1	1	1	1	0	0	0

Significant improvements were noted for several MADRS items in particular. The items are outlined in Table 4. While the patient's baseline scores for some items reflected absence of the symptom (reduced appetite, concentration difficulties, suicidal

thoughts), items with scores reflecting severe symptoms (e.g., reduced sleep, inner tension) saw remarkable improvement.

Similarly, improvements were seen in several BPRS items, including Somatic Concerns, Anxiety, Emotional withdrawal, Guilt feelings and Tension.

Additionally, improvements in maternal functioning were evidenced by improvements in the BIMF score recorded at Day 7, as outlined in Table 5, with the total score improving by 14% from 92 to 105 (out of a possible total of 120).

Several functional domains of maternal function were also assessed, as defined by Barkin et al. The improvements in each functional domain are outlined in more detail in Table 6.

Here, noteworthy improvements in self-care, psychological well-being and management were achieved, with percentage improvements ranging from 18% (management) to (44%),% (self-care). These improvements reinforce the relationship between improvement in depressive items, as assessed by the MADRS, and improvements in maternal functioning.

It is noted that the patient scored comparatively high already before treatment. In some functional domains, the score was at the maximum value, or close to it (see Table 6), so that the scope for improvement by therapy was limited.

Table 5 - BIMF scores table

No.	**BIM F item**			
		Day 0	Day 7	Δ (Day 7)
1	I am a good mother	6	6	0
2	I feel rested	0	2	2
3	I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both)	6	6	0
4	My baby and I understand each other	5	5	0
5	I am able to relax and enjoy time with my baby	5	6	1
6	There are people in my life that I can trust to care for my baby when I need a break	6	6	0
7	I am comfortable allowing a trusted friend or relative to care for my baby (can include baby's father or partner)	6	6	0
8	I am getting enough adult interaction	6	6	0

9	I am getting enough encouragement from other people	5	6	1
10	I trust my own feelings (instincts) when it comes to taking care of my baby	5	6	1
11	I take a little time each week to do something for myself	5	6	1
12	I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments)	6	6	0
13	I am taking good care of my physical needs (eating, showering, etc)	4	5	1
14	I make good decisions about my baby's health and well being	6	6	0
15	My baby and I are getting into a routine	5	6	1
16	I worry about how other people judge me (as a mother)	3	5	2
17	I am able to take care of my baby and my other responsibilities	5	5	0
18	Anxiety or worry often interferes with my mothering ability	2	5	3
19	As time goes on, I am getting better at taking care of my baby	0	1	1
20	I am satisfied with the job I am doing as a new mother	6	5	-1
	TOTAL	**92**	105	13

Table 6 - BIMF functional domain scores table

Functional Domain	**Related BIMF Items**	**Score**				
		Maximum Possible	**Day 0**	**Day 7**	**Δ (Day 7)**	**% Improvement**
Self Care	2, 11, 13	18	9	13	4	44.44%
Infant Care	12, 14	12	12	12	0	0.00%
Mother-Child Interaction	4, 5, 15	18	15	17	2	13.33%
Psychological Well-being	1, 2, 3, 5, 7, 10, 11, 16, 18, 20	60	44	53	9	20.45%
Social Support	6, 8, 9	18	17	18	1	5.88%
Management	7, 11, 13, 14, 17, 18	36	28	33	5	17.86%
Adjustment	17, 19	12	5	6	1	20.00%

Summary and Conclusions

A. An individualised dosing regimen of 6mg 5-MeO-DMT, followed by 12 mg 5-MeO-DMT administered via inhalation was well tolerated and induced an astonishing and very significant clinical response in a patient formally diagnosed with postpartum depression.

B. The clinical response occurs rapidly within 2 hours after 5-MeO-DMT administration. Such rapid onset is unusual and has not been seen with conventional classes of antidepressants, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin-reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and others, which generally take 4 to 6 weeks to show their effect.

C. The patient experienced a clinical remission within 2 hours after 5-MeO-DMT administration according to the IDR. This is highly superior to any approved therapy for postpartum depression, and also to all previously tested psychedelic agents.

D. A significant clinical response was sustained over the 7-day follow-up period, although 5-MeO-DMT was only given once and is no longer efficaciously present in the body during this time frame (see pharmacokinetic data in Example 6 above). This observation supports the superior clinical profile of 5-MeO-DMT and allows for convenient administration intervals.

E. In addition to anti-depressive effects, endpoints assessing other symptoms (such as somatic concerns, emotional withdrawal, anxiety, guilt and tension) were positively impacted, supporting the use of 5-MeO-DMT in patients with other mental diseases.

F. In addition to anti-depressive effects, endpoints assessing maternal functioning, as assessed using the BIMF, such as self-care, psychological well-being and management, were positively impacted. This supports additional benefits of 5-MeO-DMT to patients suffering from PPD beyond improvement in their core depressive symptoms.

The highlighted aspects show that 5-MeO-DMT has a significantly improved efficacy profile compared to approved pharmacological therapies for postpartum depression

and to all previously tested psychedelic agents, when used according to the present invention.

Together with the short duration of the acute psychedelic effects and the favourable safety profile, these data show that the technical problem to provide an improved psychoactive therapy in a patient with a postpartum depression is solved by the present invention.

Example 9 - Clinical trial of 5-MeO-DMT administered via inhalation to patients with bipolar II disorder

The single-arm, open-label clinical trial will involve 15 adult patients with bipolar II disorder and a current major depressive episode.

Patients who are currently taking anti-depressive medication need to discontinue or taper over time such medication.

The patients will receive a single-day individualized 5-MeO-DMT dosing regimen via inhalation after vaporization.

More in particular, the patients will receive up to three doses of 5-MeO-DMT on the administration day (Day 0): 6 mg, 12 mg, and 18 mg.

1. All patients will receive an initial dose of 6 mg 5-MeO-DMT.
2. The second dose (12 mg) will only be administered if:
    a. A peak experience (PES total score of • 75) has not been achieved following the 6 mg dose, and
    b. The 6 mg dose was safe and well-tolerated.
3. Similarly, a third dose (18 mg) will only be administered if:
    a. A peak experience (PES total score of • 75) has not been achieved following the 12 mg dose, and
    b. The 12 mg dose was safe and well-tolerated.

The patients will be assessed for a peak psychedelic experience based on the patient-scored PES described above, sedation and other endpoints after dosing. Follow-up visits are planned for Day 1, and Day 7 after the dosing day.

Selection of patients is based on the following key inclusion criteria:

1. Understands the nature of the clinical trial and has provided signed and dated written informed consent in accordance with local regulations before the conduct of any trial-related procedures.
2. Is male or female and in the age range between 18 and 64 years (inclusive) at screening.
3. Meets the trial criteria for bipolar II disorder and is experiencing a major depressive episode, as assessed by a trial psychiatrist or registered clinical psychologist:
    a. Meets the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for bipolar II disorder with a current major depressive disorder episode confirmed by the Mini-International Neuropsychiatric Interview (MINI);
    b. Has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of equal to or greater than 24 at screening and prior to first dose on Day 0;
4. Has a Young Mania Rating Scale (YMRS) total score less than or equal to 8 at screening and prior to first dose on Day 0;
5. Agrees to keep any psychotherapy unchanged, and not initiate any new psychoactive medications during the course of the trial.
6. Female patients must be either surgically sterile (hysterectomy, tubal ligation, or bilateral oophorectomy (6 months prior to screening)) or postmenopausal with amenorrhea for the last 2 years or remain completely abstinent (complete avoidance of heterosexual intercourse) or use a highly effective (failure rate <1%) medically accepted contraceptive method, including, but not limited to, bilateral tubal ligation/occlusion, hormone contraceptives that inhibit ovulation, intrauterine device (including hormone-releasing intrauterine device/systems) for 30 days before and 90 days after 5-MeO-DMT dosing and must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the pre-test day (Day -1).
7. Male patients must use prophylactic contraception (i.e., condom with spermicide or abstinence) and must not donate sperm for 30 days after 5-MeO-DMT dosing.

A potential patient who meets any of the following key exclusion criteria will be excluded from participation in this trial:

1. Has, based on history, psychiatric assessment, and evaluation of the MINI, a current or prior diagnosis of bipolar I disorder, a manic episode, a psychotic disorder, major depressive disorder (MDD) or other mood disorder with psychotic features, obsessive compulsive disorder, post-traumatic stress disorder (PTSD), autism spectrum disorder, borderline personality disorder, schizophrenia, delusional disorder, paranoid personality disorder, schizoaffective disorder, clinically significant intellectual disability, or any other psychiatric comorbidity that renders the patient unsuitable for the trial according to the investigator's judgment.
2. Has one or more first or second degree relatives with a current or previously diagnosed psychotic disorder, bipolar I disorder, or MDD with psychotic features.
3. Has significant suicide risk as defined by: (a) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, during the screening period, or at Baseline; or (b) suicidal behaviours within the past year; or (c) clinical assessment of significant suicidal risk during clinical interview; or (d) non-suicidal self-injury within the past year.
4. Has taken anti-depressive medication within 7 days or 5 half-lives (whichever is longer) prior to dosing (exception: within the last 5 weeks in the case of fluoxetine).
5. Has taken a medication with monoamine oxidase inhibitor (MAOI) activity within 14 days or 5 half-lives (whichever is longer) prior to dosing.
6. Has taken mood stabilizer therapy (e.g., lamotrigine, valproate, atypical antipsychotics) within 14 days (28 days for lithium) or 5 half-lives (whichever is longer) prior to dosing or takes mood stabilizer therapy at screening or is expected to require mood stabilizer therapy during the study (as per the investigator's judgment).
7. Has previously experienced a significant adverse reaction to a hallucinogenic or psychedelic drug according to the investigator's judgment.
8. Has known allergies or hypersensitivity or any other contraindication to 5-MeO-DMT.
9. Has any current or past clinically significant condition (e.g., severe infection, severe pulmonary disease, uncontrolled hypertension, uncontrolled diabetes, severe cardiovascular disease, severe hepatic or renal failure, severe brain disor-

der (including seizure disorder, stroke, dementia, degenerative neurologic diseases, meningitis, encephalitis, and head injury with loss of consciousness) that may interfere with the interpretation of the trial results, constitutes a health risk for the patient, or that otherwise renders the patient unsuitable for the trial according to the investigator's judgment.

10. Takes any medication or other substance that renders the patient unsuitable for the trial according to the investigator's judgment.
11. Has a clinically significant abnormality in physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory parameters which renders the patient unsuitable for the trial according to the investigator's judgment.
12. Female patient who has a positive pregnancy test at screening or on the pre-test day (Day -1), is pregnant or lactating, or plans to become pregnant during the course of the trial and up to 30 days after 5-MeO-DMT dosing.
13. Patients with DSM-5, alcohol or substance use disorder (excluding tobacco or caffeine use disorders) within 6 months prior to screening.

The primary objective of the trial is to determine the onset and durability of anti-depressive effects of a single-day individualized dosing regimen of 6 mg, 12 mg and 18 mg of 5-MeO-DMT in patients with bipolar II disorder and a current major episode of depression. Secondary objectives are to determine the effect on depressive symptoms and global clinical status; the safety and tolerability; the intensity and duration of psychoactive effects (PsE); the impact on sleep quality; the impact on cognitive outcomes of a single-day individualized dosing regimen of 6 mg, 12 mg and 18 mg of 5-MeO-DMT in patients with bipolar II disorder and a current major episode of depression.

The primary endpoint of the study is the evaluation of the anti-depressive effects of 5-MeO-DMT by the change from baseline in MADRS assessed at Day 7.

Secondary endpoints include:

- The anti-depressive effects of 5-MeO-DMT administered via inhalation evaluated by:
    - The proportion of patients in remission (MADRS ≤ 10) at 2 hours after the final study drug dosing on Day 0, and at Day 1 and Day 7;
    - Change from baseline in MADRS assessed at 2 hours after the final study drug dosing on Day 0, and at Day 1;

- The proportion of responders (• 50% reduction from baseline in MADRS total score) at 2 hours after the final study drug dosing on Day 0, and at Day 1 and Day 7;
- Change from baseline in CGI-S at 2 hours after the final study drug dosing on Day 0, and at Day 1 and Day 7.
- Change from baseline in BDRS at Day 1 and Day 7

- The safety and tolerability of 5-MeO-DMT administered via inhalation evaluated by:
  - Reporting of treatment-emergent adverse events (TEAEs);
  - Clinically significant changes from baseline in ECG, vital signs, safety laboratory assessments and spirometry assessments;
  - Assessment of sedation (Modified Observer's Assessment of Alertness and Sedation scale [MOAA/S]) following each dose (when the PsE have subsided and 60 minutes after each study drug dosing) and as part of the discharge evaluation on Day 0;
  - The incidence of adverse events (AEs) of mania or hypomania (as assessed using the DSM-5 criteria for mania/hypomania);
  - Change from baseline in YMRS assessed as part of the discharge evaluation on Day 0 and at Day 1 and Day 7;
  - Change from baseline in Clinician Administered Dissociative States Scale (CADSS) assessed as part of the discharge evaluation on Day 0 and at Day 1 and Day 7;
  - Assessment of patient discharge readiness at discharge on Day 0 using the Clinical Assessment of Discharge Readiness (CADR);
  - Change from baseline in Brief Psychiatric Rating Scale (BPRS) assessed as part of the discharge evaluation on Day 0, and at Day 1 and Day 7;
  - C-SSRS categorization based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA).
- The PsE experienced by the patients as reported 30 to 60 minutes after each dosing, when the PsE has subsided:
  - PsE assessment using the peak experience (PE) Scale (PES) to assess the achievement of a PE (PES total score • 75);
  - Challenging Experience Questionnaire (CEQ);
  - Mystical Experience Questionnaire (MEQ-30).

- Duration of the PsE, defined as the time from study drug dosing to the time when the PsE have subsided, completed 30 to 60 0minutes after each dosing.
- The impact on sleep quality as evaluated by change from pre-test day (Day -1) to Day 1 and to Day 7 in the Pittsburgh Sleep Quality Index (PSQI).
- The impact on cognitive outcomes as evaluated by change from the pre-test day (Day -1) to discharge on Day 0, to Day 1 and to Day 7 in:
    - Rapid visual information processing (RVP) test;
    - Verbal recognition memory (VRM) test;
    - Spatial working memory (SWM) test;
    - Digit symbol substitution test (DSST).

Claims

1. 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or a pharmaceutically acceptable salt thereof for use in treating a patient suffering from social/emotional withdrawal or detachment.

2. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 1, wherein the treatment reduces or eliminates social/emotional withdrawal or detachment.

3. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 2, wherein the treatment reduces or eliminates anhedonia, emotional withdrawal, affective flattening and/or reduced social engagement.

4. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 2 or 3, wherein the reduction or elimination of social/emotional withdrawal or detachment is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

5. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 2 or 3, wherein the reduction or elimination of social/emotional withdrawal or detachment occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof and wherein the reduction or elimination of social/emotional withdrawal or detachment persists until at least 6 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; in particular until at least 14 days; more preferably until

at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

6. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a mental or nervous system disorder associated with the social/emotional withdrawal or detachment.

7. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 6, wherein the patient suffering from a mental or nervous system disorder suffers from a treatment resistant form of the disorder.

8. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a disorder characterized by depressive episodes associated with the social/emotional withdrawal or detachment.

9. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 8, wherein the patient suffering from a disorder characterized by depressive episodes suffers from a treatment resistant form of the disorder.

10. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from major depressive disorder (MDD) associated with the social/emotional withdrawal or detachment.

11. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 10, wherein the patient suffering from MDD suffers from a treatment resistant form of the disorder.

12. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 10 or 11, wherein the treatment of a patient suffering from MDD associated with social/emotional withdrawal or detachment reduces or eliminates suicidal ideation.

13. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from postpartum depression (PPD) associated with the social/emotional withdrawal or detachment.

14. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 13, wherein the patient suffering from PPD suffers from a treatment resistant form of the disorder.

15. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 13 or 14, wherein the patient suffers in addition from compromised maternal functioning.

16. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 15, wherein the patient has a Barkin Index of Maternal Functioning (BIMF) score of 80 or below, such as 65 or below.

17. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 15 or 16, wherein the treatment improves maternal functioning.

18. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 17, wherein the improvement in maternal functioning is reflected by an improvement of the BIMF total score by 10% or more, preferably by 20 % or more.

19. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 17 or 18, wherein the improvement in maternal functioning, is reflected by at least an improvement in the BIMF total score on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

20. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 17 or 18, wherein the improvement in maternal functioning, as reflected by at least an improvement in the BIMF total score, occurs not later than about 6 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof and wherein the improvement in maternal functioning, as reflected by at least an improvement in the BIMF total score, persists until at least 14 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

21. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from bipolar disorder associated with the social/emotional withdrawal or detachment.

22. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 21, wherein the patient is suffering from bipolar II disorder associated with the social/emotional withdrawal or detachment.

23. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 21, wherein the patient is suffering from bipolar I disorder associated with the social/emotional withdrawal or detachment.

24. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 21 to 23, wherein the patient suffers from a current major depressive episode.

25. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 21 to 24, wherein the patient suffering from bipolar disorder suffers from a treatment resistant form of the disorder.

26. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from seasonal affective disorder associated with the social/emotional withdrawal or detachment.

27. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 26, wherein the patient suffering from seasonal affective disorder suffers from a treatment resistant form of the disorder.

28. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from persistent depressive disorder associated with the social/emotional withdrawal or detachment.

29. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 28, wherein the patient suffering from persistent depressive disorder suffers from a treatment resistant form of the disorder.

30. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from an anxiety disorder associated with the social/emotional withdrawal or detachment.

31. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 30, wherein the patient suffering from an anxiety disorder suffers from a treatment resistant form of the disorder.

32. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from generalised anxiety disorder (GAD) associated with the social/emotional withdrawal or detachment.

33. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 32, wherein the patient suffering from GAD suffers from a treatment resistant form of the disorder.

34. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from social anxiety disorder (SAD) associated with the social/emotional withdrawal or detachment.

35. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 34, wherein the patient suffering from SAD suffers from a treatment resistant form of the disorder.

36. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from an obsessive compulsive or related disorder associated with the social/emotional withdrawal or detachment.

37. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 36, wherein the obsessive compulsive or related disorder is obsessive compulsive disorder (OCD).

38. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 36 or 37, wherein the patient suffers from a treatment resistant form of the disorder.

39. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from body dysmorphic disorder (BDD) associated with the social/emotional withdrawal or detachment.

40. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 39, wherein the patient suffering from BDD suffers from a treatment resistant form of the disorder.

41. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from post-traumatic stress disorder (PTSD) associated with the social/emotional withdrawal or detachment.

42. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 41, wherein the patient suffering from PTSD suffers from a treatment resistant form of the disorder.

43. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a pain disorder associated with the social/emotional withdrawal or detachment.

44. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 43, wherein the patient is suffering from chronic pain associated with the social/emotional withdrawal or detachment.

45. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 43 or 44, wherein the patient suffers from a treatment resistant form of the disorder.

46. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from fibromyalgia associated with the social/emotional withdrawal or detachment.

47. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a mental and behavioural disorder due to psychoactive substance use associated with the social/emotional withdrawal or detachment.

48. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 47, wherein the patient is suffering from substance use disorder (SUD) associated with the social/emotional withdrawal or detachment.

49. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 47 or 48, wherein the patient suffers from a treatment resistant form of the disorder.

50. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a psychotic disorder associated with the social/emotional withdrawal or detachment.

51. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 50, wherein the patient suffering from a psychotic disorder suffers from a treatment resistant form of the disorder.

52. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from schizophrenia associated with the social/emotional withdrawal or detachment.

53. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 52, wherein the patient suffering from schizophrenia suffers from a treatment resistant form of the disorder.

54. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from dementia associated with the social/emotional withdrawal or detachment.

55. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from Alzheimer's dementia associated with the social/emotional withdrawal or detachment.

56. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from dementia with Lewy Bodies associated with the social/emotional withdrawal or detachment.

57. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from vascular dementia associated with the social/emotional withdrawal or detachment.

58. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from fronto-temporal dementia associated with the social/emotional withdrawal or detachment.

59. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from Parkinson's disease associated with the social/emotional withdrawal or detachment.

60. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from an eating disorder associated with the social/emotional withdrawal or detachment.

61. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 60, wherein the patient suffering from an eating disorder suffers from a treatment resistant form of the disorder.

62. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from an autism spectrum disorder (ASD) associated with the social/emotional withdrawal or detachment.

63. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from attention deficit hyperactivity disorder (ADHD) associated with the social/emotional withdrawal or detachment.

64. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 63, wherein the patient suffering from ADHD suffers from a treatment resistant form of the disorder.

65. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a personality disorder associated with the social/emotional withdrawal or detachment.

66. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 65, wherein the patient is suffering from schizotypal personality disorder associated with the social/emotional withdrawal or detachment.

67. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 65 or 66, wherein the patient suffers from a treatment resistant form of the disorder.

68. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from borderline personality disorder (BPD) associated with the social/emotional withdrawal or detachment.

69. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 68, wherein the patient suffering from BPD suffers from a treatment resistant form of the disorder.

70. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the social/emotional withdrawal or detachment is due to traumatic brain injury.

71. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 6 to 70, wherein the treatment leads to an improvement in the diagnosed disorder in a patient also suffering from associated social/emotional withdrawal or detachment.

72. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 71, wherein the improvement in the diagnosed disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, is observed about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

73. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 71, wherein the improvement in the diagnosed disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, occurs not later than about 2 hours after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof and wherein the improvement in the diagnosed disorder in a patient also suffering from associated social/emotional withdrawal or detachment, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, persists until at least 6 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

74. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 5, wherein the patient is suffering from a sleep disturbance associated with the social/emotional withdrawal or detachment.

75. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 74, wherein the sleep disturbance is insomnia.

76. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 74 or 75, wherein the patient suffers from an idiopathic sleep disturbance associated with the social/emotional withdrawal or detachment.

77. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 74 to 76, wherein the patient suffers from a treatment resistant form of the disorder.

78. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 74, 75 or 77, wherein the sleep disturbance occurs in a patient suffering from associated social/emotional withdrawal or detachment and also from a mental or nervous system disorders, such as disorders characterized by depressive episodes, for example Major Depressive Disorder (MDD), Bipolar Disorder (BD), such as Bipolar I Disorder and Bipolar II Disorder, Postpartum Depression (PPD), Seasonal Affective Disorder and Persistent Depressive Disorder; Anxiety Disorders, for example Generalised Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD); Obsessive Compulsive and Related Disorders, for example, Obsessive Compulsive Disorder (OCD) and Body Dysmorphic Disorder (BDD); Post-Traumatic Stress Disorder (PTSD); Pain Disorders, for example Chronic Pain and Fibromyalgia; Mental and Behavioural Disorder due to Psychoactive Substance Use, for example Substance Use Disorder (SUD); Psychotic Disor-

der, for example Schizophrenia; Dementia, for example Alzheimer's Dementia (AD); Dementia with Lewy Bodies (DLB); Vascular Dementia and Fronto-Temporal Dementia (FTD); Parkinson's Disease (PD); Eating Disorder; Autism Spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); Personality Disorder, for example Schizotypal Personality Disorder and Borderline Personality Disorder (BPD) or from a medical health conditions leading to an associated mental or nervous system condition, such as Traumatic Brain Injury (TBI).

79. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 78, wherein the treatment leads to an improvement in social/emotional withdrawal or detachment and sleep disturbance and furthermore to an improvement in the associated mental or the nervous system disorder or the medical health condition leading to an associated mental or nervous system condition.

80. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 74 to 79, wherein the treatment leads to an improvement in the sleep disturbance.

81. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 80, wherein the improvement in the sleep disturbance, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, is observed on day 1, for instance after about 24 hours; on day 7; on day 14; and/or on day 28 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

82. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 80, wherein the improvement in the sleep disturbance, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, occurs not later than about 24 hours after the last administration of 5-MeO-DMT or a pharma-

ceutically acceptable salt thereof and wherein the improvement in the sleep disturbance, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, persists until at least 6 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof; in particular until at least 14 days; more preferably until at least 28 days after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof.

83. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 80, wherein the improvement in the sleep disturbance, as reflected by a reduction in the Clinical Global Impression - Severity (CGI-S) score, is observed on day 7 after the last administration of 5-MeO-DMT or a pharmaceutically acceptable salt thereof and preferably persists until at least 14 days, more preferably until at least 28 days.

84. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 83, wherein the 5-MeO-DMT or salt thereof is administered at a dose or in a dosage regimen that causes the patient to experience a peak psychedelic experience.

85. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 84, wherein a dosage of about 4 mg to about 20 mg 5-MeO-DMT is administered, or wherein equimolar amounts of the pharmaceutically acceptable salt are administered instead of 5-MeO-DMT.

86. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 84, wherein a dosage of about 6 mg; or of about 12 mg; or of about 18 mg is administered, or wherein equimolar amounts of the pharmaceutically acceptable salt are administered instead of 5-MeO-DMT.

87. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 85, wherein the 5-MeO-DMT or salt thereof is administered in a first dosage amount for a first administration; and the 5-MeO-DMT or salt thereof is administered in zero to six subsequent administrations; wherein each subsequent administration uses a dosage amount higher than the previous administration unless the patient experiences a peak psychedelic experience.

88. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 87, wherein the 5-MeO-DMT is administered in a dosage from about 2 mg to about 8 mg for a first administration, and then increased, unless the patient has already experienced a peak psychedelic experience, to a dosage from about 8 mg to about 14 mg for a second administration, and then increased, unless the patient has already experienced a peak psychedelic experience, to a dosage from about 14 mg to about 20 mg for a third administration, or wherein equimolar amounts of the pharmaceutically acceptable salt are administered instead of 5-MeO-DMT.

89. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 88, wherein the first dosage of 5-MeO-DMT is about 6 mg, the second dosage of 5-MeO-DMT is about 12 mg, and the third dosage of 5-MeO-DMT is about 18 mg; or wherein equimolar amounts of the pharmaceutically acceptable salt are administered instead of 5-MeO-DMT.

90. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 87 to 89, wherein the interval between two administrations is not less than 1 hour and not more than 24 hours, such as about 1 to 4 hours, preferably 1 to 2 hours.

91. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 84 to 90, wherein the occurrence of a peak psychedelic experience is identified

through achievement of at least 60% of the maximum possible score in each of the four subscales (mystical, positive mood, transcendence of time and space, and ineffability) of the 30-item revised Mystical Experience Questionnaire (MEQ30) or is identified through achievement of at least 60% of the maximum possible score of the Oceanic Boundlessness (OBN) dimension of the Altered States of Consciousness (ASC) questionnaire or is identified through achievement of a Peak Experience Scale (PES) Total Score of at least 75.

92. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 91, wherein the occurrence of a peak psychedelic experience is identified through achievement of a Peak Experience Scale (PES) Total Score of at least 75.

93. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 1 to 92, wherein the 5-MeO-DMT or a pharmaceutically acceptable salt thereof is administered via inhalation or by nasal, buccal or sublingual administration.

94. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 93, wherein 5-MeO-DMT or a pharmaceutically acceptable salt thereof is administered in the form of an aerosol comprising (a) a pharmaceutically acceptable gas; (b) aerosol particles of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or a pharmaceutically acceptable salt thereof, wherein the aerosol has an aerosol particle mass density of about 0.5 mg/l to about 18 mg/l, such as to about 12.5 mg/l.

95. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claim 94, wherein the aerosol is generated by a) exposing a thin layer of 5-MeO-DMT or a pharmaceutically acceptable salt thereof, configured on a solid support, to thermal energy, and b) passing air over the thin layer to produce aerosol particles.

96. 5-MeO-DMT or a pharmaceutically acceptable salt thereof for use as in claims 93 to 95, wherein the dosage amount of 5-MeO-DMT or a pharmaceutically acceptable salt to be administered to the patient is inhaled with a single breath.

97. 5-MeO-DMT for use as in claims 93 to 96, wherein the 5-MeO-DMT is used in the form of the free base.