

METHODS OF TREATING GENERALIZED ANXIETY DISORDER

RELATED APPLICATIONS

[0001] The application claims priority to U.S. Provisional Application No. 63/608,486, filed December 11, 2023, and U.S. Provisional Application No. 63/608,396, filed December 11, 2023, the disclosures of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering lysergic acid diethylamide (LSD), or a salt thereof.

BACKGROUND

[0003] There is a need for treatment options for patients with clinically significant anxiety, including treatment of the symptoms of clinically significant anxiety. Patients with anxiety disorders often experience substantial physical and emotional discomfort, functional impairment and reduced work productivity, as well as increased rates of substance use and medical illnesses. The chronic and disabling nature of anxiety disorders is associated with substantial economic and social costs related to premature mortality, unemployment and reduced productivity. Anxiety disorders are a common concern for many people and there remains a significant need for effective treatments with reduced symptoms and higher success rates. The course of anxiety disorders is often relapsing and chronic, with most patients remaining symptomatic decades after their initial diagnosis. The current medications approved to treat generalized anxiety disorder (GAD), or symptoms thereof, have unfavorable side effect profiles, contraindications, or are ineffective. Withdrawal symptoms and undesirable adverse effects, including insomnia, nausea, nervousness, and sexual dysfunction are common with long-term use of these agents.

[0004] Lysergic acid diethylamide (LSD) is a prototypical classic hallucinogen. Effects of LSD can include altered thoughts, feelings, awareness of surroundings, dilated pupils, increased blood pressure, and increased body temperature. Therapeutic use of LSD is showing promising results for treating various neurological and behavioral disorders. LSD is not associated with compulsive drug seeking (addiction), and there are relatively few medical emergencies and adverse effect. Use of LSD is not associated with mental health problems and may even be protective. In a safe setting, no drug-related severe adverse effects have been observed after administration of LSD in healthy participants. LSD has a relatively safe physiologically profile and a single administration may have both rapid-acting and long-lasting clinical effect.

[0005] Solid oral formulations as tablets or capsules are used in clinical development and commercially

due to advantages in production, supply chain, and patient convenience. Solid oral formulations can be immediate release, dissolving instantaneously in the mouth or stomach, or extended release in which the drug release is prolonged over time. Orally disintegrating tablets (ODTs) are another solid dosage form which can increase the dissolution rate of a pharmaceutical product and promote pre-gastric absorption. A method for preparing ODTs is freeze drying with, for example, the Zydis® ODT fast-dissolve formulation (e.g., a freeze-dried oral solid dosage form that disperses almost instantly in the mouth with no water required). For drugs that have unique activity (e.g., LSD), time course and exposure impacts the timeline and nature of the pharmacodynamics (PD) effects. In instances where patient monitoring is needed, such as with LSD, a formulation that improves monitoring time by speeding up absorption, achieving increased bioavailability, or speeding up time taken to fall below threshold levels would shorten the duration of the adverse events and could shorten the duration of monitoring required. LSD is associated with prolonged alterations of perception and conscious experience which are closely linked to positive clinical effects. In the context of medical treatment and pharmaceutical products, such consciousness-altering effects are considered adverse events that may require monitoring or criteria for release. Therefore, being able to provide faster absorption of LSD and/or a lower dose of LSD resulting in a shorter time course in the body is necessary to reduce time for monitoring.

[0006] Although there are a number of medications approved to treat anxiety disorders, or symptoms thereof, many patients exhibit unfavorable side effect profiles, contraindications, or are ineffective with the currently approved therapeutics. Given that there are many patients with anxiety disorders, including GAD, who do not reach their treatment goals with currently approved therapies, there remains an unmet need for new GAD therapies with a favorable safety, tolerability and efficacy profile.

[0007] Thus, there remains a significant need for novel therapeutic approaches in treating anxiety disorders, including treating a symptom or preventing a symptom of generalized anxiety disorder.

SUMMARY

[0008] Described herein are methods of treating or preventing generalized anxiety disorder or a symptom thereof in a subject. The method may comprise administering to the subject LSD, or a salt thereof. The methods may be for treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering lysergic acid diethylamide (LSD), or a salt thereof. The LSD salt may be d-LSD D-tartrate. In some embodiments, the generalized anxiety disorder is severe generalized anxiety disorder. In some embodiments, the generalized anxiety disorder is moderate generalized anxiety disorder.

[0009] Described herein are methods of treating a symptom or preventing a symptom of generalized anxiety disorder, wherein the symptom is feeling nervous, having a sense of impending danger, panic, increased heart rate, rapid breathing, sweating, trembling, gastrointestinal problems, restlessness,

fatigue, difficulty concentrating, irritability, muscle tension, a sleep disturbance, or sexual dysfunction.

[00010] In some embodiments, the treatment described herein comprises administering LSD as an orally disintegrating tablet. The orally disintegrating tablet may comprise: LSD, or a salt thereof; a non-gelling matrix; a binder; a filler; and solvent. In some embodiments, the non-gelling matrix is maltodextrin. In some embodiments, the binder is hydroxypropyl methylcellulose. In some embodiments, the filler is mannitol. In some embodiments, the solvent is water.

[00011] The treatments described herein may comprise administering the LSD, or a salt thereof, at a freebase equivalent dose of about 25 µg to about 200 µg. In some embodiments, the LSD, or a salt thereof, is administered at a freebase equivalent dose of about 25 µg, about 50 µg, about 100 µg, about 150 µg, or about 200 µg. In some embodiments, the LSD, or a salt thereof, is administered at a freebase equivalent dose of about 100 µg.

[00012] The treatments described herein may result in a subject's serum LSD freebase concentration of between about 2 ng/mL to about 2.5 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments, an increased concentration of LSD freebase within a shorter period of time is desired to increase the onset of LSD activity for treating a symptom or preventing a symptom of generalized anxiety disorder. In some embodiments, the increase in the onset of LSD activity results in a shorter monitored treatment period. In some embodiments, the increase in the onset of LSD activity results in a faster and longer-lasting treatment of a symptom or prevention of a symptom in generalized anxiety disorder.

[00013] The treatments described herein may result in the symptom of generalized anxiety disorder being reduced or eliminated between about 6 hours to about 12 hours after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating table comprising LSD, or a salt thereof). In some embodiments, the reduction or elimination of a symptom of generalized anxiety disorder is for about 12 weeks or greater after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating table comprising LSD, or a salt thereof). In some embodiments, a fast and long-lasting reduction or elimination of a symptom is desired.

[00014] The treatments described herein may result in the subject having a Hamilton Anxiety Scale (HAM-A) improved score within about 12 weeks after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). In some embodiments, the subject has an about 20-point HAM-A improved score within about 12 weeks after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). An improvement in HAM-A score indicates that generalized anxiety disorder, or a symptom thereof, is being treated or prevented in a subject. In some embodiments, an improvement in HAM-A score is a decrease in score.

[00015] The treatments described herein may result in the subject having a reduction in Clinical Global Impressions – Severity (CGI-S) within about 12 weeks after administration of LSD, or a salt thereof

(e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). In some embodiments, the subject has an about 1.8-point reduction in CGI-S within about 12 weeks after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). A reduction in CGI-S indicates that generalized anxiety disorder, or a symptom thereof, is being treated or prevented in a subject.

[00016] The treatments described herein may result in the subject having a reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) within about 12 weeks after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). In some embodiments, the subject has an about 18-point reduction in MADRS within about 12 weeks after administration of LSD, or a salt thereof (e.g., administration of an orally disintegrating tablet comprising LSD, or a salt thereof). A reduction in MADRS indicates that generalized anxiety disorder, or a symptom thereof, is being treated or prevented in a subject.

[00017] The treatments described herein may be administered once to the subject for a specified period of time. After one administration of LSD, or a salt thereof, for a specified period of time, the subject may be readministered LSD, or a salt thereof. In some embodiments, the LSD, or salt thereof, is administered one to four times per year. In some embodiments, the LSD, or salt thereof, is administered once every about 12 weeks. The schedule of administration of LSD, or a salt thereof, of once ever about 12 weeks may be desired to decrease the time a subject is monitored during treatment.

[00018] The treatments described herein may be monotherapies (e.g., the subject is not administered a second agent for the treatment of generalized anxiety disorder or depression).

[00019] The subject described herein may also have depression.

[00020] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[00021] Various objects and advantages and a more complete understanding of the present invention are apparent and more readily appreciated by reference to the following Detailed Description and to the appended claims when taken in conjunction with the accompanying in Drawings wherein:

[00022] FIG. 1 is a diagram of a design schema for a clinical study.

[00023] FIG. 2 depicts HAM-A change from baseline in a subject with GAD after treatment with d-LSD D-tartrate.

[00024] FIG. 3 depicts HAM-A response rate at Week 12 in a subject with GAD after treatment with d-LSD D-tartrate.

[00025] FIG. 4 depicts CGI-S Scores at Week 12 in a subject with GAD after treatment with d-LSD D-tartrate.

[00026] FIG. 5 depicts MADRS change from baseline in a subject with GAD after treatment with d-

LSD D-tartrate.

[00027] FIG. 6 is a representation of d-LSD D-tartrate salt.

[00028] FIG. 7 is a photograph of Zydis ODT containing LSD.

[00029] FIG. 8 is a diagram of a study design for comparing a capsule and ODT formulation of d-LSD D-tartrate.

[00030] FIG. 9 is a graph of mean $\pm$ SE concentration versus time for d-LSD D-tartrate in an ODT formulation.

[00031] FIG. 10 is a graph of mean $\pm$ SE concentration versus time for d-LSD D-tartrate in capsule and ODT formulations.

[00032] FIG. 11 is a graph of mean concentration versus time for absorption phase for d-LSD D-tartrate in capsule and ODT formulations.

[00033] FIG. 12 is a close up view of the graph of FIG. 11 from 0 through 15 minutes.

[00034] FIG. 13 is a chart showing a summary of concentration by time point for d-LSD D-tartrate capsule and ODT formulations.

[00035] FIG. 14 is a graph of mean concentration versus time for d-LSD D-tartrate in capsule and ODT formulations showing a threshold of 0.5 ng/mL.

[00036] FIG. 15 is a graph of mean concentration versus time for d-LSD D-tartrate in capsule and ODT formulations showing a threshold of 1 ng/mL.

[00037] FIG. 16 is a graph of PK versus any subjective effects for d-LSD D-tartrate in capsule and ODT formulations showing a threshold of 1 ng/mL.

[00038] FIG. 17 is a graph of mean $\pm$ SE concentration versus time for OH metabolite PK in d-LSD D-tartrate in capsule and ODT formulations.

[00039] FIG. 18 is a chart showing comparison of crossover results for PK of the ODT formulation relative to the capsule formulation.

[00040] FIG. 19 is a graph showing crossover results of PK of the ODT formulation relative to the capsule formulation.

[00041] FIGs. 20A-20C are graphs showing VAS profile for ODT and capsule formulation of mean $\pm$ SE versus, FIG. 20A shows any drug effect for period 1, FIG. 20B shows good drug effect for period 1, and FIG. 20C shows bad drug effect for period 1.

[00042] FIG. 21 is a graph of DSRC times for the ODT and capsule formulation for period 1.

DETAILED DESCRIPTION

[00043] Described herein are treatments and preventions of generalized anxiety, or a symptom thereof, with LSD, or a salt thereof. In some embodiments, the LSD is formulated as a capsule or tablet. In some embodiments, the tablet is an orally disintegrating tablet. In some embodiments, the administration of an orally disintegrating tablet comprising LSD, or a salt thereof, has favorable pharmacokinetic properties as compared to the administration of a capsule comprising LSD, or a salt thereof. While all

LSD salts are contemplated, the LSD salt may be d-LSD D-tartrate. Also described herein are doses and schedules of administration of LSD. In some embodiments, the dose of LSD is the dose of the LSD freebase. For example, if a dosage is recited for d-LSD D-tartrate, the dose recited is the amount of the LSD freebase equivalent of d-LSD D-tartrate and not the amount of d-LSD D-tartrate.

[00044] Also described herein are parameters for assessing the treatment or prevention of symptoms of generalized anxiety disorder in a subject. In some embodiments, the assessment is by measurement of Hamilton Anxiety Scale (HAM-A), Clinical Global Impressions – Severity (CGI-S), or Montgomery–Åsberg Depression Rating Scale (MADRS).

I. Treatment or Prevention of Symptoms of Generalized Anxiety Disorder

[00045] The methods described herein may be for the treatment of a subject with generalized anxiety disorder, or a symptom thereof. The methods described herein may be for the treatment of a symptom or prevention of a symptom of generalized anxiety disorder in a subject. In some embodiments, the treatment is a treatment of the symptoms associated with generalized anxiety disorder.

[00046] The generalized anxiety disorder may be severe generalized anxiety disorder or moderate generalized anxiety disorder. In some embodiments, the symptom is symptom of severe generalized anxiety disorder. In some embodiments, the symptom is a symptom of moderate generalized anxiety disorder.

[00047] When the treatment or prevention is directed toward a symptom of generalized anxiety disorder, the symptom is feeling nervous, having a sense of impending danger, panic, increased heart rate, rapid breathing, sweating, trembling, gastrointestinal problems, restlessness, fatigue, difficulty concentrating, loss of interest, lack of pleasure, grinding of teeth, constriction in chest, tinnitus, blurring of vision, increased frequency of micturition, irritability, muscle tension, a sleep disturbance, or sexual dysfunction.

[00048] In some embodiments, the symptom of generalized anxiety disorder is feeling nervous. In some embodiments, the symptom of generalized anxiety disorder is having a sense of impending danger. In some embodiments, the symptom of generalized anxiety disorder is panic. In some embodiments, the symptom of generalized anxiety disorder is increased heart rate. In some embodiments, the symptom of generalized anxiety disorder is rapid breathing. In some embodiments, the symptom of generalized anxiety disorder is sweating. In some embodiments, the symptom of generalized anxiety disorder is trembling. In some embodiments, the symptom of generalized anxiety disorder is gastrointestinal problems. In some embodiments, the symptom of generalized anxiety disorder is restlessness. In some embodiments, the symptom of generalized anxiety disorder is fatigue. In some embodiments, the symptom of generalized anxiety disorder is difficulty concentrating. In some embodiments, the symptom of generalized anxiety disorder is irritability. In some embodiments, the symptom of generalized anxiety disorder is muscle tension. In some embodiments, the symptom of generalized anxiety disorder is a sleep disturbance. In some embodiments, the symptom of generalized anxiety

disorder is sexual dysfunction. In some embodiments, the symptom of generalized anxiety disorder is loss of interest. In some embodiments, the symptom of generalized anxiety disorder is lack of pleasure. In some embodiments, the symptom of generalized anxiety disorder is grinding of teeth. In some embodiments, the symptom of generalized anxiety disorder is constriction in chest. In some embodiments, the symptom of generalized anxiety disorder is tinnitus. In some embodiments, the symptom of generalized anxiety disorder is blurring of vision. In some embodiments, the symptom of generalized anxiety disorder is increased frequency of micturition.

[00049] In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering lysergic acid diethylamide (LSD), or a salt thereof. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a composition comprising lysergic acid diethylamide (LSD), or a salt thereof. In one aspect, the present disclosure provides use of lysergic acid diethylamide (LSD), or a salt thereof, for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides use of a composition comprising lysergic acid diethylamide (LSD), or a salt thereof, for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides lysergic acid diethylamide (LSD), or a salt thereof, for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a composition comprising lysergic acid diethylamide (LSD), or a salt thereof, for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of lysergic acid diethylamide (LSD), or a salt thereof, in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00050] In one aspect, the exposure level of LSD freebase is tested in the subject's blood to determine completion of the treatment session.

[00051] In embodiments where an LSD salt is used, it may be any pharmaceutically acceptable salt of LSD. In some embodiments, the LSD salt is d-LSD D-tartrate.

[00052] In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering d-LSD D-tartrate. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a composition comprising d-LSD D-tartrate. In one aspect, the present disclosure provides use of d-LSD D-tartrate for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides use of a composition comprising d-LSD D-tartrate for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides d-LSD D-tartrate for use in treating a

symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a composition comprising d-LSD D-tartrate for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of d-LSD D-tartrate in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00053] The methods described herein may be effective in reducing gastrointestinal side effects associated with the administration of LSD. In some embodiments, the reduced gastrointestinal side effects are due to administration of an orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has reduced gastrointestinal side effects after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to administration of a capsule comprising d-LSD D-tartrate.

[00054] When the subject that has generalized anxiety disorder, the subject may also have depression. In some embodiments, the subject is not undergoing a treatment for anxiety or depression prior to the administration of LSD, or a salt thereof. In some embodiments, LSD, or a salt thereof, is administered as a monotherapy. In some embodiments, the subject is not administered a second agent for the treatment of generalized anxiety disorder or depression. In some embodiments, the subject is not administered a second agent for the treatment of generalized anxiety disorder. In some embodiments, the subject is not administered a second agent for the treatment of depression.

II. Formulation

[00055] The LSD, or a salt thereof, described herein may be formulated for oral administration. In some embodiments, the LSD, or a salt thereof, is administered as a composition. In some embodiments, the composition comprising LSD, or a salt thereof, is formulated in a capsule or tablet. In some embodiments, the LSD, or a salt thereof, is administered as a capsule. International Application No. PCT/US2022/040653 further discloses the preparation of the capsule. In some embodiments, the LSD, or a salt thereof, is administered as a tablet.

[00056] When the LSD, or a salt thereof, is formulated as a tablet, the tablet may be an orally disintegrating tablet. International Application No. PCT/US2022/040636 further discloses the preparation of the orally disintegrating tablet. In some embodiments, the orally disintegrating tablet is a lyophilized orally disintegrating tablet. In some embodiments, the d-LSD D-tartrate is administered as an orally disintegrating tablet. An orally disintegrating tablet is capable of disintegrating or dispersing within an interval of less than 60 seconds after being placed in contact with a physiological fluid such as saliva. In some embodiments, the orally disintegrating tablet is capable of dispersing within an interval of about 1 to about 60 seconds, about 1 to about 30 seconds, about 1 to about 10 seconds, or about 1 to about 5 seconds after being placed in contact with a physiological fluid such as saliva.

[00057] Also when an orally disintegrating tablet is used, it may be prepared as a stock solution. The stock solution may be utilized to prepare the tablet for administration to a subject with generalized anxiety disorder.

[00058] In some embodiments, the orally disintegrating tablet comprises:

- a. LSD, or a salt thereof;
- b. a non-gelling matrix;
- c. a binder;
- d. a filler; and
- e. solvent.

[00059] When an orally disintegrating tablet is used and the LSD salt is d-LSD D-tartrate, d-LSD D-tartrate may be present in the stock solution in an amount of less than about 1%. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 1% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.9% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.8% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.7% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.6% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.5% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.4% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.3% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.2% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.1% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.09% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.08% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.07% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.06% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.05% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.04% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.03% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.02% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet stock solution comprises less than about 0.01% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 1% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.9% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet

comprises less than about 0.8% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.7% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.6% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.5% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.4% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.3% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.2% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.1% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.09% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.08% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.07% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.06% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.05% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.04% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.03% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.02% d-LSD D-tartrate. In some embodiments, the orally disintegrating tablet comprises less than about 0.01% d-LSD D-tartrate.

[00060] The formulation of LSD described herein may comprise a non-gelling matrix. In some embodiments, the non-gelling matrix is a non-gelling gelatin (including fish gelatin), maltodextrin, modified starches, starch ethers, low molecular weight dextrans, or low to intermediate molecular weight cellulose gums. In some embodiments, the non-gelling matrix is described in U.S. Pat. No. 10,548,839.

[00061] When maltodextrin is used as the non-gelling matrix in the orally disintegrating tablet described herein, maltodextrin may be present in an amount of about 2% to about 10% of the total stock solution formulation. In some embodiments, the orally disintegrating tablet stock solution comprises about 2% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 3% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 4% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 5% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 6% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 7% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 8% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 9% maltodextrin. In some embodiments, the orally disintegrating tablet stock solution comprises about 10% maltodextrin.

[00062] When maltodextrin is used as the non-gelling matrix in the orally disintegrating tablet described herein, maltodextrin may be present in an amount of about 15% to about 77% of the formulation. In

some embodiments, the orally disintegrating tablet comprises about 15% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 20% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 25% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 30% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 35% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 40% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 41% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 42% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 43% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 44% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 45% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 46% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 47% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 48% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 49% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 50% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 55% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 60% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 65% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 70% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 75% maltodextrin. In some embodiments, the orally disintegrating tablet comprises about 77% maltodextrin.

[00063] The formulation of LSD described herein may comprise a binder. In some embodiments, the binder is acacia gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), or starch.

[00064] When hydroxypropyl methylcellulose is used as the binder in the orally disintegrating tablet described herein, the hydroxypropyl methylcellulose may be present in an amount of about 1% to about 5% of the total stock solution formulation. In some embodiments, the orally disintegrating tablet stock solution comprises about 1% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet stock solution comprises about 2% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet stock solution comprises about 3% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet stock solution comprises about 4% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet stock solution comprises about 5% hydroxypropyl methylcellulose.

[00065] When hydroxypropyl methylcellulose is used as the binder in the orally disintegrating tablet described herein, the hydroxypropyl methylcellulose may be present in an amount of about 8% to about 38% of the formulation. In some embodiments, the orally disintegrating tablet comprises about 8% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 9% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises

about 10% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 15% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 20% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 25% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 30% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 35% hydroxypropyl methylcellulose. In some embodiments, the orally disintegrating tablet comprises about 38% hydroxypropyl methylcellulose.

[00066] The formulation of LSD described herein may comprise a filler. In some embodiments, the filler is lactose (including anhydrous), mannitol, dicalcium phosphate, calcium sulfate, starch (starch as used herein can include dry or pre-gelled), cellulose (including microcrystalline cellulose), kaolin, sodium chloride, sorbitol, trehalose, or sucrose.

[00067] When mannitol is used as the filler in the orally disintegrating tablet described herein, the mannitol may be present in an amount of about 2% to about 10% of the total stock solution formulation. In some embodiments, the orally disintegrating tablet stock solution comprises about 2% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 3% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 4% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 5% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 6% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 7% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 8% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 9% mannitol. In some embodiments, the orally disintegrating tablet stock solution comprises about 10% mannitol.

[00068] When mannitol is used as the filler in the orally disintegrating tablet described herein, the mannitol may be present in an amount of about 15% to about 77% of the formulation. In some embodiments, the orally disintegrating tablet comprises about 15% mannitol. In some embodiments, the orally disintegrating tablet comprises about 20% mannitol. In some embodiments, the orally disintegrating tablet comprises about 25% mannitol. In some embodiments, the orally disintegrating tablet comprises about 30% mannitol. In some embodiments, the orally disintegrating tablet comprises about 35% mannitol. In some embodiments, the orally disintegrating tablet comprises about 36% mannitol. In some embodiments, the orally disintegrating tablet comprises about 37% mannitol. In some embodiments, the orally disintegrating tablet comprises about 38% mannitol. In some embodiments, the orally disintegrating tablet comprises about 38.3% mannitol. In some embodiments, the orally disintegrating tablet comprises about 39% mannitol. In some embodiments, the orally disintegrating tablet comprises about 40% mannitol. In some embodiments, the orally disintegrating tablet comprises about 45% mannitol. In some embodiments, the orally disintegrating tablet comprises about 50% mannitol. In some embodiments, the orally disintegrating tablet comprises about 55% mannitol. In some

embodiments, the orally disintegrating tablet comprises about 60% mannitol. In some embodiments, the orally disintegrating tablet comprises about 65% mannitol. In some embodiments, the orally disintegrating tablet comprises about 70% mannitol. In some embodiments, the orally disintegrating tablet comprises about 75% mannitol. In some embodiments, the orally disintegrating tablet comprises about 77% mannitol.

[00069] The formulation of LSD described herein may comprise a solvent. When water is used as the solvent in the orally disintegrating tablet described herein, the water may be present in an amount of less than 10% water of the formulation. In some embodiments, the orally disintegrating tablet comprises less than 9% water. In some embodiments, the orally disintegrating tablet comprises less than 8% water. In some embodiments, the orally disintegrating tablet comprises less than 7% water. In some embodiments, the orally disintegrating tablet comprises less than 6% water. In some embodiments, the orally disintegrating tablet comprises less than 5% water. In some embodiments, the orally disintegrating tablet comprises less than 4% water. In some embodiments, the orally disintegrating tablet comprises less than 3% water. In some embodiments, the orally disintegrating tablet comprises less than 2% water. In some embodiments, the orally disintegrating tablet comprises less than 1% water.

[00070] In some embodiments, the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[00071] In some embodiments, the orally disintegrating tablet stock solution comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 2% to about 10% maltodextrin;
- c. about 1% to about 5% hydroxypropyl methylcellulose;
- d. about 2% to about 10% mannitol; and
- e. water.

[00072] In some embodiments, the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[00073] In some embodiments, the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;

- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

III. Use of the Formulation

[00074] The formulation described herein may be used for the treatment of a subject with generalized anxiety disorder, or a symptom thereof. The formulation described herein may be used for the treatment of a symptom or prevention of a symptom of generalized anxiety disorder in a subject. In some embodiments, the treatment is a treatment of the symptoms associated with generalized anxiety disorder.

[00075] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[00076] In some embodiments, the present disclosure provides use of an orally disintegrating tablet, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[00077] In some embodiments, the present disclosure provides an orally disintegrating tablet, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00078] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00079] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

[00080] In some embodiments, the present disclosure provides use of an orally disintegrating tablet, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[00081] In some embodiments, the present disclosure provides an orally disintegrating tablet, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00082] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

IV. Dose and Schedule of Administration

[00083] LSD, or a salt thereof, described herein may be further administered to a subject at a specified dose or administration schedule. When the LSD, or a salt thereof, is administered at a specified dose, the dose corresponds to the freebase equivalent of the LSD salt. The schedule of administration may also include frequency and length of administration.

a. Dose

[00084] When LSD, or a salt thereof, is administered to a subject, the dose is between about 25 µg to about 200 µg, wherein the amount of LSD correlates to the amount of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 25 µg, about 50 µg, about 100 µg, about 150 µg, or about 200 µg of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 25 µg of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 50 µg of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 100 µg of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 150 µg of the freebase equivalent of LSD. In some embodiments, the LSD, or a salt thereof, is administered at a dose of about 200 µg of the freebase equivalent of LSD.

[00085] When d-LSD D-tartrate is administered to a subject, the dose is between about 25 µg to about 200 µg, wherein the amount of LSD correlates to the amount of the freebase equivalent of LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 25 µg, about 50 µg, about 100 µg, about 150 µg, or about 200 µg of the freebase equivalent of LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 25 µg of the freebase equivalent of LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 50 µg of the freebase equivalent of

LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 100 µg of the freebase equivalent of LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 150 µg of the freebase equivalent of LSD. In some embodiments, d-LSD D-tartrate is administered at a dose of about 200 µg of the freebase equivalent of LSD.

[00086] In some embodiments, about 146 µg of the d-LSD D-tartrate is equivalent to about 100 µg of LSD freebase.

[00087] When LSD, or a salt thereof, is administered at a dose of about 100 µg of the freebase equivalent of LSD the subject's symptom of generalized anxiety disorder may be treated or prevented. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg LSD, or a salt thereof. In one aspect, the present disclosure provides use of a dose of about 100 µg LSD, or a salt thereof, for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg LSD, or a salt thereof, for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg LSD, or a salt thereof, in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg d-LSD D-tartrate. In one aspect, the present disclosure provides use of a dose of about 100 µg d-LSD D-tartrate for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg d-LSD D-tartrate for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg d-LSD D-tartrate in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00088] When LSD, or a salt thereof, is administered to a subject, the symptom of generalized anxiety disorder may be reduced or eliminated between about 6 hours to about 24 hours after administration. For example, the symptom of generalized anxiety disorder may be reduced or eliminated between about 6 hours to about 12 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 6 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 7 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 8 hours after administration of the orally disintegrating tablet comprising LSD, or a

salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 9 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 10 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 11 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 12 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 24 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[00089] When d-LSD D-tartrate is administered to a subject, the symptom of generalized anxiety disorder may be reduced or eliminated between about 6 hours to about 12 hours after administration. For example, the symptom of generalized anxiety disorder may be reduced or eliminated between about 6 hours to about 12 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 6 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 7 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 8 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 9 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 10 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 11 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated about 12 hours after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[00090] When the LSD, or a salt thereof, is administered the subject's symptoms may be eliminated for a period of time greater than 10 weeks. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 12 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 16 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 20 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some

embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 24 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[00091] When the d-LSD D-tartrate is administered the subject's symptoms may be eliminated for an period of time greater than 10 weeks. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 12 weeks or greater after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 16 weeks or greater after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 20 weeks or greater after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the symptom of generalized anxiety disorder is reduced or eliminated for about 24 weeks or greater after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

b. Schedule of Administration

[00092] When LSD, or a salt thereof, is administered to a subject, LSD, or a salt thereof, is administered intermittently. In some embodiments, the LSD, or salt thereof is administered at a frequency of one to four times per year. In some embodiments, the LSD, or a salt thereof, is administered one time per year. In some embodiments, the LSD, or a salt thereof, is administered two times per year. In some embodiments, the LSD, or a salt thereof, is administered three times per year. In some embodiments, the LSD, or a salt thereof, is administered four times per year. In some embodiments, the LSD, or a salt thereof, is administered weekly. In some embodiments, the LSD, or a salt thereof, is administered monthly. In some embodiments, the LSD, or a salt thereof, is administered between once per week and once per year. In some embodiments, the LSD, or a salt thereof, is administered once to a subject.

[00093] When LSD, or a salt thereof, is administered to a subject, the administration may be followed by a drug holiday. In some embodiments, the drug holiday is from about one week to about one year. In some embodiments, the drug holiday is from about one to about four months.

[00094] When LSD, or a salt thereof, is administered to a subject the frequency may be once every about 10 to about 20 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 10 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 12 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 14 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 16 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 18 weeks. In some embodiments, the LSD, or a salt thereof, is administered once every about 20 weeks.

[00095] When d-LSD D-tartrate is administered to a subject, d-LSD D-tartrate is administered at a frequency of one to four times per year. In some embodiments, d-LSD D-tartrate is administered one time per year. In some embodiments, d-LSD D-tartrate is administered two times per year. In some embodiments, d-LSD D-tartrate is administered three times per year. In some embodiments, d-LSD D-

tartrate is administered four times per year.

[00096] When d-LSD D-tartrate is administered to a subject the frequency may be once every about 10 to about 20 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 10 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 12 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 14 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 16 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 18 weeks. In some embodiments, d-LSD D-tartrate is administered once every about 20 weeks.

[00097] In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg LSD, or a salt thereof one to four times per year. In one aspect, the present disclosure provides use of a dose of about 100 µg LSD, or a salt thereof, one to four times per year for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg LSD, or a salt thereof, one to four times per year for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg LSD, or a salt thereof, one to four times per year in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg d-LSD D-tartrate freebase equivalent one to four times per year. In one aspect, the present disclosure provides use of a dose of about 100 µg d-LSD D-tartrate freebase equivalent one to four times per year for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg d-LSD D-tartrate freebase equivalent one to four times per year for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg d-LSD D-tartrate freebase equivalent one to four times per year in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00098] In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg LSD, or a salt thereof once every about 12 weeks. In one aspect, the present disclosure provides use of a dose of about 100 µg LSD, or a salt thereof, once every about 12 weeks for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg LSD, or a salt thereof, once every about 12 weeks for use in treating a symptom of generalized anxiety disorder or preventing a symptom of

generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg LSD, or a salt thereof, once every about 12 weeks in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg d-LSD D-tartrate freebase equivalent once every about 12 weeks. In one aspect, the present disclosure provides use of a dose of about 100 µg d-LSD D-tartrate freebase equivalent once every about 12 weeks for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides a dose of about 100 µg d-LSD D-tartrate freebase equivalent once every about 12 weeks for use in treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder. In one aspect, the present disclosure provides the use of a dose of about 100 µg d-LSD D-tartrate freebase equivalent once every about 12 weeks in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[00099] For the avoidance of doubt, the dose of about 147 µg d-LSD D-tartrate correlates to about 100 µg of the LSD freebase. For the avoidance of doubt, the dose of about 100 µg d-LSD D-tartrate freebase equivalent correlates to about 100 µg of the LSD freebase.

[000100] When the LSD is formulated in an orally disintegrating tablet, the dose and frequency may be as described herein. For example, the orally disintegrating tablet may be administered one to four times per year or once every about 10 to about 20 weeks at an LSD freebase equivalent dose of about 100 µg.

[000101] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[000102] In some embodiments, the present disclosure provides use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000103] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[000104] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[000105] In some embodiments, the present disclosure provides use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000106] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and

e. less than 10% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[000107] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

[000108] In some embodiments, the present disclosure provides use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1%% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000109] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[000110] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;

- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[000111] In some embodiments, the present disclosure provides use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000112] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[000113] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[000114] In some embodiments, the present disclosure provides use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;

- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000115] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

[000116] In some embodiments, the present disclosure provides a method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

[000117] In some embodiments, the present disclosure provides use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

for the treatment of a symptom of generalized anxiety disorder or prevention of a symptom of generalized anxiety disorder.

[000118] In some embodiments, the present disclosure provides the use of an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;

- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water,

in the manufacture of a medicament for treating a symptom of generalized anxiety disorder or preventing a symptom of generalized anxiety disorder.

V. Analysis Parameters

[000119] In determining the effectiveness of a treatment described herein, the subject's serum concentration may be analyzed for the presence of LSD freebase. The presence of LSD freebase at an increased concentration over a period of time less than five hours may indicate that the formulation is effective in treating a symptom or preventing a symptom of generalized anxiety disorder with LSD, or a salt thereof. Blood sampling for LSD freebase analysis occurred at multiple time points during treatment with LSD, or a salt thereof (e.g., at pre-dose (about 15 minutes prior to dose $\pm$ 5 minutes), and about 5 minutes, about 10 minutes, and about 15 minutes post-dose (with a sampling window of $\pm$ 1 minute), as well as at about 30 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 5 hours, about 6 hours, about 8 hours, about 12 hours, and about 24 hours post-dose (with a sampling window of $\pm$ 5 minutes).

[000120] The effectiveness of a treatment described herein may also be determined through subject participation in post treatment questionnaires, symptom reporting, and subject monitoring. A subject's decrease in symptoms of generalized anxiety disorder is considered treatment of a symptom of generalized anxiety disorder.

[000121] The methods described herein can also include the subject wearing a smartwatch and using a smartphone with built-in sensors to passively record heart rate, audio data, accelerometric data, angular velocity, orientation, number of steps, and activity type. The data recorded by the smartwatch may be utilized by a medical professional to monitor the individual throughout a treatment session.

[000122] When a subject reports their own outcome measurements it may be according to the Patient Global Impression scale, Sheehan Disability Scale, EQ-5D-5L, Pittsburgh Sleep Quality Index, or Arizona Sexual Experiences Questionnaire. A subject may self-report their outcome by reporting their symptoms, or treatment thereof, to a medical professional.

a. Pharmacokinetics

[000123] When a subject is administered LSD, or a salt thereof, according to the instant disclosure, the LSD exhibits rapid absorption and systemic bioavailability. The administration of LSD, or a salt thereof, in an orally disintegrating tablet provides increased absorption and systemic bioavailability as compared to administration of LSD in a capsule. Detectable levels of LSD freebase from an orally disintegrating

tablet may be observed within 5 to 30 minutes, 5 to 15 minutes, or 5 to 10 minutes. The $C_{\max}$ of the LSD freebase from an orally disintegrating tablet is between about 0.9 to 5.4 ng/mL (e.g., 0.798 to 4.60 ng/mL, or 1.75 to 3.65 ng/mL). The AUC_{0-24} of the LSD freebase from an orally disintegrating tablet is between about 5.6 to about 45 ng•hr/mL (e.g., 3.34 to 33.5 ng•hr/mL, or 10.9 to 25.9 ng•hr/mL). The $AUC_{\inf}$ of the LSD freebase from an orally disintegrating tablet is between about 5.9 to about 48.0 ng•hr/mL (e.g., 3.68 to 35.3 ng•hr/mL, or 11.59 to 27.49 ng•hr/mL). The $T_{\max}$ after administration of LSD, or a salt thereof, in an orally disintegrating tablet is between about 1.0 hours to about 4 hours (e.g., 0.47 to 3.67 hours or 1.27 to 2.87 hours). The $T_{1/2}$ of the LSD freebase in an orally disintegrating tablet is between about 2.5 hours to about 10.3 hours (e.g., 1.37 to 8.3 hours or 3.21 to 6.89 hours). Administration of an orally disintegrating tablet comprising LSD, or a salt thereof, provides a time to symptom resolution that is between a time about 6 to about 12 hours on average (e.g., 6 to 10 hours on average or 8 to 10 hours on average). The administration of an orally disintegrating tablet comprising LSD, or a salt thereof, provides a resolving of acute perceptual effects from about 50% of patients by about 8 hours, about 70% of patients by about 10 hours, and about 40% of patients by about 7 hours.

[000124] When an orally disintegrating tablet comprising LSD, or a salt thereof, is administered as described in the instant disclosure, a greater peak concentration of LSD freebase as compared to administration of LSD, or a salt thereof, in a different formulation at a comparable dose. In some embodiments, the orally disintegrating tablet comprising LSD, or a salt thereof, provides a greater peak concentration of LSD freebase as compared to a capsule comprising LSD, or a salt thereof.

[000125] In some embodiments, the subject's serum LSD freebase concentration is between about 2 ng/mL to about 2.5 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.1 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.2 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.3 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.4 ng/mL within about five hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.5 ng/mL within about five hours after administration of the orally disintegrating tablet.

[000126] In some embodiments, the subject's serum LSD freebase concentration is between about 2 ng/mL to about 2.5 ng/mL within about four hours after administration of the orally disintegrating tablet.

[000127] In some embodiments, the subject's serum LSD freebase concentration is about 2 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments,

the subject's serum LSD freebase concentration is about 2.1 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.2 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.3 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.4 ng/mL within about four hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.5 ng/mL within about four hours after administration of the orally disintegrating tablet.

[000128] In some embodiments, the subject's serum LSD freebase concentration is between about 2 ng/mL to about 2.5 ng/mL within about three hours after administration of the orally disintegrating tablet.

In some embodiments, the subject's serum LSD freebase concentration is about 2 ng/mL within about three hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.1 ng/mL within about three hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.2 ng/mL within about three hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.3 ng/mL within about three hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.4 ng/mL within about three hours after administration of the orally disintegrating tablet. In some embodiments, the subject's serum LSD freebase concentration is about 2.5 ng/mL within about three hours after administration of the orally disintegrating tablet.

[000129] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.2 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.2 ng/mL higher within four hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.2 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000130] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.3 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet

comprising d-LSD D-tartrate is about 0.3 ng/mL higher within four hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.3 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000131] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.4 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.4 ng/mL higher within four hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.4 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000132] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.5 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.5 ng/mL higher within four hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.5 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000133] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.6 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.6 ng/mL higher within four hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.6 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000134] In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.7 ng/mL higher within five hours as compared to administration of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.7 ng/mL higher within four hours as compared to administration

of a capsule comprising d-LSD D-tartrate. In some embodiments, the subject's serum LSD freebase concentration after administration of an orally disintegrating tablet comprising d-LSD D-tartrate is about 0.7 ng/mL higher within three hours as compared to administration of a capsule comprising d-LSD D-tartrate.

[000135] In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate.

[000136] In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 15% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate. In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 16% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate. In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 17% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate. In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 18% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate. In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 19% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate. In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased about 20% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate.

[000137] In some embodiments, the bioavailability of LSD freebase (e.g., C_{max}) is increased from about 15% to about 20% after administration of an orally disintegrating tablet comprising d-LSD D-tartrate as compared to a capsule comprising d-LSD D-tartrate.

[000138] In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action of about 0.5 hour. In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action of about 1 hour. In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action of about 1.5 hours. In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action of about 2 hours. In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action of about 2.5 hours.

[000139] In some embodiments, an orally disintegrating tablet comprising d-LSD D-tartrate has an onset of action that is 50% faster than the onset of action of a capsule comprising d-LSD D-tartrate.

[000140] The onset of action may be related to measuring LSD freebase concentration in the blood or measuring a subjective effect of the drug.

[000141] In some embodiments, administration of an orally disintegrating tablet comprising d-LSD D-

tartrate provides a decrease in concentration of LSD freebase in subject serum to below 1 ng/mL within 12 hours of administration of the orally disintegrating tablet.

[000142] In some embodiments, administration of a capsule comprising d-LSD D-tartrate provides a decrease in concentration of LSD freebase in subject serum to below 1 ng/mL within 24 hours of administration of the orally disintegrating tablet.

[000143] In some embodiments, administration of an orally disintegrating tablet comprising d-LSD D-tartrate provides a decrease in concentration of LSD freebase in subject serum to below 1 ng/mL in half the time as compared to administration of a capsule comprising d-LSD D-tartrate,

wherein the faster decrease in serum concentration of the orally disintegrating tablet comprising d-LSD D-tartrate results in a shorter duration of adverse events requiring monitoring by a healthcare practitioner.

[000144] In some embodiments, administration of an orally disintegrating tablet comprising d-LSD D-tartrate provides a decrease in concentration of LSD freebase in subject serum to below 1 ng/mL in half the time as compared to administration of a capsule comprising d-LSD D-tartrate,

wherein the faster decrease in serum concentration of the orally disintegrating tablet comprising d-LSD D-tartrate results in a shorter duration of perceptual effects.

[000145] In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 7.5 ng•hr/mL and about 30 ng•hr/mL.

[000146] In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 7.73 ng•hr/mL and about 29.13 ng•hr/mL. In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 8.0 ng•hr/mL and about 27.0 ng•hr/mL. In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 8.28 ng•hr/mL and about 25.27 ng•hr/mL. In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 11.0 ng•hr/mL and about 20.0 ng•hr/mL. In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is between about 11.71 ng•hr/mL and about 17.42 ng•hr/mL.

[000147] In some embodiments, the AUC_{0-24} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 μ g of the LSD freebase equivalent of d-LSD D-tartrate is higher than the AUC_{0-24} for d-LSD D-tartrate after administration of a capsule comprising the equivalent dose of LSD freebase.

[000148] In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally

disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 8.0 ng•hr/mL and about 35.0 ng•hr/mL. In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 8.35 ng•hr/mL and about 31.85 ng•hr/mL. In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 8.87 ng•hr/mL and about 27.56 ng•hr/mL. In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 10.0 ng•hr/mL and about 20.0 ng•hr/mL. In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 12.87 ng•hr/mL and about 18.30 ng•hr/mL.

[000149] In some embodiments, the AUC_{inf} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is higher than the AUC_{inf} for LSD freebase after administration of a capsule comprising the equivalent dose of LSD freebase.

[000150] In some embodiments, the $AUC_{0-C_{max}}$ for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 0.5 ng•hr/mL and about 10.0 ng•hr/mL. In some embodiments, the $AUC_{0-C_{max}}$ for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 0.76 ng•hr/mL and about 6.41 ng•hr/mL. In some embodiments, the $AUC_{0-C_{max}}$ for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 1.01 ng•hr/mL and about 5.45 ng•hr/mL. In some embodiments, the $AUC_{0-C_{max}}$ for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 1.44 ng•hr/mL and about 3.72 ng•hr/mL.

[000151] In some embodiments, the $AUC_{0-C_{max}}$ for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is higher than the $AUC_{0-C_{max}}$ for LSD freebase after administration of a capsule comprising the equivalent dose of LSD freebase.

[000152] In some embodiments, the T_{max} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 1 to about 3.5 hours. In some embodiments, the T_{max} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 1.38 hours to 3 hours.

[000153] In some embodiments, the T_{max} for the LSD freebase after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is lower

than the $T_{\max}$ for LSD freebase after administration of a capsule comprising the equivalent dose of LSD freebase.

[000154] In some embodiments, the subject experience symptom resolution after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 6 hours to 12 hours.

[000155] In some embodiments, the subject experience symptom resolution after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 6 hours to 10 hours.

[000156] In some embodiments, the subject experience symptom resolution after administration of an orally disintegrating tablet comprising 100 µg of the LSD freebase equivalent of d-LSD D-tartrate is between about 8 hours to 10 hours.

b. Hamilton Anxiety Scale (HAM-A)

[000157] When a subject is administered LSD, or a salt thereof, as described in the instant disclosure, the treatment is measured by a reduction in Hamilton Anxiety Scale (HAM-A) score. Severe generalized anxiety disorder is classified by a Hamilton Anxiety Scale (HAM-A) score greater than 25, while moderate generalized anxiety disorder is classified by a HAM-A score of 16-24. After treatment, a subject may have a HAM-A score below 16. In some embodiments, treatment results in a HAM-A score below 8. In order to determine an initial HAM-A score of a subject, the subject's HAM-A score is measured at screening and baseline prior to administration of LSD, or a salt thereof. In some embodiments, a subject to be treated with LSD, or a salt thereof, as described herein, has an initial HAM-A score higher than about 17 (e.g., 20).

[000158] When a HAM-A score is measured, the medical professional assess the following items in a subject: anxious mood, tension, fears, insomnia, intellect, depressed mood, somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and general behavior at the interview. Each of the criterion are assess on a scale of 0 to 4, wherein 4 is the most severe symptoms. After administration of a GAM-A assessment, the medical professional may provide an assessment of the Montgomery-Åsberg Depression Rating Scale (MADRS).

[000159] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000160] In some embodiments, the subject has between an about 15-point and about 25-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000161] In some embodiments, the subject has an about 15-point HAM-A improved score within about

12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 16-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 17-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 18-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 19-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 20-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 21-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 22-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 23-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 24-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 25-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000162] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

In some embodiments, the subject has between an about 15-point and about 25-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000163] In some embodiments, the subject has an about 15-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 16-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 17-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 18-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 19-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating

tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 20-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 21-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 22-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 23-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 24-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 25-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000164] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of less than 10 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000165] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 10 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 9 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 8 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 7 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 6 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 5 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 4 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 3 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 2 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 1 about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000166] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of less than 10 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000167] In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 10 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 9 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 8 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 7 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 6 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 5 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 4 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 3 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 2 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has a Hamilton Anxiety Scale (HAM-A) score of 1 about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

c. Clinical Global Impressions – Severity (CGI-S)

[000168] When a subject is administered LSD, or a salt thereof, as described in the instant disclosure, the treatment is measured by a reduction in Clinical Global Impressions – Severity (CGI-S). After treatment a subject may have a reduction in CGI-S between about 1.5-points and 2.0-points. CGI-S is measured at least one week after administration of LSD, or a salt thereof. In some embodiments, the subject shows a CGI-S score change from 7 to 6, 6 to 5, 7 to 5, 6 to 4, or any CGI-S score lower than the CGI-S score prior to treatment. The reduction in CGI-S may be measured about two days, one week, two weeks, four weeks, eight weeks, or 12 weeks after treatment.

[000169] When the CGI-S scale is assessed in a subject the severity of the illness is determined as compared to the medical professionals understanding and prior assessments of subjects with generalized anxiety disorder. A CGI-S scale is from 0-7, with 7 being a more severe illness.

[000170] In some embodiments, the subject has a reduction in Clinical Global Impressions – Severity (CGI-S) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000171] In some embodiments, the subject has between an about 1.5-point and 2.0-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000172] In some embodiments, the subject has an about 1.5-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 1.6-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 1.7-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 1.8-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 1.9-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 2.0-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000173] In some embodiments, the subject has a reduction in Clinical Global Impressions – Severity (CGI-S) within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000174] In some embodiments, the subject has between an about 1.5-point and 2.0-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

In some embodiments, the subject has an about 1.5-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 1.6-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 1.7-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 1.8-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 1.9-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 2.0-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

d. Montgomery-Åsberg Depression Rating Scale (MADRS)

[000175] When a subject is administered LSD, or a salt thereof, as described in the instant disclosure, the treatment is measured by a reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS). After treatment a subject may have a reduction in MADRS between about 15-points and 20-points. MADRS is measured at least one week after administration of LSD, or a salt thereof.

[000176] When MADRS is assessed in a subject, a medical profession determines the depression severity. The MADRS assessment includes a questionnaire including 10 questions that are ranked from 0-6, wherein 6 indicates severe or continuous present of depression symptoms. When a subject is determined to have a high MADRS score, then the subject has a severe condition. The maximum MADRS score is 60.

[000177] When a subject is treated according to the methods of the instant disclosure, a decrease in score by about 50% indicates a successful response. In some embodiments, the subject has an about 50% decrease in MADRS score after treatment with LSD, or a salt thereof. In some embodiments, a subject has been treated when the subject is determined to have a score of less than or equal to about 10.

[000178] In some embodiments, the subject has a reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000179] In some embodiments, the subject has between an about 15-point and 20-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000180] In some embodiments, the subject has an about 15-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 16-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 17-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 18-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 19-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof. In some embodiments, the subject has an about 20-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

In some embodiments, the subject has a reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000181] In some embodiments, the subject has between an about 15-point and 20-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000182] In some embodiments, the subject has an about 15-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some

embodiments, the subject has an about 16-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 17-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 18-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 19-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate. In some embodiments, the subject has an about 20-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising d-LSD D-tartrate.

[000183] In some embodiments, the dose is a the dose of the freebase equivalent of d-LSD D-tartrate.

Definitions

[000184] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[000185] As used herein, the term "subject" refers to an organism, for example, a mammal (e.g., a human, a non-human mammal, a non-human primate, a primate, a laboratory animal, a mouse, a rat, a hamster, a gerbil, a cat, a dog).

[000186] Unless explicitly indicated otherwise, the terms "approximately" and "about" are synonymous. In some embodiments, "approximately" and "about" refer to the recited amount, value, or duration $\pm 5\%$, $\pm 4.5\%$, $\pm 4\%$, $\pm 3.5\%$, $\pm 3\%$, $\pm 2.5\%$, $\pm 2\%$, $\pm 1.75\%$, $\pm 1.5\%$, $\pm 1.25\%$, $\pm 1\%$, $\pm 0.9\%$, $\pm 0.8\%$, $\pm 0.7\%$, $\pm 0.6\%$, $\pm 0.5\%$, $\pm 0.4\%$, $\pm 0.3\%$, $\pm 0.2\%$, $\pm 0.1\%$, $\pm 0.09\%$, $\pm 0.08\%$, $\pm 0.07\%$, $\pm 0.06\%$, $\pm 0.05\%$, $\pm 0.04\%$, $\pm 0.03\%$, $\pm 0.02\%$, or $\pm 0.01\%$. In another embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 2.5\%$, $\pm 2\%$, $\pm 1.75\%$, $\pm 1.5\%$, $\pm 1.25\%$, $\pm 1\%$, $\pm 0.9\%$, $\pm 0.8\%$, $\pm 0.7\%$, $\pm 0.6\%$, $\pm 0.5\%$. In yet another embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 1\%$. In yet another embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 0.5\%$. In yet another embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 0.1\%$.

[000187] The term "effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, e.g., inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be given in unit dosage form .

[000188] The terms "administer," "administering," "administration," and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action.

[000189] As used herein, "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, a symptom of a disease, condition, symptom of a condition, disorder,

or symptom of a disorder and includes the administration of LSD, or a salt thereof. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[000190] As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[000191] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non- health-care professionals.

[000192] "Generalized anxiety disorder" as used herein refers to a condition that is characterized by persistent and excessive worry. Generalized anxiety disorder is present when an individual has difficulty controlling worry on more days than not for at least six months and has at least three defined symptoms (such as feeling nervous, irritable, on edge, having a sense of impending danger, panic, or doom, having an increased heart rate, breathing rapidly (hyperventilation), sweating, and/or trembling, feeling weak or tired, difficulty concentrating, having trouble sleeping, and experiencing gastrointestinal (GI) problems). Generalized anxiety disorder is different from anxiety brought on by a specific stressor, such as illness.

EXEMPLARY EMBODIMENTS

[000193] Exemplary Embodiment 1A. A method of treating Generalized Anxiety Disorder (GAD), including the step of:

administering a serotonin-2A receptor agonist to an individual suffering from GAD.

[000194] Exemplary Embodiment 2A. A method of treating moderate GAD, including the step of:

administering a serotonin-2A receptor agonist to an individual suffering from moderate GAD.

[000195] Exemplary Embodiment 3A. A method of treating severe GAD, including the step of:

administering a serotonin-2A receptor agonist to an individual suffering from severe GAD.

[000196] Exemplary Embodiment 4A. A method of improving Hamilton Anxiety scale scores, including the steps of:

administering a Hamilton Anxiety scale to an individual suffering from GAD;

administering a serotonin-2A receptor agonist to the individual; and

producing improved Hamilton Anxiety scale scores.

[000197] Exemplary Embodiment 5A. A method of treating an anxiety disorder, including the step of:

administering a serotonin-2A receptor agonist to an individual suffering from an anxiety disorder without concomitant therapy.

[000198] Exemplary Embodiment 6A. A method of treating anxiety and depression, including the steps of:

administering a serotonin-2A receptor agonist to an individual suffering from anxiety and depression; and

treating anxiety and depression at the same time.

[000199] Exemplary Embodiment 7A. A method of rapidly treating GAD, including the steps of:

administering a serotonin-2A receptor agonist to an individual suffering from GAD;
and

producing an improvement in GAD symptoms within 48 hours of administration.

[000200] Exemplary Embodiment 8A. A method of treating GAD and reducing risk of suicide in an individual, including the steps of:

administering a serotonin-2A receptor agonist to an individual suffering from GAD;
and

preventing suicidality or suicidal ideation in the individual during and after treatment.

[000201] Exemplary Embodiment 9A. A method of reducing or treating adverse effects of serotonin-2A receptor agonists, including the steps of:

administering a serotonin-2A receptor agonist to an individual;

administering an adverse effect reducing agent to the individual; and

reducing or treating adverse effects caused by the serotonin-2A receptor agonist.

[000202] Exemplary Embodiment 1B. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a serotonin-2A receptor agonist, wherein said pharmaceutical composition is in a form of an oral solid molded fast-dispersing and fast-disintegrating dosage form.

[000203] Exemplary Embodiment 2B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said serotonin-2A receptor agonist is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, psilocin, mescaline, 3,4-methylenedioxymethamphetamine (MDMA), R-MDMA, S-MDMA, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), salts thereof, tartrates thereof, solvates thereof, isomers thereof, analogs thereof, homologues thereof, and deuterated forms thereof.

[000204] Exemplary Embodiment 3B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition is capable of disintegrating or dispersing within an interval selected from 1 to 60 seconds, 1 to 30 seconds, 1 to 10 seconds, and 2 to 8 seconds, after being placed in contact with a physiological fluid.

[000205] Exemplary Embodiment 4B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said fluid is saliva.

[000206] Exemplary Embodiment 5B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides detectable levels of said serotonin-2A receptor

agonist within to 30 minutes, 5 to 15 minutes, and 5 to 10 minutes.

[000207] Exemplary Embodiment 6B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides a greater peak concentration per unit of drug dosed compared to other solid oral formulations of said serotonin-2A receptor agonist.

[000208] Exemplary Embodiment 7B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides a C_{max} or AUC that is within $\pm 20\%$ of the values for other solid oral formulations of said serotonin-2A receptor agonist.

[000209] Exemplary Embodiment 8B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides a T_{max} that is between a time selected from 1 to 3.5 hours, and 1.38 to 3 hours.

[000210] Exemplary Embodiment 9B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides a time to symptom resolution that is between a time selected from 6 to 12 hours on average, 6 to 10 hours on average, and 8 to 10 hours on average.

[000211] Exemplary Embodiment 10B. The pharmaceutical composition of Exemplary Embodiment 1B, wherein said pharmaceutical composition provides a resolving of acute perceptual effects selected from 50% of patients by 8 hours, 70% of patients by 10 hours, and 40% of patients by 7 hours .

[000212] Exemplary Embodiment 11B. A method of treating an individual, including the steps of:

administering to the individual a serotonin-2A receptor agonist in a fast-disintegrating orally disintegrating tablet (ODT); and

treating the individual.

[000213] Exemplary Embodiment 12B. The method of Exemplary Embodiment 11B, wherein the serotonin-2A receptor agonist is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, psilocin, mescaline, 3,4-methylenedioxymethamphetamine (MDMA), R-MDMA, S-MDMA, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), salts thereof, tartrates thereof, solvates thereof, isomers thereof, analogs thereof, homologues thereof, and deuterated forms thereof.

[000214] Exemplary Embodiment 13B. The method of Exemplary Embodiment 11B, wherein said administering step provides faster absorption, faster bioavailability, and faster time to maximum concentration which provides faster time to desired clinical effects of the serotonin-2A receptor agonist than other solid oral formulations of the serotonin-2A receptor agonist.

[000215] Exemplary Embodiment 14B. The method of Exemplary Embodiment 11B, wherein said administering step provides lower variability in exposure of LSD than other solid oral formulations of LSD between 10 minutes to 120 minutes, between 2 and 6 hours, and between 6 and 24 hours.

[000216] Exemplary Embodiment 15B. The method of Exemplary Embodiment 14B, wherein said administering step provides less variability in duration of perceptual effects than other solid oral

formulations of LSD.

[000217] Exemplary Embodiment 16B. The method of Exemplary Embodiment 14B, further including, after said treating step, the step of taking a blood sample of the individual, determining an exposure level of LSD, and releasing the individual from a treatment session based on the exposure level.

[000218] Exemplary Embodiment 17B. The method of Exemplary Embodiment 14B, further including, after said treating step, the step of conducting a clinical evaluation of the individual, determining whether the side effects of the serotonin-2A receptor agonist have concluded, and releasing the individual from a treatment session based on the clinical evaluation.

[000219] Exemplary Embodiment 18B. The method of Exemplary Embodiment 14B, further including, after said treating step, the step of the individual conducting a functional test, determining whether the side effects of the serotonin-2A receptor agonist have concluded, and releasing the individual from a treatment session based on the functional test.

[000220] Exemplary Embodiment 19B. The method of Exemplary Embodiment 14B, further including, after said treating step, the step of the individual completing a questionnaire, determining whether the side effects of the serotonin-2A receptor agonist have concluded, and releasing the individual from a treatment session based on the questionnaire.

[000221] Exemplary Embodiment 20B. The method of Exemplary Embodiment 14B, wherein said administering step provides faster systemic bioavailability of OH-LSD than other solid oral formulations of serotonin-2A receptor agonists.

[000222] Exemplary Embodiment 21B. The method of Exemplary Embodiment 11B, wherein said administering step is further defined as administering a lower dose of the serotonin-2A receptor agonist than with other solid oral formulations of the serotonin-2A receptor agonist to obtain the same concentration in the individual.

[000223] Exemplary Embodiment 22B. The method of Exemplary Embodiment 11B, further including the step of modifying administration of the solid oral immediate release formulation and affecting a second peak concentration of the serotonin-2A receptor agonist in plasma of the individual.

[000224] Exemplary Embodiment 23B. The method of Exemplary Embodiment 11B, further including the step of the individual wearing a smartwatch and using a smartphone and utilizing built-in sensors of the smartwatch and smartphone to passively record heart rate, audio data, accelerometric data, angular velocity, orientation, number of steps, and activity type.

[000225] Exemplary Embodiment 24B. The method of Exemplary Embodiment 23B, further including the step of sending data recorded with the smartwatch and smartphone to a mobile device of a medical professional and the medical professional monitoring the individual throughout a treatment session.

[000226] Exemplary Embodiment 25B. The method of Exemplary Embodiment 11B, wherein the individual has trouble swallowing, is elderly, or has dementia.

[000227] Exemplary Embodiment 26B. The method of Exemplary Embodiment 11B, wherein said treating step is further defined as treating a condition or disease chosen from the group consisting of

anxiety disorders, depression, headache disorder, obsessive compulsive disorder (OCD), personality disorders, stress disorders, drug disorders, gambling disorder, eating disorder, body dysmorphic disorder, pain, neurodegenerative disorders, autism spectrum disorder, eating disorders, and neurological disorders.

[000228] Exemplary Embodiment 27B. The method of Exemplary Embodiment 11B, wherein the serotonin-2A receptor agonist is LSD and is in a form chosen from free base and salt.

[000229] Exemplary Embodiment 28B. The method of Exemplary Embodiment 27B, wherein the LSD is in a salt form and the salt is chosen from the group consisting of hydrochloride, hydrobromide, maleate, tartrate, citrate, phosphate, fumarate, sulfate, mesylate, acetate, and oxalate.

[000230] Exemplary Embodiment 29B. The method of Exemplary Embodiment 27B, wherein said administering step is further defined as administering 0.01-1 mg of LSD.

[000231] Exemplary Embodiment 30B. A method of providing rapid absorption and/or bioavailability of a serotonin-2A receptor agonist, including the steps of:

administering to the individual a serotonin-2A receptor agonist in a fast-disintegrating orally disintegrating tablet (ODT); and

providing systemic bioavailability of the serotonin-2A receptor agonist in the individual within 5 minutes.

[000232] Exemplary Embodiment 31B. The method of Exemplary Embodiment 30B, wherein the serotonin-2A receptor agonist is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, psilocin, mescaline, 3,4-methylenedioxymethamphetamine (MDMA), R-MDMA, S-MDMA, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), salts thereof, tartrates thereof, solvates thereof, isomers thereof, analogs thereof, homologues thereof, and deuterated forms thereof.

[000233] Exemplary Embodiment 32B. The method of Exemplary Embodiment 31B, wherein the serotonin-2A receptor agonist is LSD and is in a form chosen from free base and salt.

[000234] Exemplary Embodiment 33B. The method of Exemplary Embodiment 32B, wherein the LSD is in a salt form and the salt is chosen from the group consisting of hydrochloride, hydrobromide, maleate, tartrate, citrate, phosphate, fumarate, sulfate, mesylate, acetate, and oxalate.

[000235] Exemplary Embodiment 34B. The method of Exemplary Embodiment 31B, wherein said administering step is further defined as administering 0.01-1 mg of LSD.

[000236] Exemplary Embodiment 35B. A method of determining when a treatment session is over for a serotonin-2A receptor agonist, including the steps of:

taking a blood sample of the individual undergoing a treatment session with an orally disintegrating tablet (ODT) formulation of the serotonin-2A receptor agonist;

determining an exposure level of the serotonin-2A receptor agonist in the

individual; and

releasing the individual from the treatment session based on the exposure level.

[000237] Exemplary Embodiment 36B. The method of Exemplary Embodiment 35B, wherein the serotonin-2A receptor agonist is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, psilocin, mescaline, 3,4-methylenedioxymethamphetamine (MDMA), R-MDMA, S-MDMA, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), salts thereof, tartrates thereof, solvates thereof, isomers thereof, analogs thereof, homologues thereof, and deuterated forms thereof.

[000238] Exemplary Embodiment 37B. The method of Exemplary Embodiment 35B, further including after said determining step, an evaluation step chosen from the group consisting of conducting a clinical evaluation of the individual, the individual conducting a functional test, the individual completing a questionnaire, and combinations thereof, determining whether the side effects of the serotonin-2A receptor agonist have concluded, and releasing the individual from a treatment session based on results of the evaluation step.

[000239] Exemplary Embodiment 38B. The method of Exemplary Embodiment 35B, wherein said determining step allows the individual to be released from the treatment session earlier than with other solid oral formulations of the serotonin-2A receptor agonist.

[000240] Exemplary Embodiment 1C. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering lysergic acid diethylamide (LSD), or a salt thereof.

[000241] Exemplary Embodiment 2C. The method of Exemplary Embodiment 1C, wherein the LSD salt is d-LSD D-tartrate.

[000242] Exemplary Embodiment 3C. The method of Exemplary Embodiment 1C or Exemplary Embodiment 2C, wherein the LSD is administered as an orally disintegrating tablet.

[000243] Exemplary Embodiment 4C. The method of Exemplary Embodiment 3C, wherein the orally disintegrating tablet comprises:

- a. LSD, or a salt thereof;
- b. a non-gelling matrix;
- c. a binder;
- d. a filler; and
- e. solvent.

[000244] Exemplary Embodiment 5C. The method of Exemplary Embodiment 4C, wherein the LSD salt is d-LSD D-tartrate.

[000245] Exemplary Embodiment 6C. The method of Exemplary Embodiment 4C, wherein the non-gelling matrix is maltodextrin.

[000246] Exemplary Embodiment 7C. The method of Exemplary Embodiment 4C, wherein the binder is hydroxypropyl methylcellulose.

[000247] Exemplary Embodiment 8C. The method of Exemplary Embodiment 4C, wherein the filler is mannitol.

[000248] Exemplary Embodiment 9C. The method of Exemplary Embodiment 4C, wherein the solvent is water.

[000249] Exemplary Embodiment 10C. The method of any one of Exemplary Embodiments 4C-9C, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[000250] Exemplary Embodiment 11C. The method of any one of Exemplary Embodiments 4C-10C, wherein the orally disintegrating tablet stock solution comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 2% to about 10% maltodextrin;
- c. about 1% to about 5% hydroxypropyl methylcellulose;
- d. about 2% to about 10% mannitol; and
- e. water.

[000251] Exemplary Embodiment 12C. The method of any one of Exemplary Embodiments 4C-10C, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[000252] Exemplary Embodiment 13C. The method of any one of Exemplary Embodiments 4C-10C or 12C, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

[000253] Exemplary Embodiment 14C. The method of any one of Exemplary Embodiments 1C-13C,

wherein the LSD, or the freebase equivalent of a salt thereof, is administered at a dose of about 25 µg to about 200 µg.

[000254] Exemplary Embodiment 15C. The method of any one of Exemplary Embodiments 1C-14C, wherein the LSD, or the freebase equivalent of a salt thereof, is administered at a dose of about 25 µg, about 50 µg, about 100 µg, about 150 µg, or about 200 µg.

[000255] Exemplary Embodiment 16C. The method of any one of Exemplary Embodiments 1C-15C, wherein the LSD, or the freebase equivalent of a salt thereof, is administered at a dose of about 100 µg.

[000256] Exemplary Embodiment 17C. The method of any one of Exemplary Embodiments 3C-16C, wherein the subject's serum LSD freebase concentration is between about 2 ng/mL to about 2.5 ng/mL within about four hours after administration of the orally disintegrating tablet.

[000257] Exemplary Embodiment 18C. The method of any one of Exemplary Embodiments 1C-17C, wherein the generalized anxiety disorder is severe generalized anxiety disorder.

[000258] Exemplary Embodiment 19C. The method of any one of Exemplary Embodiments 1C-18C, wherein the generalized anxiety disorder is moderate generalized anxiety disorder.

[000259] Exemplary Embodiment 20C. The method of any one of Exemplary Embodiments 1C-19C, wherein the symptom of generalized anxiety disorder is feeling nervous, having a sense of impending danger, panic, increased heart rate, rapid breathing, sweating, trembling, gastrointestinal problems, restlessness, fatigue, difficulty concentrating, irritability, muscle tension, a sleep disturbance, or sexual dysfunction.

[000260] Exemplary Embodiment 21C. The method of any one of Exemplary Embodiments 3C-20C, wherein the symptom of generalized anxiety disorder is reduced or eliminated between about 6 hours to about 12 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000261] Exemplary Embodiment 22C. The method of any one of Exemplary Embodiments 3C-21C, wherein the symptom of generalized anxiety disorder is reduced or eliminated for about 12 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000262] Exemplary Embodiment 23C. The method of any one of Exemplary Embodiments 3C-22C, wherein the subject has a Hamilton Anxiety Scale (HAM-A) improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000263] Exemplary Embodiment 24C. The method of any one of Exemplary Embodiments 3C-23C, wherein the subject has an about 20-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000264] Exemplary Embodiment 25C. The method of any one of Exemplary Embodiments 1C-24C, wherein the subject is not administered a second agent for the treatment of generalized anxiety disorder or depression.

[000265] Exemplary Embodiment 26C. The method of any one of Exemplary Embodiments 3C-25C,

wherein the subject has a reduction in Clinical Global Impressions – Severity (CGI-S) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000266] Exemplary Embodiment 27C. The method of any one of Exemplary Embodiments 3C-26C, wherein the subject has an about 1.8-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000267] Exemplary Embodiment 28C. The method of any one of Exemplary Embodiments 1C-27C, wherein the subject has depression.

[000268] Exemplary Embodiment 29C. The method of any one of Exemplary Embodiments 3C-28C, wherein the subject has a reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000269] Exemplary Embodiment 30C. The method of any one of Exemplary Embodiments 3C-29C, wherein the subject has an about 18-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

[000270] Exemplary Embodiment 31C. The method of any one of Exemplary Embodiments 1C-30C, wherein the LSD, or salt thereof, is administered one to four times per year.

[000271] Exemplary Embodiment 32C. The method of any one of Exemplary Embodiments 1C-31C, wherein the LSD, or salt thereof, is administered once every about 12 weeks.

[000272] Exemplary Embodiment 33C. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[000273] Exemplary Embodiment 34C. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

[000274] Exemplary Embodiment 35C. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg lysergic acid

diethylamide (LSD), or the freebase equivalent of a salt thereof.

[000275] Exemplary Embodiment 36C. The method of Exemplary Embodiment 35C, wherein the LSD, or a salt thereof, is administered as an orally disintegrating tablet.

[000276] Exemplary Embodiment 37C. The method of Exemplary Embodiment 35C or Exemplary Embodiment 36C, wherein the LSD, or a salt thereof, is administered one to four times per year.

[000277] Exemplary Embodiment 38C. The method of Exemplary Embodiment 35C or Exemplary Embodiment 36C, wherein the LSD, or a salt thereof, is administered once every about 12 weeks.

[000278] Exemplary Embodiment 39C. The method of any one of Exemplary Embodiments 33C-38C, wherein the orally disintegrating tablet stock solution comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 2% to about 10% maltodextrin;
- c. about 1% to about 5% hydroxypropyl methylcellulose;
- d. about 2% to about 10% mannitol; and
- e. water.

[000279] Exemplary Embodiment 40C. The method of any one of Exemplary Embodiments 33C-38C, wherein the orally disintegrating tablet comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

[000280] Exemplary Embodiment 41C. The method of any one of Exemplary Embodiments 33C-38C or 40C, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. 87% water.

EXAMPLES

[000281] The disclosure is further described in detail by reference to the following experimental examples. These examples are provided for the purpose of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the disclosure should in no way be construed as being limited to the following examples, but rather should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Example 1. A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of D-LSD D-tartrate (also referred to as MM-120) for the Treatment of Anxiety Symptoms.

Target Population

[000282] Adults with clinically significant symptoms of anxiety (as defined by a Hamilton Anxiety Rating Scale [HAM-A] Total Score of 20 or greater) who meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for generalized anxiety disorder (GAD)

Number of Subjects Planned

[000283] Approximately 180.

Study Objectives

Primary Objective

[000284] To determine the dose-response signal and assess the dose-response relationship of four doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 4. MM-120 is depicted in FIG. 6.

Key Secondary Objective

[000285] To determine the dose-response signal and assess the dose-response relationship of four doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 8.

Secondary Objectives

[000286] To determine the dose-response signal and assess the dose-response relationship of four doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to End of Study.

[000287] To determine whether d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) improves functionality and quality of life measures in subjects with anxiety symptoms, including improvements in the following: Depressive symptoms, Anxiety symptoms, Functional disability, Quality of life, Sleep, Sexual function.

Safety Objective

[000288] To assess the safety and tolerability of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) after oral administration in subjects with anxiety symptoms.

Study Design

[000289] This is a Phase 2, multi-center, randomized, double-blind, parallel-group, dose-finding study to assess the effect of four doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) for the treatment of anxiety symptoms in subjects diagnosed with GAD. FIG. 1 depicts the design schema.

[000290] The study enrolled approximately 180 male and female subjects 18 years to < 75 years of age at Screening who met DSM-5 criteria for GAD and had a minimum HAM-A Total Score of 20. Potential subjects who had contraindicated medical or psychiatric conditions or who were taking concomitant

medications, supplements or other therapeutics that are contraindicated (e.g., due to drug-drug interaction potential, or anxiolytic or antidepressant function) that cannot be paused were excluded from the study. Subjects on contraindicated concomitant medications, supplements or other therapeutics at Screening (Visit 1) underwent a medication taper prior to advancing to Baseline (Visit 2); for subjects on prescribed medications to treat anxiety, depression or other mood disorders, the medication taper was overseen by a psychiatrist based on acceptable local practice standards.

[000291] Potential study subjects who provided informed consent had eligibility evaluated/confirmed at 3 visits: 1. Screening (Visit 1); 2. Baseline (Visit 2), and 3. Day 1/Randomization (Visit 3A). To streamline eligibility determinations, sites also had the option of implementing a 'Prescreen' prior to Visit 1.

[000292] Randomization occurred following the final assessment of eligibility on Day 1/Randomization (Visit 3A). Eligible subjects were randomized in a 1:1:1:1 ratio to receive a single dose of either investigational drug d-LSD D-tartrate (25, 50, 100 or 200 µg freebase equivalent) or placebo in a controlled clinical setting, which was administered during the Dosing Session (Visit 3B) on Day 1.

[000293] Prior to Day 1/Randomization & Dosing Session (Visits 3A & 3B), subjects were given preparatory education about the planned intervention.

[000294] Throughout the Dosing Session (Visit 3B) on Day 1, subjects were supported by a team of appropriately trained and qualified Dosing Session Monitors who were in the room with the subject at all times. A site-designated licensed physician is available or on call and were able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency; events requiring intervention should have been discussed with the Sponsor as soon as the situation permits, but implementation of the intervention should not have been delayed. The Subject Education and Safety Management Framework for this study was included in the Dosing Session Monitor Manual, which provided detailed information for education prior to Day 1/Dosing Session (Visit 3B), Dosing Session safety monitoring and management procedures, Dosing Session Monitor qualifications, and requirements that must have been met in order to release the subject from the clinic at the end of the Dosing Session (Visit 3B).

[000295] After Day 1/Randomization & Dosing Session (Visits 3A & 3B), subjects had scheduled visits on Day 2 (Visit 4), Week 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), Week 8 (Visit 8), and Week 12 (Visit 9).

[000296] At Week 4 (the study's primary endpoint), the efficacy of d-LSD D-tartrate in treating anxiety symptoms was evaluated as the change from Baseline in the HAM-A Total Score. HAM-A and several additional questionnaires were administered throughout the study, as outlined in the Schedule of Activities, to further evaluate efficacy and/or the subjects' experiences taking study drug.

[000297] Subjects were assessed for safety and tolerability throughout the study by monitoring the type, frequency, and severity of AEs, vital signs, ECG findings, and clinical laboratory assessments.

Eligibility Criteria*Inclusion Criteria*

1. Age ≥ 18 to < 75 years at Screening (Visit 1).
2. Body weight of ≥ 50 kg.
3. Body mass index [BMI] ≥ 18 to ≤ 38 mg/kg².
4. Diagnosis of DSM-5 generalized anxiety disorder based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
5. HAM-A Total Score ≥ 20 at Screening (Visit 1) and Baseline (Visit 2).
6. Ability and willingness to provide written, informed consent prior to initiation of any study-related procedures and to adhere to all study requirements. NOTE: The subject (i.e., not a legally authorized representative) must be cognitively able to understand the requirements of the study and provide the informed consent.
7. Acceptable overall medical condition to be safely enrolled into and to complete the study, at the discretion of the Investigator.
8. Ability to swallow capsules.

Exclusion Criteria

1. Women of childbearing potential (WOCBP) (persons physiologically capable of becoming pregnant) who are unwilling or unable to use a highly effective method of contraception, for the duration of the study, or Men physiologically capable of fathering a child who are sexually active with WOCBP but are unwilling or unable to use barrier contraception (e.g., condom with or without spermicidal cream or jelly) for the duration of the study.

NOTE: Abstinence is not considered an acceptable form of birth control for WOCBP.

2. Women who are currently pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.
3. Sperm or egg donation during the study.
4. Prior history (lifetime diagnosis) or known first-degree relative (i.e., mother/father/full siblings) with a lifetime diagnosis of schizophrenia spectrum, or other psychotic disorders or bipolar disorder (bipolar I, bipolar II or cyclothymic disorder).
5. Lifetime diagnosis of Posttraumatic Stress Disorder.
6. Other current psychiatric disorders that, in the opinion of the Investigator, may confound the results of the study (e.g., major depressive disorder, obsessive-compulsive disorder, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa or bulimia nervosa).
7. Current untreated clinically significant sleep disorder that, in the opinion of the Investigator, may confound the results of the study (e.g., obstructive sleep apnea, narcolepsy).
8. Significant loss of hearing or vision that, in the opinion of the Investigator, may confound the results of the study or interfere with the ability of Dosing Session Monitor(s) or other site staff to provide adequate oversight to the subject during the Day 1/Dosing Session (Visit 3B).

9. History of alcohol or substance use disorder within 12 months prior to Screening (Visit 1) (includes diagnosis of alcohol or drug use disorder per the MINI)

NOTE: Current use or a history of use of nicotine-containing products is not excluded.

10. Has a significant risk of suicide attempt based upon medical history, in the opinion of the Investigator, or has active suicidal ideation from 3 months prior to Screening (Visit 1) and up to Day 1/Randomization (Visit 3A), as evidenced by a “Yes” response to the Columbia-Suicidality Severity Rating Scale (C-SSRS) Suicidal Ideation section Question 4 or Question 5.

11. Has either attempted suicide or been hospitalized due to suicide risk within 5 years prior to Screening (Visit 1) and up to Day 1/Randomization (Visit 3A), as evidenced by medical history of suicide or a “Yes” response in the following Suicidal Behavior sections of the C-SSRS: Actual Attempt, Interrupted Attempt or Aborted Attempt. Note: For any “Yes” responses in these sections, the site should inquire about the approximate date when the event occurred.

12. Greater than 10 instances of psychedelic use in the past 10 years, including microdosing. Any instance of psychedelic use in the past 2 years including microdosing (including use as part of a clinical trial).

13. History of illicit substance use in the past 10 years as defined as >10 uses of any illicit substance (does not include cannabis). Illicit drug use includes any use of cocaine, crack, heroin/opioids, or methamphetamine. This does not include misuse of over the counter drugs.

14. History of ketamine use including: ketamine therapy within the past 3 months before screening (including as part of a clinical trial); illicit use of ketamine >10 uses in the past 10 years; or use of ketamine for treatment of an excluded condition (see exclusion criteria #4, #5, #6)

15. Positive urine dipstick result for benzodiazepines or drugs of abuse at Baseline (Visit 2) or Day 1/Randomization (Visit 3A). Note: If the subject has a positive urine dipstick result at Screening (Visit 1) for any of these analytes, the subject may begin a taper of the substance(s) and will not be excluded if the results are negative at Baseline (Visit 2) and Day 1/Randomization (Visit 3A). The Sponsor’s Medical Monitor or designee should be consulted if the site staff/Investigator has questions about a urine dipstick result, particularly if the result is due to medication prescribed by a licensed physician or use of cannabis.

16. Current use at Baseline (Visit 2) or Day 1/Randomization (Visit 3A) of any prescribed psychotropic medication.

17. Unwillingness or inability to discontinue prohibited concomitant medications, supplements or other therapeutics (prescription or over-the-counter).

18. Any form of medicinal therapy should be stable 3 months prior to screening with no plan to start, stop or alter the use of any prescribed medications, supplements or other therapeutics from Baseline (Visit 2) until End of Study. Note: Exclusion does not apply to medications that need to be tapered for inclusion in the study and reference is to achieving and maintaining a steady state.

19. Any form of non-medicinal therapy should be stable 3 months prior to screening with no

plan to start, stop or alter the use of psychotherapy, acupuncture, hypnosis, or other similar therapy from the time of providing informed consent until End of Study.

20. Plan to start, stop or alter the use of nicotine-containing products from the time of providing informed consent until End of Study. NOTE: Current use or a history of use of nicotine-containing products is not excluded.

21. Treatment with deep brain stimulation (DBS), vagus nerve stimulation (VNS), electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) within 3 months prior to Screening (Visit 1) or a plan to receive treatment with any of these from the time of providing informed consent until End of Study.

22. Acute infection and/or antibiotic treatment within 30 days prior to Baseline.

23. Any chronic infection, including human immunodeficiency virus (HIV), hepatitis B, or hepatitis C, unless the subject is asymptomatic and is expected to remain asymptomatic during the study and, in the opinion of the Investigator, the infection is unlikely to confound the results of the study.

24. Has had a major trauma or surgery in the 3 months prior to Screening (Visit 1) or any time between Screening and Day 1/Randomization (Visit 3A), has surgery scheduled to occur during the study or has had open biopsy within 3 months prior to Screening (Visit 1).

25. History of malignancy or treatment of malignancy within 2 years prior to Screening (Visit 1) (excluding resected basal cell or squamous cell carcinoma of the skin or carcinoma in situ [CIS] cervix that has been resolved without further treatment).

26. Any of the following cardiovascular conditions or findings:

a. Hemodynamically significant uncorrected cardiac valve disease or hypertrophic/restrictive cardiomyopathy.

b. Any cardiovascular event requiring hospitalization within 12 months prior to Screening (Visit 1) (e.g., stroke, myocardial infarction [MI]).

c. A diagnosis of congenital or long QT syndrome, or personal history of syncope or family history of arrhythmia, a first degree relative with sudden or unexplained death at a young age (under 40 years).

d. History of uncorrected life-threatening arrhythmia or any unstable rhythm, ventricular, supraventricular or atrial arrhythmia with a rapid rate, unless treated with a reliable measure to prevent recurrence (e.g., implantable cardioverter defibrillator or catheter ablation), including second- or third-degree atrioventricular (AV) block or sinus node disease if not successfully treated with a pacemaker or ablation.

e. History of cardiovascular disease, including but not limited to coronary artery disease, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction (within 1 year prior to Screening [Visit 1]), angina pectoris (within 1 year prior to Screening [Visit 1]), coronary artery bypass graft or artificial heart valve (within 1 year prior to Screening [Visit 1]), stroke, transient ischemic attack (TIA) or any other clinically significant arrhythmia.

f. Uncontrolled hypertension.

g. Blood pressure (BP) outside the range of 90-140 mmHg systolic BP or 50-90 mmHg diastolic BP after an approximately 5 minutes of rest. NOTE: If the first measurement of a subject's BP is outside the allowable range, a second recording is allowed after an additional approximately 5 minutes rest.

h. Heart rate < 45 beats/minute or > 90 beats/minute after an approximately 5-minute rest at Screening and Baseline. NOTE: If the first measurement of a subject's heart rate is outside the allowable range, a second recording is allowed after an additional approximately 5 minutes rest.

i. Orthostatic hypotension at Screening (Visit 1) or Baseline (Visit 2), defined as a decrease of more than 20 mmHg in systolic BP or 10 mmHg in diastolic BP, or both, following a change from a supine position to a standing position (measured within 1 to 3 minutes of standing); or orthostatic intolerance (e.g., developing symptoms upon standing). NOTE: If the first measurement of a subject's change in BP exceeds the allowable decrease, a second recording is allowed after an additional approximately 5-minute supine rest.

j. Any clinically significant abnormal electrocardiogram (ECG) finding (e.g., atrial fibrillation) at Screening (Visit 1) or Baseline (Visit 2), as determined by the Investigator or study site designated physician or, if needed, in consultation with a cardiologist.

k. Resting QT interval corrected using Fridericia's formula (QTcF) ≥ 450 msec (male) or ≥ 460 msec (female) at Baseline (Visit 2) or inability to determine QTcF.

l. Presence of risk factors for Torsades de pointes (TdP), including long QT syndrome, uncontrolled hypokalemia or hypomagnesemia, history of cardiac failure, history of clinically significant/symptomatic bradycardia, family history of idiopathic sudden death or congenital long QT syndrome, or concomitant use of a torsadogenic medication that cannot be discontinued prior to Baseline (Visit 2).

27. Have evidence of clinically significant hepatic disorder (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 2.0x upper limit of normal [ULN]).

28. Moderate-to-severe renal impairment, indicated by an estimated glomerular filtration rate (eGFR) of < 50 mL/min/1.73 m² at Screening (Visit 1), based on the Cockcroft-Gault formula.

29. Use of any other investigational drugs, devices, therapies or other advanced therapies that, in the opinion of the Investigator, may confound the study results (e.g., stem cell transplantation, gene therapy) within 30 days prior to Screening (Visit 1). Participation in observational trials must be approved by the Sponsor.

30. Presence or history of neurological (e.g., seizures except febrile resolved before age 5) or psychiatric disorder(s) or any illness (including clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular or musculoskeletal system or clinically significant immunological, endocrine, or metabolic diseases) that, in the opinion of the Investigator, may pose additional risk to the

subject from participation in the study or may confound the results of the study.

31. Any other condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the Investigator, may pose additional risk to the subject from participation in the study, may interfere with the subject's ability to comply with study procedures, may make participation in the study not in the subject's best interest or may confound the results of the study.

32. Prior history or ongoing neuropsychiatric signs or symptoms associated with COVID-19 such as development of, or current disorder, during or after a covid infection including anxiety, memory loss, confusion, depression, delirium, agitation, or psychosis.

33. Use of potent CYP2D6 inhibitors is excluded while the use of moderate CYP2D6 inhibitors is allowed by Investigator discretion. *In vitro* studies suggest that certain cytochrome P450 (CYP) enzymes contribute to the metabolism of LSD. In particular, genetically determined CYP2D6 functionality significantly influenced the pharmacokinetics of oral LSD in healthy volunteers. Subjects with no functional CYP2D6 (i.e., poor metabolizers) had longer LSD half-lives and approximately 75% higher parent drug and O-H-LSD plasma exposure compared with carriers of functional CYP2D6. Because of the potential for differences in D-LSD D-tartrate metabolism, dosing session lengths are expected to vary from a minimum of 8 hours to up to 12 hours or longer in some cases.

Study Treatment

[000298] Subjects were randomized 1:1:1:1:1 to receive a single dose of one of the following blinded treatments:

- 25 µg (freebase-equivalent) of D-LSD D-tartrate (n ≈ 36)
- 50 µg (freebase-equivalent) of D-LSD D-tartrate (n ≈ 36)
- 100 µg (freebase-equivalent) of D-LSD D-tartrate (n ≈ 36)
- 200 µg (freebase-equivalent) of D-LSD D-tartrate (n ≈ 36)
- Placebo (n ≈ 36)

[000299] All treatments were administered orally. All subjects received a total of 8 capsules (combination of capsules containing d-LSD D-tartrate and/or placebo capsules, depending on their randomized dose), which were to be taken together as the subject's single dose of study drug.

Duration of Treatment

[000300] Subjects received a single dose of study drug during the trial. The trial duration was up to approximately 17 weeks, over the following study periods: Screening Period, lasting up to 30 days; Baseline & Dosing Period, lasting up to 5 days; and Follow-Up Period, lasting approximately 12 weeks. There were 9 scheduled in-clinic visits across these 3 study periods. The total duration of the study conduct (first subject first visit to last subject last visit) was expected to be approximately 18 months.

Endpoints/Outcome Measures

Primary Endpoint

[000301] To determine the dose-response signal and assess the dose-response relationship of 4 doses

of MM-120 (i.e., d-LSD D-tartrate) (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week. Measure change in HAM-A Total Score from Baseline to Week 4.

Key Secondary Endpoint

[000302] To determine the dose-response signal and assess the dose-response relationship of 4 doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 8. Measure change in HAM-A Total Score from Baseline to Week 8.

Secondary Endpoints

[000303] To determine the dose-response signal and assess the dose-response relationship of 4 doses of d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to End of Study. Measure change in HAM-A Total Score from Baseline to End of Study.

[000304] To determine whether d-LSD D-tartrate (25, 50, 100, or 200 µg freebase-equivalent) improves functionality and quality of life measures in subjects with anxiety symptoms, including improvements in the following: Depressive symptoms, Anxiety symptoms, Functional disability, Quality of life, Sleep, and Sexual function. Measure change from Baseline to Week 1, Week 2 (where applicable), Week 4, Week 8, and End of Study in score for the following measures:

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Clinical Global Impression – Severity (CGI-S) Scale
- Clinical Global Impression – Improvement (CGI-I) Scale
- Patient Global Impression – Severity (PGI-S) Scale
- Patient Global Impression – Change (PGI-C) Scale
- Sheehan Disability Scale (SDS)
- EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)
- Pittsburgh Sleep Quality Index (PSQI)
- Arizona Sexual Experiences Questionnaire (ASEX)

Safety Endpoints

[000305] Safety is evaluated based on the following measure/assessments:

- Adverse events
- Vital signs (heart rate, blood pressure, respiration rate, temperature)
- 12-lead safety ECG
- Physical examination
- C-SSRS
- Safety laboratory evaluation

Statistical Methods

[000306] This study utilizes the Multiple Comparison Procedure-Modelling (MCP-Mod) approach to analyze the primary outcome measure. The MCP-Mod is a hybrid approach that combines hypothesis testing and modeling in a structured manner to analyze Phase 2 dose-finding studies to find suitable dose(s) for confirmatory Phase 3 trials.

[000307] A total sample of 180 subjects (36 per dose arm and 36 for the placebo arm) was required to ensure a mean power $> 87\%$ for an MCP-Mod analysis rejecting the hypothesis of a constant dose-response curve using the multiple comparisons procedure (MCP), assuming a null placebo response, a maximum standardized effect of 0.6 within the doses range, and a common standard deviation within the dose arms, if a study-wise one-sided type-1 error rate < 0.05 is required. The analysis assumes 4 doses of active medication (25, 50, 100, and 200 μg freebase-equivalent) and placebo.

Assessment of Efficacy

[000308] The primary outcome measure for this study is the Hamilton Anxiety Rating Scale (HAM-A); a validated anxiety rating scale that has been used extensively in clinical trials (including numerous FDA registration trials) to assess anxiety symptoms across a range of psychiatric diagnoses. It has been widely used as the standard primary outcome in randomized controlled trials as an indicator of the effectiveness of pharmacological and psychologic interventions against anxiety in a variety of patient populations. The change in HAM-A score from baseline to post-treatment was used as the primary efficacy endpoint supporting approval of venlafaxine, paroxetine, escitalopram and duloxetine.

[000309] The HAM-A has been used as a standard reliable and valid tool for measuring treatment response in clinical trials with an indication of generalized anxiety disorder (GAD). Specifically, studies have shown that the HAM-A has inter-rater reliability (measured by interclass correlation) ranging from 0.74-0.98, as well as appropriate test-retest reliability (interclass correlation = 0.86) and validity (against the Covi Anxiety Scale, Spearman correlation = 0.63) (Bruss 1994; Maier 1988).

[000310] Based on the myriad of patient populations that are sensitive to the HAM-A, the long history of use in new drug application enabling clinical trials and established validity, the HAM-A scale is fit-for-purpose to assess anxiety symptoms in subjects with GAD.

Study Population Considerations

[000311] Eligibility for this study was based in part on a minimum HAM-A Total Score of 20. This was to target enrollment to a population of subjects who had significant anxiety that were sensitive to measurement by the HAM-A. A HAM-A Total Score of 17 and above has been used as a cut-off for inclusion in clinical trials for GAD medications. Additionally, to ensure that only subjects with relatively stable anxiety severity were enrolled, the HAM-A was completed at Screening (Visit 1) and Baseline (Visit 2) and the Total Score from both assessments must have been at least 20 points; this exclusion criterion helped prevent enrolling subjects with transient anxiety related to daily stressors. These measures together ensured that the study population consisted of subjects with clinically significant anxiety that is sensitive to measurement by the HAM-A.

[000312] The primary endpoint for the current study was change in HAM-A Total Score from Baseline

to Week 4. To assess the durability of effect, the key secondary endpoint of change in HAM-A Total Score from Baseline to Week 8 was used.

[000313] Subjects were required to taper off any prohibited anxiolytics, antidepressants or other medications, supplements or therapeutics used to treat anxiety, depression or other mood disorders prior to randomization into the study.

Summary

[000314] The use of LSD for anxiety in prior studies has yielded safe, tolerable and efficacious results. Given that there are GAD patients who do not reach their treatment goals with currently approved therapies, there remains an unmet need for new therapeutic approaches with favorable safety, tolerability, and efficacy profiles.

Dose Rationale

[000315] The doses of 25, 50, 100 and 200 µg MM-120 (d-LSD D-tartrate freebase equivalent) used in the current study were selected based on preliminary evidence of safety and clinical effect. Dose increases from 100 µg to 200 µg have been associated with an increase in “bad drug effect” while not resulting in increased “overall or good drug effect,” but doses within this range (and above) have been demonstrated to be safe.

[000316] The minimal recognizable (“threshold”) dose of LSD in humans (i.e., the dose at which psychoactive effects are perceivable by patients on average) is reported to be approximately 10-25 µg and doses above 50-75 µg typically produce an altered state of consciousness (including enhanced capacity for introspection, altered psychological functioning and perceptual changes such as illusions, pseudo-hallucinations, synesthesia and alterations of thinking and time experience). Under supportive supervised conditions (i.e., appropriate set and setting) and at doses up to 200 µg LSD freebase-equivalent, adverse drug reactions were typically mild and resolved within a day. Transient anxiety, short-lived headaches, nausea and mild increases in heart rate and blood pressure were the most commonly reported adverse events (AEs).

[000317] The 4 individual dose levels of d-LSD D-tartrate in the current study have been selected to assess the dose-response relationship over a wide dose range that has been previously shown to be safe in clinical trials; and the functional mechanism of action, specifically the extent to which psychedelic effects mediate clinical outcomes. The rationale for each dose level is provided in Table 1.

Table 1

Dose of D-LSD D-tartrate (µg) (Freebase-equivalent)	Rationale
0	Placebo control – an inactive placebo is the most appropriate control for the Multiple Comparison Procedure-Modelling (MCP-Mod) statistical approach to be used in the current study and for characterization of dose-response
25	Threshold dose – minimum dose at which psychoactive effects are

Dose of D-LSD D-tartrate (µg) (Freebase-equivalent)	Rationale
	perceivable by patients on average
50	Dose that is above threshold but unlikely to result in significant “psychedelic effects”
100	Lower of two doses that reliably results in a “psychedelic effect” while minimizing “bad drug effect”
200	Higher of two doses that reliably results in a “psychedelic effect”

Study Drugs

[000318] All study drugs were supplied as a solid dosage form (capsules). Table 2 provides a description of the study drugs. Each subject receives a total of 8 capsules (combination of active and/or placebo) to provide their randomly assigned total dose as follows:

- Subjects randomized to a total dose of 25 µg receive 1 active capsule + 7 placebo capsules.
- Subjects randomized to a total dose of 50 µg receive 2 active capsules + 6 placebo capsules.
- Subjects randomized to a total dose of 100 µg receive 4 active capsules + 4 placebo capsules.
- Subjects randomized to a total dose of 200 µg receive 8 active capsules.
- Subjects randomized to placebo receive 8 placebo capsules.

Table 2

Study Drug	Total Dose ^a (Freebase-equivalent)	Frequency; Route of Administration; Product Description	Use
MM-120 (d-LSD D-tartrate)	25, 50, 100 or 200 µg	Single dose; oral; capsule containing 25 µg MM-120 (D-LSD D-tartrate) freebase-equivalent blended with “generally recognized as safe” (GRAS) excipients	Investigational product
Placebo	Not applicable	Single dose; oral; capsule containing GRAS excipients	Blinding

Directions for Administration of Study Drug

[000319] Study drug (d-LSD D-tartrate at 25, 50, 100 or 200 µg freebase equivalent or placebo) was administered under blinded conditions. To maintain the blind, all subjects received a total of 8 capsules, which were a combination of active capsules each containing 25 µg d-LSD D-tartrate freebase equivalent and/or placebo capsules, depending on the subject’s randomized dose (see Table 2). All 8 capsules were taken together as the subject’s single dose of study drug. Administration of study drug occurred only during Day 1/Dosing Session (Visit 3B).

[000320] Subjects took the 8 study drug capsules orally with ad libitum water. Subjects had 15 minutes to swallow all 8 capsules. Administration of study drug was witnessed by the Investigator and/or Dosing Session Monitor(s), and the subject subsequently was monitored at all times until released from the clinic by the study site designated physician.

Screening and Efficacy Questionnaires

Mini-International Neuropsychiatric Interview (MINI)

[000321] The MINI was administered at Screening (Visit 1) to help determine subject eligibility. The psychiatric interview using the MINI was conducted by a certified site rater. DSMs may administer the MINI if qualified. The MINI was a short structured diagnostic interview for the major psychiatric disorders in DSM-III-R, DSM-IV and DSM-5 and ICD-10. The standard MINI assesses the 17 most common disorders in mental health. It takes approximately 15 minutes to administer.

Columbia-Suicide Severity Rating Scale (C-SSRS)

[000322] The C-SSRS was used to assess the subject's suicidal ideation (severity and intensity) and behavior during screening and throughout the study. The C-SSRS Baseline/Screening Version was administered by the Investigator or designee at Screening (Visit 1) and used recall periods of lifetime and over the past 3 months. The C-SSRS – SLV Version was used at all other visits where the C-SSRS was to be administered. The C-SSRS is a validated outcome assessment tool that evaluates suicidal ideation or behavior defined within 11 categories (5 subtypes of suicidal ideation, 5 subtypes of suicidal behavior, and 1 subtype of self-injurious behavior without suicidal intent) with binary responses (yes/no).

[000323] No Participants reported active suicidal ideation or suicidal behavior following treatment with MM120.

Hamilton Anxiety Rating Scale (HAM-A)

[000324] The HAM-A was used as the primary outcome measure for this study for the evaluation of anxiety symptoms. It was administered to determine eligibility at Screening (Visit 1) and Baseline (Visit 2) and was administered at additional visits. The HAM-A took approximately 20 minutes to administer.

[000325] The HAM-A was completed by a central rater (see further details below). The HAM-A consists of the following 14 items that encompass both psychological and somatic symptoms of anxiety:

1. Anxious mood
2. Tension
3. Fears
4. Insomnia
5. Intellectual
6. Depressed mood
7. Somatic (muscular)
8. Somatic (sensory)

9. Cardiovascular symptoms
10. Respiratory symptoms
11. Gastrointestinal symptoms
12. Genitourinary symptoms
13. Autonomic symptoms
14. Behavior at interview (general)

[000326] The central rater must be appropriately trained/qualified to administer the HAM-A. The central rater assesses the extent to which the subject displays each given criterion and give a rating on a scale of 0-4, where 4 represents the most severe symptoms.

[000327] A central rater located remotely from the site is used to administer and score the HAM-A. As much as possible, the HAM-A should be administered at approximately the same time of the day across each of the individual subject's study visits. Following completion of the HAM-A, the central rater will administer the MADRS. At the site, the evaluations must be conducted with the subject in a private room with the door closed; no study site staff should be in the room during the assessment.

Montgomery-Åsberg Depression Rating Scale (MADRS)

[000328] The MADRS was administered during the study at the visits. The MADRS takes approximately 15-20 minutes to administer.

[000329] An appropriately trained/qualified central rater located remotely from the site is used to administer and score the MADRS, as was described for the HAM-A (including plans for completing a safety report risk assessment, reporting AE, SAE, and/or AESIs suggestive of abuse potential to the site, and immediately contacting the site in case of any emergent risk to the subject's safety). As much as possible, the MADRS was administered at approximately the same time of the day across each of the individual subject's study visits. The MADRS was administered by the central rater after completion of the HAM-A.

[000330] The MADRS is used to assess depression severity and to detect changes due to antidepressant treatment. This questionnaire includes 10 clinician-completed items. Each of the 10 questions is scored with a range of 0-6 points. An item score of 0 indicates item not present or normal, while an item score of 6 indicates severe or continuous presence of the symptoms. The total possible score is 60, and higher scores represent a more severe condition. A decrease in score by $\geq 50\%$ indicates a response to treatment, and an actual score of ≤ 10 indicates a remission of symptoms.

[000331] At Week 1 post-treatment, participants from the 100 µg MM120 and 200 µg MM120 dose groups experienced clinically significant reductions (versus placebo) in total MADRS scores with mean reductions in scores of 17.6 and 17.4 points, respectively, compared with an 11.0-point reduction in placebo-treated participants ($p=0.0174$ and $p=0.0206$).

[000332] At Week 2 and Week 4 post-treatment, participants from the 100 µg MM120 and 200 µg MM120 dose groups experienced clinically and statistically significant reductions (versus placebo) in total MADRS scores with mean reductions of 17.3 and 18.8 points, respectively for Week 2 ($p=0.0190$

and $p=0.0034$) and 18.1- and 18.3-point mean score reductions, respectively at Week 4 ($p=0.0338$ and $p=0.0282$).

[000333] At Week 8, participants from the 200 µg MM120 dose group experienced statistically significant reductions in total MADRS scores ($p=0.0190$) and participants from the 100 µg MM120 dose group had nominal reductions (versus placebo) in total MADRS scores ($p=0.0816$).

[000334] At Week 12 post-treatment, mean MADRS total scores were reduced by 18.7 and 19.9 points for participants from the 100 µg MM120 and 200 µg MM120 dose groups, respectively, and were statistically significant ($p=0.0229$ and $p=0.0073$, respectively).

Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression – Improvement (CGI-I)

[000335] The Clinical Global Impression (CGI) scales were administered during the study at the visits. Sites made every effort to maintain the same rater for the same subject for the CGI-S/I. The CGI-S/I rater may not function as a DSM or the study site designated physician as they may be functionally unblinded on dosing session day.

[000336] **CGI-S:** The CGI-S scale is used to assess the subject's current severity of illness at the time of the assessment relative to the clinician's past experience with patients who have the same diagnosis. The CGI-S comprises 1 Investigator-completed (or trained rater-completed) item with 7 possible ratings (1-7 points), where a higher score indicates more severe illness.

[000337] Baseline values were similar across all treatment groups. At Day 2 post-treatment, participants from the 100 µg MM120 and 200 µg MM120 dose groups experienced statistically significant reductions in CGI-S with mean reductions of 1.8 and 1.4 units compared with 0.7-unit reduction with placebo (LS mean change from Baseline in CGI-S difference to placebo: $p=0.0001$ and $p=0.0117$) for the 100 µg MM120 and 200 µg MM120 dose groups, respectively.

[000338] At all other timepoints post-Baseline, participants from the 100 µg MM120 and 200 µg MM120 dose groups had clinically and statistically significant improvements in CGI-S as evidenced by greater than 2-unit reductions in CGI-S which was sustained through Week 12.

[000339] **CGI-I:** The CGI-I scale is used to measure the clinician's assessment of how much the subject's illness has improved or worsened relative to Baseline (Visit 2). The CGI-I comprises 1 Investigator-completed (or trained rater-completed) item with 7 possible ratings (1-7 points), where a lower score indicates improvement, and a higher score indicates worsening.

[000340] CGI-I values were similar across all timepoints in the placebo group. At Day 2 and Week 1 post-treatment, participants from all MM120 dose groups experienced statistically significant changes in CGI-I compared with placebo. At Week 2, the 50 µg, 100 µg, and 200 µg dose groups had statistically significant changes in CGI-I compared with placebo. The 25 µg also had reduced values compared to placebo but was not statistically significant ($p=0.0567$).

[000341] At all other timepoints post-Baseline, participants from the 100 µg MM120 and 200 µg MM120 dose groups had statistically significant improvements in CGI-I through Week 12.

Patient Global Impression – Severity (PGI-S) and Patient Global Impression – Change (PGI-C)

[000342] The Patient Global Impression (PGI) scales were administered during the study at the visits. The PGI-S/C were patient reported outcome measures.

[000343] The PGI scale is the patient-reported outcome counterpart to the CGI scale. The PGI is adapted to the patient population and can be used to measure disease severity (PGI-S) or change in clinical status (PGI-C).

[000344] The PGI-S and PGI-C each comprise 1 subject-completed item with 5 possible ratings (1-5). In the case of PGI-S, a higher score indicates more severe illness. In the case of PGI-C, a lower score indicates change for the better (improvement in symptoms) and a higher score change for the worse (worsening symptoms).

[000345] Baseline values were similar across all treatment groups. At Day 2 post-treatment, participants from all treatment groups experienced small reductions in PGI-S with mean reductions of 0.4 to 0.7 units compared with 0.4-unit reduction with placebo (not statistically significant). At Week 1 post-treatment, participants from all MM120 dose groups experienced statistically significant changes in PGI-S with score reductions of 1.2 to 1.6 units compared with placebo (reduction of 0.7 units).

[000346] At Week 2 and Week 4, participants from the 100 µg MM120 and 200 µg MM120 dose groups had statistically significant improvements in PGI-S compared with placebo-treated participants. At Week 8, participants from the 200 µg treatment group had statistically significant improvements in PGI-S compared with placebo-treated participants. By Week 12, differences in PGI-S between MM120 and placebo were negligible.

[000347] *PGI-C*. At Day 2 and Week 1 post-treatment, the 50 µg, 100 µg, and 200 µg dose groups had statistically significant changes in PGI-C compared with placebo. The 25 µg also had reduced values compared to placebo but was not statistically significant (Day 2 $p=0.0606$ and Week 1 $p=0.1475$). The 100 µg dose group had statistically significant changes in PGI-C compared with placebo at all other timepoints post-treatment through Week 12. The 200 µg dose group also had reduced values compared to placebo but was not statistically significant ($p=0.1133$) at Week 8 or Week 12 ($p=0.0534$).

Sheehan Disability Scale (SDS)

[000348] The SDS was administered during the study at the visits. The SDS was a patient reported outcome measure.

[000349] The SDS is a composite of 3 self-rated items designed to measure the extent to which 3 major domains in the patient's life (work, social life/leisure activities and family life/home responsibilities) are functionally impaired by psychiatric or medical symptoms. The SDS is used to assess the extent to which these 3 major domains in the subject's life are functionally impaired.

[000350] Baseline values were similar across all treatment groups. All treatment groups showed post-baseline improvements as evidenced by reduced total scores. At Week 1, the 100 µg and 200 µg MM120 dose groups had mean changes of -14.6 and -13.6, respectively, compared with placebo-treated participants with a mean change of -7.4. This trend continued through Week 12.

EQ-5D-5L

[000351] The EQ-5D-5L was administered during the study at the visits. The EQ-5D was a patient reported outcome measure.

[000352] The EQ-5D has been developed by the EuroQol Group and can be used to evaluate health outcomes over a wide range of health conditions and treatments. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS).

[000353] The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. In the EQ-5D-5L version, each dimension has 5 levels of responses: no problems, slight problems, moderate problems, severe problems, and extreme problems.

[000354] The EQ VAS records the subject's self-rated health on a 20-cm vertical VAS, with endpoints labeled as "the best health you can imagine" and "the worst health you can imagine."

[000355] Baseline values for the EQ-5D-5L dimension - Mobility were similar across the treatment groups, with 83% to 95% of participants reporting no problems. One participant from the 25 µg MM120 treatment group reported a score of 4 ('severe problems') at Week 12. This participant reported scores of 2 to 4 across all dimensions at all timepoints (except for "Usual Activities" at Week 2, which they reported as 1), including Baseline. Most participants reported no changes to this dimension throughout the treatment period.

[000356] For the dimension of Self-care, most participants (78% to 90%) reported no problems at Baseline and no participants reported severe problems at any time post-treatment. In the 100 µg and 200 µg MM120 treatment groups, 5 (12.5%) and 6 (15.0%) participants, respectively, reported 'slight problems' at Baseline and the placebo-treatment group reported 3 (7.7%) with 'slight problems' at Baseline. By Week 12, 1 (2.5%) participant in each of the 100 and 200 µg MM120 treatment groups still reported 'slight problems', and the other participants improved to 'no problems.' In the placebo-treated participants, at Week 12, 3 (7.7%) participants still reported 'slight problems' and 1 (2.6%) participant reported 'moderate problems'.

[000357] Across all treatment groups for the dimension of Usual Activities, participants reported the range of severity of problems from 'no problems' in 26% to 36% for all treatment groups, including placebo, to level 5 ('extreme problems') in 2 (5.0%) participants at Baseline in the 200 µg MM120 treatment group. At Weeks 1, 2, 4, 8 and 12, no participants reported 'extreme problems,' and fewer reported 'severe' or 'moderate' problems, except the placebo group Week 1, the same number of participants (3 (7.7%)) reported 'severe problems' at Baseline and Week 1).

[000358] Baseline reporting of 'no problems' for the dimension of Pain/Discomfort ranged from 20% to 39% across the treatment groups with 'slight problems' reported in 26% to 50% of participants and 'moderate problems' reported in 22% to 33% of participants. After Week 4, 44% to 63% reported 'no problems,' 21% to 33% reported 'slight problems,' and 5% to 11% reported 'moderate problems,' indicating a shift to more positive reporting .

[000359] The EQ-5D-5L dimension for Anxiety/Depression at Baseline had several participants with level 5 ('extreme problems') including 3 (7.7%) in the 25 µg treatment group, 7 (19.4%) in the 50 µg

treatment group, 6 (15.0%) in the 100 µg treatment group and 7 (17.5%) in the 200 µg treatment group. The placebo group had no participants reporting 'extreme problems' at Baseline. Participants with level 4, 'severe problems,' included 19 (48.7%) in the 25 µg treatment group, 12 (33.3%) in the 50 µg treatment group, 12 (30.0%) in the 100 µg treatment group, 14 (35.0%) in the 200 µg treatment group and 17 (43.6%) participants in the placebo group. By Week 4, 2 participants (each in the 25 µg treatment group (5.1%) and 100 µg treatment group (5.0%)) still reported 'extreme problems' plus one participant (2.6%) from the placebo-treated group. 'Severe problems' were reported in 2 (5.1%) in the 25 µg treatment group, 5 (13.9%) in the 50 µg treatment group, 2 (5.0%) in the 100 µg treatment group, 1 (2.5%) in the 200 µg treatment group, and 4 (10.3%) participants from the placebo group, indicating a shift to more positive reporting.

Pittsburgh Sleep Quality Index (PSQI)

[000360] The PSQI was administered during the study at the visits. The PSQI was a patient reported outcome measure.

[000361] The PSQI assesses sleep quality and disturbances over the preceding month. This questionnaire includes 19 self-rated questions and 5 questions rated by the bed partner or roommate (if available).

[000362] Responses to the 19 self-rated questions are included in the PSQI scoring, with the items combined to score the following 7 components:

1. Subjective sleep quality
2. Sleep latency
3. Sleep duration
4. Habitual sleep efficiency
5. Sleep disturbance
6. Use of sleeping medication
7. Daytime dysfunction.

[000363] Each of the 7 components has a Component Score with a range of 0-3 points. The 7 Component Scores are added to yield a single Global Score, with a range of 1-21 points. A Global Score of 0 indicates no difficulty, while a Global Score of 21 indicates severe difficulty in all areas.

[000364] Baseline values were similar across all treatment groups. All treatment groups showed post-baseline improvements as evidenced by reduced total scores but there were minimal differences in the scores between MM120 treatment groups and placebo treatment at any timepoint.

Arizona Sexual Experiences Questionnaire (ASEX)

[000365] The ASEX was administered during the study at the visits. The ASEX is a patient reported outcome measure.

[000366] The ASEX is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm over the past week. Possible total scores on the ASEX range of 5-30, with a higher score indicating more sexual dysfunction.

[000367] The Baseline scores for males ranged from 4 to 24 and for females, Baseline scores ranged from 7 to 28. Baseline scores were similar between treatment groups. At Weeks 1, 2, 4 and 12 post-treatment, ASEX total scores were more greatly reduced in females from the 100 µg treatment group than in males. In the 200 µg treatment groups, males had greater point reductions in Weeks 4, and 8. Smaller total score reductions were seen in the 25 and 50 µg dose groups in males and females with a range 0.4 to 2.7-point reductions. Female participants from the placebo treatment group had a greater reduction in ASEX scores at Weeks 4 to 12 compared to females from the 100 µg and 200 µg treatment groups and males receiving placebo had little to no reduction of scores to Week 12.

[000368] Overall, there was a decrease in the number of female participants with sexual dysfunction in the 100 µg and 200 µg groups at Week 1 to Week 12. There was also a considerable decrease in the number of male participants with sexual dysfunction in the 100 µg and 200 µg groups at Week 1 to Week 12.

Other Patient-Reported Outcomes

[000369] Other patient-reported outcomes (PROs) were administered. Information about these instruments is briefly summarized below.

[000370] The following instruments were administered during the study to explore dose response on drug effects, altered perception and mystical experience: Drug Effect VAS, MEQ30, and/or 5D-ASC.

[000371] Additionally, the following instrument is administered during the study to explore whether functional unblinding of study drug may have occurred: Treatment assignment/blinding question.

[000372] **Drug Effect VAS:** The Drug Effect VAS was administered the day after dosing, at Day 2 (Visit 4), to retrospectively assess the subject's perception of drug effects experienced during Day 1/Dosing Session (Visit 3B). The Drug Effect VAS is a patient-reported outcome measure. A series of single-item VASs is used to measure the extent to which the subject experienced each of the following: "any drug effect," "good drug effect," "bad drug effect," "drug liking," "fear," "nausea," "alteration of vision," "alteration of sense of time," and "the boundaries between myself and my surroundings seem to blur."

[000373] Baseline VAS scores were similar across all treatment groups. At Week 1 post-treatment, scores increased in all treatment groups, including placebo, but mean values for MM120-treated (100 µg and 200 µg MM120) participants increased by more than 2-fold the score change seen in placebo-treated participants. VAS scores were greater in MM120 treatment groups over placebo-treated participants at all time points through Week 12 in all MM120 treatment groups.

[000374] **Mystical Experience Questionnaire (MEQ30):** The MEQ30 was administered the day after dosing, at Day 2 (Visit 4), to retrospectively assess the subject's mystical experience during Day 1/Dosing Session (Visit 3B). The MEQ30 is patient-reported outcome measure.

[000375] The MEQ30 is a psychometrically validated instrument that includes 30 self-rated questions. The 30 items are combined into the following 4 subscales:

1. Mystical (unity, noetic quality, sacredness)

2. Positive mood
3. Transcendence of time and space
4. Ineffability

[000376] Each of the 4 subscales contributes to the MEQ30 total score, which has a range of 0-150 points. The MEQ30 total score is computed by taking the average response to all items and reported as a percentage. Subject is considered to have had a “complete mystical experience” when $\geq 60\%$ of the maximum possible score is achieved on all 4 factor subscales.

[000377] **5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC):** The 5D-ASC was administered the day after dosing, at Day 2 (Visit 4), to retrospectively assess the subject’s peak alteration of consciousness during Day 1/Dosing Session (Visit 3B) as compared with their normal waking consciousness. 5D-ASC is a patient-reported outcome measure.

[000378] The 5D-ASC includes 94 self-rated items (visual analog scales). It is well-validated and has been used to characterize the acute subjective effects of LSD in experimental studies. The 94 items are combined into the following 5 subscales/dimensions with 11 lower-order scales defined for the first 3 subscales/dimension:

- Oceanic boundlessness (derealization and depersonalization associated with positive emotional states, ranging from heightened mood to euphoric exaltation); subscales within this dimension include:
 - Experience of unity
 - Spiritual experience
 - Blissful state
 - Insightfulness
- Anxious ego dissolution (ego disintegration and loss of self-control phenomena associated with anxiety); subscales within this dimension include:
 - Disembodiment
 - Impaired control of cognition
 - Anxiety
- Visionary restructuralization; subscales within this dimension include:
 - Complex imagery
 - Elementary imagery
 - Audio-visual synesthesia
 - Changed meaning of percepts
 - Auditory alterations
 - Vigilance reduction.

[000379] Overall, for all parameters, the total 5D-ASC scores increased with increasing dose in participants receiving MM120. Scores from placebo-treated participants were a fraction of those of the

25 µg treatment group.

[000380] Treatment Assignment/Blinding Question: On Day 2 (Visit 4), a 5-point Likert scale was used to evaluate each subject's assessment of whether they received active study drug or placebo during Day 1/Dosing Session (Visit 3B). The treatment assignment question is a patient-reported outcome measure. Subjects are asked to indicate which of the following statements they agree with the most:

I am positive I received active drug

I think I received active drug

I cannot tell whether I received active drug or placebo

I think I received placebo

I am positive I received placebo.

Subject Release on Dosing Day/ Dosing Release Checklist

[000381] Study subjects were kept under continuous observation for a minimum of 12 hours following investigational drug administration.

[000382] Beginning approximately 8 hours after drug administration, the Dosing Release Checklist was performed by the site-designated licensed physician (MD/DO) to evaluate the subject's psychological and physiological status. This included an evaluation to ascertain that the subject no longer meets DSM-5 criteria for Hallucinogen Intoxication. Subjects were assessed for release criteria starting at 8 hours (± 10 minutes) post-administration and subsequently assessed at approximately 9, 10, 11 and 12 hours (± 10 minutes) post-dose. The Dosing Session Release Checklist was administered hourly (± 10 minutes) until all release criteria were met. At a minimum, the Dosing Release Checklist was completed at 8- and 12-hours post-dose. If the subject did not meet criteria for release at 12 hours post-dose, the Dosing Session Release Checklist would be repeated approximately every hour (± 10 minutes) until all criteria were met and the subject is deemed eligible for release. Subjects were kept under continuous observation until their release was deemed safe by the site-designated licensed physician.

[000383] In order to be eligible for release, subjects MUST: Self-report readiness for release (i.e., physical and mental readiness, and understanding of restrictions), be deemed eligible for safe release in the medical judgment of the study site-designated licensed physician, and have no active suicidal ideation or behavior as determined by the C-SSRS. And must NOT: Meet DSM-5 criteria for Hallucinogen Intoxication, display clinically significant psychomotor depression, activation or other signs or symptoms, or display clinically significant abnormal mental status.

Results

[000384] The study enrolled 198 subjects with a 79% 12-week completion rate in high dose groups (i.e., 100 ug and 200 ug dose groups). Participant demographics are provided in Table 3-1 and baseline characteristics are provided in Table 3-2.

Table 3-1

	25 µg MM120 (N=39)	50 µg MM120 (N=36)	100 µg MM120 (N=40)	200 µg MM120 (N=40)	Placebo (N=39)	Overall (N=194)
Age (Years)						
n	39	36	40	40	39	194
Mean (SD)	38.0 (12.08)	45.3 (14.23)	42.7 (14.79)	42.1 (13.53)	38.7 (12.66)	41.3 (13.61)
Sex, n (%)						
Female	20 (51.3)	20 (55.6)	16 (40.0)	28 (70.0)	26 (66.7)	110 (56.7)
Male	19 (48.7)	16 (44.4)	24 (60.0)	12 (30.0)	13 (33.3)	84 (43.3)
Race, n (%)						
Asian	1 (2.6)	3 (8.3)	0 (0)	1 (2.5)	2 (5.1)	7 (3.6)
Black or African American	3 (7.7)	2 (5.6)	1 (2.5)	3 (7.5)	6 (15.4)	15 (7.7)
White	33 (84.6)	29 (80.6)	36 (90.0)	33 (82.5)	30 (76.9)	161 (83.0)
Multiple	1 (2.6)	0 (0)	1 (2.5)	1 (2.5)	0 (0)	3 (1.5)
Other	1 (2.6)	2 (5.6)	2 (5.0)	1 (2.5)	1 (2.6)	7 (3.6)
Not Reported	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	1 (0.5)
Ethnicity, n (%)						
Hispanic or Latino	5 (12.8)	6 (16.7)	6 (15.0)	6 (15.0)	8 (20.5)	31 (16.0)
Not Hispanic or Latino	34 (87.2)	29 (80.6)	34 (85.0)	34 (85.0)	31 (79.5)	162 (83.5)
Not Reported	0 (0)	1 (2.8)	0 (0)	0 (0)	0 (0)	1 (0.5)
BMI (kg/m ²) [1]						
Mean (SD)	25.9 (4.58)	28.1 (4.94)	26.1 (4.99)	25.9 (4.75)	25.6 (4.16)	26.3 (4.72)

BMI = body mass index; SD = standard deviation

The Full Analysis Set is defined as all randomized participants with a valid baseline HAM-A assessment and at least one post-baseline HAM-A assessment.

Percentages are based on the number of participants in the Full Analysis Set in each dose-level (N).

[1] BMI measurements taken at initial screening visit.

Table 3-2

	Statistics	25 µg MM120 (N=39)	50 µg MM120 (N=36)	100 µg MM120 (N=40)	200 µg MM120 (N=40)	Placebo (N=39)
Time (years) from GAD Diagnosis [1]	n	39	36	40	40	39
	Mean (SD)	10.25 (9.282)	13.24 (9.995)	12.65 (10.874)	13.33 (10.782)	12.41 (9.397)
	Median	7.00	12.85	11.15	11.00	11.00
	Min, Max	0.0, 38.0	0.0, 36.0	0.0, 42.5	0.0, 41.0	0.1, 35.0
Baseline HAM-A Total Score	n	39	36	40	40	39
	Mean (SD)	30.2 (6.05)	30.3 (5.71)	29.3 (6.42)	31.0 (6.98)	30.3 (6.56)
	Median	30.0	29.5	29.0	30.0	30.0
	Min, Max	20, 42	21, 42	20, 43	20, 50	20, 45
Baseline MADRS Total Score	n	39	36	40	40	39
	Mean (SD)	25.4 (7.58)	27.7 (8.30)	26.5 (7.99)	28.9 (8.31)	27.6 (9.69)
	Median	26.0	27.5	27.0	28.5	28.0
	Min, Max	12, 38	13, 48	11, 45	12, 49	12, 48
Baseline PSQL Global Score	n	39	36	40	40	38
	Mean (SD)	10.7 (3.40)	11.1 (3.43)	11.0 (3.47)	10.1 (3.33)	10.9 (4.15)
	Median	11.0	11.0	11.0	10.5	11.0
	Min, Max	5, 17	3, 18	4, 18	4, 16	4, 19
Baseline CGI- S	n	39	36	40	40	39
	Mean (SD)	4.9 (0.75)	4.9 (0.62)	4.8 (0.75)	5.1 (0.73)	4.9 (0.61)
	Median	5.0	5.0	5.0	5.0	5.0
	Min, Max	3, 6	4, 6	3, 6	4, 6	4, 6
Baseline PGI- S	n	39	36	40	40	39
	Mean (SD)	3.8 (0.63)	3.8 (0.62)	3.7 (0.66)	3.7 (0.72)	3.7 (0.58)
	Median	4.0	4.0	4.0	4.0	4.0
	Min, Max	3, 5	3, 5	3, 5	2, 5	3, 5

	Statistics	25 µg MM120 (N=39)	50 µg MM120 (N=36)	100 µg MM120 (N=40)	200 µg MM120 (N=40)	Placebo (N=39)
Baseline SDS	n	39	36	40	40	39
Total Score	Mean (SD)	18.7 (5.10)	17.6 (5.60)	19.2 (5.25)	19.9 (5.44)	18.9 (4.08)
	Median	19.0	19.0	20.5	20.0	19.0
	Min, Max	6, 29	5, 28	6, 27	8, 30	10, 26
Baseline ASEX Total	n	20	20	15	28	26
Score - Female	Mean (SD)	15.1 (3.41)	16.6 (4.51)	14.9 (4.67)	16.6 (3.71)	15.7 (4.78)
	Median	14.5	16.0	15.0	15.0	15.0
	Min, Max	11, 22	10, 28	8, 23	12, 26	7, 25
Baseline ASEX Total	n	19	16	24	12	13
Score - Male	Mean (SD)	14.2 (3.52)	13.8 (4.18)	12.8 (3.87)	13.6 (5.85)	11.8 (3.48)
	Median	15.0	13.5	12.0	13.0	12.0
	Min, Max	7, 18	7, 22	6, 21	4, 24	6, 20
Baseline ASEX	Female, n (%)	20	20	16	28	26
Dysfunction	With Sexual Dysfunction	16 (80.0)	15 (75.0)	12 (75.0)	16 (57.1)	13 (50.0)
	Without Sexual Dysfunction	4 (20.0)	5 (25.0)	4 (25.0)	12 (42.9)	13 (50.0)
	Male, n (%)	19	16	24	12	13
	With Sexual Dysfunction	8 (42.1)	7 (43.8)	7 (29.2)	5 (41.7)	2 (15.4)
	Without Sexual Dysfunction	11 (57.9)	9 (56.3)	17 (70.8)	7 (58.3)	11 (84.6)

[000385] Primary and secondary endpoints were met with a 48% clinical remission rate of GAD subjects at Week 12. Subjects exhibited a 7.7-point improvement over placebo ($d=0.81$, $p=0.003$). The maximum observed effect size of 0.81 was more than double the standard of care (e.g., benzodiazepines, SSRIs, and buspirone).

[000386] After a single dose of 100 µg of MM120, subjects exhibited:

- 1.8 point reduction in CGI-S within 24 hours ($p<0.0001$) (FIG. 4);
- 21.9-point improvement in HAM-A at Week 12 ($p=0.0025$) (FIG. 2 and FIG. 3);
- 18.7-point improvement in MADRS at Week 12 (FIG. 5);
- Favorable tolerability with most adverse events limited to dosing day; and
- No additional therapy was needed.

[000387] MM120 was well-tolerated in subjects with GAD with mild-to-moderate adverse events (99%). Minimal (2.5%) treatment emergent adverse events led to study withdrawal and there were no drug-related serious adverse events that were deemed related to MM120 administration. There was no observed suicidal or self-injurious behavior and less than or equal to two participants per arm reported suicidal ideation during the study with no indication of increased suicidality or suicide-related risk. See Table 4 for adverse event overview.

Table 4

Preferred Term Participants (%) with Adverse Events	Day of Dosing				
	MM120				Placebo (N=39)
	25 µg (N=39)	50 µg (N=40)	100 µg (N=40)	200 µg (N=40)	
Illusion	12 (30.8)	18 (45.0)	24 (60.0)	30 (75.0)	3 (7.7)
Nausea	3 (7.7)	11 (27.5)	16 (40.0)	23 (57.5)	1 (2.6)
Headache	4 (10.3)	7 (17.5)	9 (22.5)	9 (22.5)	6 (15.4)
Hallucination, visual	6 (15.4)	9 (22.5)	9 (22.5)	6 (15.0)	1 (2.6)
Euphoric mood	2 (5.1)	5 (12.5)	11 (27.5)	6 (15.0)	1 (2.6)
Anxiety	0	3 (7.5)	3 (7.5)	5 (12.5)	0
Mydriasis	1 (2.6)	7 (17.5)	8 (20.0)	4 (10.0)	1 (2.6)
Hyperhidrosis	1 (2.6)	4 (10.0)	9 (22.5)	5 (12.5)	0
Paraesthesia	2 (5.1)	2 (5.0)	2 (5.0)	8 (20.0)	2 (5.1)
Fatigue	1 (2.6)	5 (12.5)	3 (7.5)	3 (7.5)	0
Blood pressure increase	2 (5.1)	3 (7.5)	4 (10.0)	4 (10.0)	0
Dizziness	3 (7.7)	2 (5.0)	3 (7.5)	4 (10.0)	1 (2.6)
Tremor	0	3 (7.5)	2 (5.0)	8 (20.0)	0
Thinking abnormal	1 (2.6)	2 (5.0)	4 (10.0)	5 (12.5)	0
Altered state of consciousness	1 (2.6)	0	5 (12.5)	1 (2.5)	0
Vomiting	0	2 (5.0)	2 (5.0)	5 (12.5)	0
Pseudo-hallucination	0	3 (7.5)	3 (7.5)	4 (10.0)	0
Balance disorder	0 (0)	4 (10.0)	3 (7.5)	2 (5.0)	1 (2.6)
Feeling abnormal	1 (2.6)	2 (5.0)	0	0	1 (2.6)
COVID-19	0	0	0	0	0
Disturbance in attention	1 (2.6)	5 (12.5)	0	0 (0)	0 (0)
Emotional distress	2 (5.1)	0 (0)	1 (2.5)	3 (7.5)	1 (2.6)
Decreased appetite	1 (2.6)	1 (2.5)	0	2 (5.0)	0 (0)

Preferred Term Participants (%) with Adverse Events	After Dosing				
	MM120				Placebo (N=39)
	25 µg (N=39)	50 µg (N=40)	100 µg (N=40)	200 µg (N=40)	
Illusion	1 (2.6)	1 (2.5)	1 (2.5)	0	0
Nausea	0	0	1 (2.5)	2 (5.0)	1 (2.6)
Headache	1 (2.6)	2 (5.0)	3 (7.5)	0	0
Hallucination, visual	1 (2.6)	0	0	0	0
Euphoric mood	0	0	0	0	0
Anxiety	1 (2.6)	1 (2.5)	0	0	1 (2.6)
Mydriasis	0	0	0	0	0
Hyperhidrosis	0	0	0	0	0
Paraesthesia	0	0	0	0	0
Fatigue	0 (0)	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.6)
Blood pressure increase	0	0	0	0	0
Dizziness	0	0	0	0	0
Tremor	0	0	1 (2.5)	0	0
Thinking abnormal	0	0	1 (2.5)	0	0
Altered state of consciousness	0	0	0	0	0
Vomiting	0	0	0	0	0
Pseudo-hallucination	0	0	0	0	0
Balance disorder	0	0	0	0	0
Feeling abnormal	0	0	0	4 (10.0)	1 (2.6)
COVID-19	1 (2.6)	0	1 (2.5)	0	0
Disturbance in attention	0	1 (2.5)	1 (2.5)	0	0
Emotional distress	0	0	0	1 (2.5)	0
Decreased appetite	0	0	1 (2.5)	2 (5.0)	0

Example 1A. Two Solid Oral Formulations of D-LSD D-tartrate, a Fast-Dispersing Orally Disintegrating Tablet and an Immediate Release Powder in Capsule

[000388] A solid oral formulation of d-LSD D-tartrate in a fast dispersing orally disintegrating tablet (ODT) was produced which comprises d-LSD D-tartrate (100 µg freebase equivalent), a non-gelling matrix forming excipient, a filler excipient, and a binding agent fully dissolved in water. The ODT formulation composition stock solution is provided in Tables 1A-1, 1A-2, and 1A-3 and the finished tablet is shown in FIG. 7. The ODT formulation disintegrates in less than 60 seconds demonstrating the rapid dispersion. International Application No. PCT/US2022/040636 further discloses the preparation of the ODT and is incorporated herein by reference in its entirety.

Table 1A-1 - d-LSD D-tartrate stock solution formulation for orally disintegrating tablets

Function	Component	Approximate Wt%
Drug	d-LSD D tartrate	< 1%
Non-gelling matrix	Maltodextrin	2-10%
Binder	Hydroxypropyl Methylcellulose	1-5%
Filler	Mannitol	2-10%
Solvent	Water	qs to 100%

Table 1A-2 - d-LSD D-tartrate formulation range for orally disintegrating tablets

Function	Component	Approximate Wt%
Drug	d-LSD D tartrate	< 1%
Non-gelling matrix	Maltodextrin	15-77%
Binder	Hydroxypropyl Methylcellulose	8-38%
Filler	Mannitol	15-77%
Solvent	Water	N/A **

**Removed during processing to < 10% residual (e.g., < 5% residual)

Table 1A-3 - d-LSD D-tartrate stock solution composition for orally disintegrating tablets

Function	Component	Approximate Wt%
Drug	d-LSD D tartrate	< 1%
Non-gelling matrix	Maltodextrin	6%
Binder	Hydroxypropyl Methylcellulose	2%
Filler	Mannitol	5%
Solvent	Water	87%

[000389] A second d-LSD D-tartrate formulation (25 µg freebase equivalent) was developed as powder in a capsule, using moisture activated dry granulation to produce the formulated powder. The capsule formulation is provided in Tables 1A-4. The capsule formulation is the granulation powder formulation which is filled into a hydroxypropyl methylcellulose capsule. The formulation powder, which contains pregelatinized starch, mannitol, croscarmellose sodium, mesoporous silica, hypromellose (hydroxypropyl methylcellulose), and water, was made by moisture activated dry granulation and once filled in hypromellose capsule shells demonstrated immediate release (i.e., dissolution occurs in less than 30 minutes). The drug loading in the formulation powder was less than 1% by weight. International Application No. PCT/US2022/040653 further discloses a preparation of the capsule and is incorporated herein by reference in its entirety.

Table 1A-4 - d-LSD D-tartrate granulation powder formulation for capsule preparation

Function	Component	Approximate Wt%
Drug	d-LSD D tartrate	< 1%
Filler	Mannitol	68%
Absorbent	Pregelatinized starch	24%
Disintegrant	Croscarmellose sodium	3%
Binder	Hypromellose	2%
Glidant	Silicon dioxide (e.g., mesoporous silica)	1%
Solvent	Purified water	2%

Example 2A. Phase 1, Open-label Study to Compare the Pharmacokinetics of Two Formulations of d-LSD D-tartrate in Healthy Volunteers

Study objectives

Primary:

[000390] To characterize and compare the single-dose pharmacokinetics (PK) of d-LSD D-tartrate orally disintegrating tablets (ODT) and d-LSD D-tartrate capsules as measured by maximum concentration (C_{max}), areas under the plasma concentration-time curves (AUC_{0-t}, AUC_∞), and half-life of d-LSD D-tartrate.

Secondary:

[000391] To characterize the PK of two formulations of d-LSD D-tartrate and major d-LSD D-tartrate metabolites in plasma, as measured by C_{max}, AUC_{0-t}, and AUC_∞.

[000392] To compare subjective effects as measured by a visual analog scale (VAS) subjective effects questionnaire assessed at one or more timepoints during the duration of acute perceptual effects.

[000393] To compare subjective drug effects as measured by the 5-Dimensional Altered States of Consciousness (5D-ASC) scale administered within 24 hours after dosing.

Safety:

[000394] To compare the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI) suggestive of abuse potential, and AEs resulting in study discontinuation.

[000395] To compare the absolute values and changes from baseline in clinical laboratory tests (hematology and serum chemistry), vital signs (respiratory rate, body temperature, supine blood pressure, and supine pulse rate).

[000396] To compare the frequency of subjects with suicidal ideation or suicidal behavior using the Columbia Suicide Severity Rating Scale (C-SSRS).

Study Design

[000397] A Phase 1, multi-center (up to two sites), open-label, randomized, two-period, two-sequence cross-over, within-subject study was performed to compare the plasma PK profile of d-LSD D-tartrate

following dosing with d-LSD D-tartrate capsule formulation to the plasma PK profile observed following dosing with d-LSD D-tartrate ODT formulation following a single dose. An overview of the study design is shown in FIG. 8. Blood sampling for PK analysis occurred at pre-dose (15 minutes prior to dose $\pm$ 5 minutes), and 5 minutes, 10 minutes, and 15 minutes post-dose (with a sampling window of $\pm$ 1 minute), and at 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, and 24 hours post-dose (with a sampling window of $\pm$ 5 minutes). Blood samples were collected using an indwelling peripheral venous cannula which subjects have implanted the morning of each dosing day (i.e., Visit 2a for Evaluation Period 1 and Visit 4a for Evaluation Period 2). Prior to dosing, all subjects ate a light snack of approximately 500 calories, standardized and provided by the sites, and did not consume any food after dosing until at least 6 hours post dose.

[000398] The study enrolled at least 24 (and up to 30) healthy male and female subjects, 18 years to $\leq$ 55 years of age.

[000399] Subjects reported to the clinical research unit (CRU) for a screening visit (Visit 1) following an overnight fast (at least 10 hours) and all screening procedures and evaluations were completed within 21 days before Visit 2a (Baseline). During the screening visit, subjects who meet the eligibility criteria were provided with preparatory education including receipt of the Patient Education Session Manual (PESM), which included details about the study drug (d-LSD D-tartrate) and explained the planned activities and procedures to be conducted in the study. The PESM was also reviewed with the subject and the Dosing Session Monitor (DSM) during Visit 2a and Visit 4a. The Dosing Session Monitor Manual (DSMM) must be reviewed and understood by all Dosing Session Monitors prior to their participation in monitoring any subjects during their dosing in this study. The DSMM provided detailed information regarding credentials, training requirements, and instructions on the proper management of each dosing session day. Both PESM and DSMM provide information regarding details and criteria for release from in-patient hospitalization at the CRU at Visit 3 and Visit 5.

[000400] Eligible subjects returned to the CRU for Visit 2a following an overnight fast (at least 10 hours). They were admitted as inpatients and underwent pre-dose safety assessments and urine drug screen (UDS) and pregnancy testing. The results of the UDS and pregnancy test (where applicable) must be negative for the subject to have proceed to study drug dosing. At Visit 2a, site personnel assisted the subjects in putting on an Apple Watch and setting up an iPhone equipped with the MSMS™ application for monitoring during the dosing session. Subjects wore this device during the entirety of the dosing session.

[000401] A venous cannula was implanted, and a pre-dose blood sample was collected. All subjects ate a light snack of approximately 500 calories, standardized and provided by the sites prior to dosing, and did not consume any food until at least 6 hours post dose. This standardized meal was designed to mimic the conditions in a prior clinical trial in order to make accurate assumptions regarding the PK profile observed in this trial, relative to the efficacy and safety observed. Subjects were dosed with study drug within 30 minutes of eating the snack.

[000402] Subjects randomized to receive capsules took study drug capsules of d-LSD D-tartrate orally with 250 mL of water.

[000403] Subjects randomized to receive ODT took the ODT formulation of d-LSD D-tartrate by placing the study drug on top of the tongue allowing the tablet to disintegrate. Subjects were NOT permitted to drink water with the ODT dosing; however, at least 15 minutes after ODT dosing subjects should drink up to 250 mL of water.

[000404] A total of at least 12 (up to 15) subjects received 100 µg d-LSD D-tartrate freebase-equivalent capsule (administered as 4 × 25 µg capsules) and 12 to 15 subjects received 100 µg d-LSD D-tartrate ODT (each ODT contains 146.4 µg LSD-D-tartrate which is equivalent to 100 µg of LSD freebase). All capsules or ODT must be consumed within 1 to 2 minutes of distribution to the subject. Following dosing, subjects remained as inpatients in the CRU for 24 hours post-dose.

[000405] At all times during the dosing session, subjects were monitored by two site personnel as follows: Via a direct video monitoring link, a site medical staff member monitored the dosing session at all times through post-dose hour 16 if deemed necessary, to ensure patient safety. Subjects were also physically monitored by a trained DSM, who remained in the dosing room with the subject for the first 6 hours post-dose. Between 6- and 8-hours post-dose, they were monitored at least every half-hour by the DSM. From 8-hours post-dose through 16-hours post-dose they were monitored by the DSM at least every hour or until release criteria are achieved.

[000406] In order to establish the relationship between PK and subjective effects of d-LSD D-tartrate, subjects completed a short Drug Effects VAS subjective effects assessment at 5 minutes and 15 minutes post-dose with a sampling window of ±1 minute, and 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post-dose with a sampling window of ±5 minutes. A more comprehensive evaluation of subjective effects following dosing with d-LSD D-tartrate, the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) scale, was administered 24 hours after dosing at Visit 3 and Visit 5. Site personnel stop passive data collection and removed the MSMS Apple Watch and iPhone from the subject approximately 12-hours after dosing. The venous cannula was removed, and subjects were discharged at Visit 3 upon conclusion of the 24-hour post-dose evaluation period (in Evaluation Period 1), once they meet the requirements for discharge.

[000407] Following Evaluation Period 1, during the Washout Period and between Visit 3 and Visit 4a, subjects received a phone call or teleconference from the site, to assess safety, by collecting AEs, concomitant medications, and C-SSRS, and to schedule Visit 4a within the allotted time window. All subjects dosed in Evaluation Period 1 returned to the CRU to undergo crossover treatment 12 ± 2 days after their first dose in Evaluation Period 2.

[000408] Following an overnight fast (at least 10 hours), at Visit 4a (Evaluation Period 2), subjects repeated pre-dose procedures and evaluations, a new venous cannula was implanted in the same fashion as in Evaluation Period 1, and safety labs, including serum HCG if visit date is >28 days from screening, UDS, and urine pregnancy screen was performed. Site personnel again assisted the subjects in putting

on an Apple Watch and setting up an iPhone equipped with the MSMS application. Subjects again reviewed preparatory education about the planned study drug (MM-120) with the DSM. For dosing in Evaluation Period 2, subjects ate a light snack of approximately 500 calories, standardized and provided by the sites prior to dosing, and then received the appropriate study drug within 30 minutes of eating and did not consume any food until at least 6 hours post dose. Subjects who received d-LSD D-tartrate capsules in Evaluation Period 1 (Visit 2b) received d-LSD D-tartrate ODT 100 µg, in Evaluation Period 2 provided as a single ODT containing 146.4 µg LSD-D-tartrate which is equivalent to 100 µg of LSD freebase and subjects who received d-LSD D-tartrate ODT in Evaluation Period 1 (Visit 2b) receive d-LSD D-tartrate 100 µg capsule in Evaluation Period 2, administered as 4×25 µg capsules. All capsules or ODT must have been consumed within 1 to 2 minutes of distribution to the subject. Following dosing, subjects remained in the study unit for 24 hours post-dose.

[000409] Site personnel stopped passive data collection and removed the Apple Watch and iPhone from the subject after approximately 12 hours post dosing. The venous cannula was removed, and subjects were discharged at Visit 5 upon conclusion of the 24-hour post-dose evaluation period (in Evaluation Period 2), once they meet the requirements for discharge.

[000410] A licensed health care professional (with prescribing rights) was available at all times for emergency medical or psychiatric intervention per local standard of care.

[000411] Following discharge, subjects return to the CRU for Visit 6, 14 days after their second dose of a d-LSD D-tartrate for evaluation of safety and End-of-Study (EOS) assessments.

Discharge Criteria

[000412] Release from Dosing Session: Beginning approximately 6 hours after drug administration, assessments were performed to evaluate the participant's psychological and physiological status. This includes completion of the Dosing Session Release Checklist to ascertain that the participant no longer meets DSM-5 criteria for Hallucinogen Intoxication and does not display physiological changes suggestive of serotonin syndrome. The release checklist must be completed by the study site-designated licensed staff member (physician or designee). The Dosing Session Release Checklist was assessed starting at 6 hours post dose and repeated each 30 minutes (± 10 minutes) until post dose Hour 8. At Hour 8, if the release criteria were met, participants were not required to continue to be observed. If the release criteria were not met, the participant undertakes the Dosing Release Checklist each hour (± 10 minutes) until the criteria are met or a minimum of 16 hours have elapsed post dose. Participants were discharged after a 24-hour post-dose period once they meet the requirements for discharge from the Clinical Research Unit.

[000413] Discharge From Clinical Research Unit: [11]SEP Discharge from the CRU may only occur if the following conditions are satisfied: Participants meet the criteria for release from continuous in-person monitoring as described in the DSMM, evidencing that the participant no longer meets DSM-5 criteria for Hallucinogen Intoxication and is not displaying physiological changes suggestive of serotonin syndrome.

[000414] Participants were presenting a low risk of self-harm and suicide, evidenced by no clinically significant change between pre- and post-dose C-SSRS assessments. Participants who newly answer 'Yes' to suicidal ideation items 1-3 on post-dose C-SSRS required further assessment of suicide risk and safety planning by a site licensed physician prior to discharge. Participants answering 'Yes' to suicidal ideation items 4-5 or who displayed self-injurious behavior during admission to the CRU may be considered for referral to Accident and Emergency (A&E) or local National Health Service (NHS) mental health crisis services.

[000415] Participants were provided with post-dose education, as described in Section 9.9 of the DSMM.

[000416] All ongoing adverse events were reviewed by a licensed physician.

[000417] Participants were provided with an emergency contact card and have received clear instructions around contacting the 24/7 doctor on-call and their follow-up visit arrangements.

[000418] Review by the Principal or Sub-Investigator confirms all necessary actions have been completed and that the participant is safe to discharge.

Eligibility Criteria

Inclusion Criteria

1. Age ≥ 18 to 55 years (inclusive) at Visit 1.
2. Healthy as determined by a responsible physician, based on medical evaluation including medical history, psychiatric history, physical examinations, prior and concomitant medications, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory evaluations.
3. Suitable venous access for cannulation and repeated venipuncture.
4. Body mass index (BMI) between 18.0 and 30.0 kg/m² and weight of at least 50 kg and no more than 100 kg, inclusive at Screening.
5. Able and willing to provide written, informed consent prior to initiation of any study-related procedures and to adhere to all study requirements. *Note: The subject (ie, not a legally authorized representative) must be cognitively able to understand the requirements of the study and provide written informed consent.*
6. Able to swallow capsules.

Exclusion Criteria

1. Women of childbearing potential (WOCBP) (ie, persons physiologically capable of becoming pregnant) who are unwilling or unable to use a highly effective method of contraception, as defined in Appendix A, for the duration of the study (Screening through the subject's last visit), OR Males physiologically capable of fathering a child who are sexually active with WOCBP but are unwilling or unable to use barrier contraception (e.g., condom with or without spermicidal cream or jelly; WOCBP partner should use a highly effective form of contraception) for the duration of the study (Screening through the subject's last visit).
2. Females who are currently pregnant or breastfeeding or plan to become pregnant or

breastfeed during the study.

3. Sperm or egg donation during the study.

4. Prior history (lifetime diagnosis) or known first-degree relative (ie, mother/father/full siblings) with a lifetime diagnosis of schizophrenia spectrum or other psychotic disorders (except substance-/medication-induced or due to another medical condition) or bipolar disorder.

5. Has a significant risk of suicide attempt based upon medical history, in the opinion of the Investigator, or has active suicidal ideation within the past 12 months prior to Screening (Visit 1) and up to Visit 2a, as evidenced by a “Yes” response to the Columbia- Suicidality Severity Rating Scale (C-SSRS) Suicidal Ideation section Question 4 or Question 5.

6. Has either attempted suicide or been hospitalized due to suicide risk within 5 years prior to Screening (Visit 1) and up to Visit 2a, as evidenced by medical history of suicide or a “Yes” response in the following Suicidal Behavior sections of the C-SSRS: Actual Attempt, Interrupted Attempt or Aborted Attempt. *Note: For any “Yes” responses in these sections, the site should inquire about the approximate date when the event occurred.*

7. Has a past or current psychiatric disorder as indicated by the Mini International Neuropsychiatric Interview (MINI) or medical/psychiatric records (e.g., Major Depressive Disorder, anxiety disorders, obsessive-compulsive disorder, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa or bulimia nervosa).

8. Has a current or past diagnosis of Post-Traumatic Stress Disorder (PTSD).

9. Current untreated clinically significant sleep disorder (e.g., obstructive sleep apnea, narcolepsy). *Note: Subjects who require treatment with sleep aids such as benzodiazepines, tricyclic antidepressants (TCA), other anti- depressants (trazodone, mirtazapine, nefazodone) will be excluded from the study. Over the counter (OTC) sleep aids may be permitted per Investigator’s discretion.*

10. Has significant loss of hearing or vision that in the opinion of investigator may interfere with the activities of the study or the ability of the Dosing Session Monitors or site staff to provide adequate oversight to the subject.

11. Any intake of grapefruit, grapefruit juice, Seville oranges, or other products containing grapefruit or Seville oranges within 7 days before admission to the CRU and during the study period.

12. History of alcohol or substance use disorder within 12 months prior to Screening (Visit 1) (includes diagnosis of alcohol or drug use disorder) OR any illicit use of psychedelics (LSD, psilocybin, MDMA, ketamine, etc.) within the past 3 months.

13. Positive urine dipstick result for illicit drug use at Visit 2a.

14. Use of over-the-counter medications, prescription drugs, vitamins, dietary supplements, vaccines, herbal supplements, including CBD, within 5 half-lives OR 14 days (whichever is longer) prior to first dose of study drug. In particular:

use of potent CYP3A4/5 inhibitors or inducers; the use of moderate CYP3A4/5 inhibitors is allowed at Investigator discretion

medications, in addition to those listed above, that may be expected to significantly interfere with the metabolism or excretion of study drug, which may be associated with a significant drug interaction with study drug, or that may pose a significant risk to the subject's participation in the study.

15. Nicotine-dependence.

16. Any chronic infection, including human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.

17. Any acute infection and/or antibiotic treatment within 30 days prior to Visit 2a.

18. Any major trauma, surgery, or open biopsy in the 3 months prior to Visit 1 or has planned/scheduled surgery during the study period.

19. History of malignancy or treatment of malignancy within 2 years prior to Screening (Visit 1) (excluding resected basal cell or squamous cell carcinoma of the skin or carcinoma in situ [CIS] cervix that has been resolved without further treatment).

20. Any of the following cardiovascular conditions or findings:

a. Hemodynamically significant uncorrected cardiac valve disease or hypertrophic/restrictive cardiomyopathy.

b. Any cardiovascular event requiring hospitalization within 12 months prior to Screening (Visit 1) (e.g., stroke, myocardial infarction [MI]).

c. History of life-threatening arrhythmia or any unstable rhythm, ventricular, supraventricular or atrial arrhythmia with a rapid rate.

d. History of cardiovascular disease, including but not limited to coronary artery disease, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction (within 1 year prior to Screening [Visit 1]), angina pectoris (within 1 year prior to Screening [Visit 1]), coronary artery bypass graft or artificial heart valve (within 1 year prior to Screening [Visit 1]), stroke, transient ischemic attack (TIA) or any other clinically significant arrhythmia.

e. Uncontrolled hypertension, defined as undergoing or requiring current treatment, in the opinion of the Investigator.

f. Blood pressure (BP) outside the range of 90-140 mmHg systolic BP or 50-90 mmHg diastolic BP after approximately 5-minutes seated relaxation. *NOTE: If the first measurement of a subject's BP is outside the allowable range, a second recording is allowed after an additional approximately 5-minute supine.*

g. Orthostatic hypotension at Screening (Visit 1), defined as a decrease of more than 20 mmHg in systolic BP or 10 mmHg in diastolic BP, or both, following a change from a supine position to a standing position (measured within 3 minutes of standing); or orthostatic intolerance (e.g., developing symptoms upon standing). *NOTE: If the first measurement of a subject's change in BP exceeds the allowable decrease, a second recording is allowed after an additional approximately 5-minute supine rest.*

h. Heart rate <45 beats/minute or >90 beats/minute after an approximately 5-minute supine rest *NOTE: If the first measurement of a subject's heart rate is >90 beats/minute, a second recording is allowed after an additional approximately 5-minute supine rest.*

i. Postural tachycardia, defined as a sustained increase in standing heart rate of at least 30 beats/minute (compared with supine heart rate) within 10 minutes of standing without a decrease in BP, or symptomatic tachycardia

j. Any clinically significant abnormal ECG finding (e.g., atrial fibrillation) at Visit 1, Visit 2a, or Visit 4a, as determined by the Investigator (in consultation with a cardiologist, if needed)

k. Resting QT interval corrected using Fridericia's formula (QTcF) ≥ 450 msec (male) or ≥ 460 msec (female) at Visit 1 or Visit 2a and Visit 4a or inability to determine QTcF

l. Presence of risk factors for Torsades de pointes (TdP), including long QT syndrome, uncontrolled hypokalemia or hypomagnesemia, history of cardiac failure, history of clinically significant/symptomatic bradycardia, family history of idiopathic sudden death or congenital long QT syndrome, or concomitant use of a torsadogenic medication that cannot be discontinued prior to Visit 2a

21. Have evidence of clinically significant hepatic disorder (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $> 1.5 \times$ the upper limit of normal [ULN]) at Screening.

22. Moderate-to-severe renal impairment, indicated by an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m² at Visit 1, based on the Cockcroft-Gault formula at Visit 1 *Note: These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.*

23. Use of any other investigational drugs or other advanced experimental therapies within 1 year prior to Visit 1.

24. Any other condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the Investigator, may pose additional risk to the subject from participation in the study, may interfere with the subject's ability to comply with study procedures, or may make participation in the study not in the subject's best interest.

Study Treatments

Investigational product, dosage and mode of administration:

[000419] d-LSD D-tartrate Capsules: Each single oral capsule contained 36.6 µg LSD D-tartrate which is equivalent to 25 µg of LSD freebase, blended with "generally recognized as safe" (GRAS) excipients and filled into Hypromellose capsules. Refer to Example 1. Four (4) capsules are administered per dose.

[000420] d-LSD D-tartrate ODT: Each single orally disintegrating tablet contained 146.4 µg LSD-D-tartrate which is equivalent to 100 µg of LSD freebase, formulated with GRAS excipients. The ODT

formulation used disintegrates in less than 60 seconds, as described in Example 1A.

Duration of Treatment

[000421] Each subject received 2 doses of d-LSD D-tartrate, 12 ± 2 days apart in Evaluation Periods 1 and 2 and inclusive of a 12 ± 2 -day washout period prior to end-of-study visit.

Criteria for Evaluation

Pharmacokinetics

[000422] The following PK parameters were calculated for d-LSD D-tartrate capsules and d-LSD D-tartrate ODT in this study: C_{max}, time to maximum plasma concentration (T_{max}), terminal rate constant (λ_z), area under the plasma concentration-time curve from zero to 24 hours after dosing (AUC₀₋₂₄), area under the plasma concentration-time curve from zero to time of the last measurable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time zero to infinity (AUC_∞), half-life (t_{1/2}), apparent volume of distribution of the terminal phase (V_z/F), and apparent plasma clearance (CL/F).

[000423] All subjects provide plasma samples for possible detection and identification of d-LSD D-tartrate metabolites (OH metabolite).

Safety

[000424] Safety and tolerability was assessed by the incidence and severity of AEs, vital sign assessments, C-SSRS, clinical laboratory assessments, and physical examinations.

Passive Data Collection

[000425] Subjects were provided with a smartphone (Apple iPhone) and a smartwatch (Apple Watch) equipped with the application MSMS™ which utilized built-in sensors to passively record the following data: heart rate, audio data, accelerometric data, angular velocity (gyroscope), orientation (compass), number of steps (pedometer), and activity type.

[000426] The MSMS™ was designed to obtain information on a subject's physiological state via a smart watch and a smart phone and display these data on the DSM's tablet in near real-time during a treatment session. The MSMS™ displayed data pre- and post-administration to the DSM to assist them in monitoring a subject throughout a treatment session. The DSM receives a pre-calibrated and pre-set device toolkit, consisting of a tablet, smart phone, smart watch, and use instructions.

[000427] Smart watch - The smart watch collects the following data from the subject: heart rate (HR), acceleration 50Hz, and composite motion: orientation, steps, and activity.

[000428] Smart phone - The smart phone collects the following data from the subject: acceleration, orientation, motion, distance, steps, and activity.

[000429] The devices are connected to a cloud server located in UK and data is securely transmitted and stored.

Results

[000430] FIG. 10 is a graph of mean $\pm$ SE concentration versus time for d-LSD D-tartrate in capsule and ODT formulations (FIG. 9 depicting ODT only).

[000431] Table 3A shows a summary of PK parameters for d-LSD D-tartrate in capsule and ODT formulations. Parameters were summarized as mean $\pm$ SD (geomean), except $T_{\max}$ which was summarized as median (min, max). This shows that the average $C_{\max}$ and AUC increased given the same unit of drug dosed, and increased absorption is equal to greater maximum concentration achieved, and greater overall concentration over time achieved per unit of drug dosed. $T_{\max}$ also decreased in ODT formulation versus capsule formulation, and showed faster absorption, which can result in faster onset of clinical effects.

Table 3A

Treatment	$T_{\max}$ (hr)	$C_{\max}$ (ng/mL)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	Half-life (hr)
Capsule (N=25)	2.5 (1.0, 6.0)	2.64 $\pm$ 0.987 (2.48)	15.4 $\pm$ 5.27 (14.5)	16.4 $\pm$ 5.69 (15.5)	4.54 $\pm$ 1.27 (4.38)
ODT (N=28)	2.0 (1.0, 4.0)	2.70 $\pm$ 0.951 (2.54)	18.4 $\pm$ 7.53 (17.1)	19.5 $\pm$ 7.91 (18.1)	5.05 $\pm$ 1.84 (4.77)

[000432] FIG. 10 is a graph of mean $\pm$ SE concentration versus time for D-LSD D-tartrate in capsule and ODT formulations. FIG. 11 is a graph of mean concentration versus time for absorption phase (up to 4 hours post-dose) for d-LSD D-tartrate in capsule and ODT formulations. FIG. 12 is a close up view of the graph of FIG. 11 from 0 through 15 minutes. There was faster absorption (i.e., time to first detectability, time to maximum concentration) with the ODT formulation versus the capsule formulation. The drug was also absorbed to greater extent for the ODT formulation.

[000433] FIG. 13 is a chart showing a summary of concentration by time point for d-LSD D-tartrate capsule and ODT formulations. The ODT formulation had lower variability in exposure at later time points, which was consistent with faster absorption. Reduced later-variability can shorten the duration of the exposure and shorten the duration of the perceptual effects (which are adverse events). Therefore, the ODT formulation provides reduced variability in exposure at later time points, that is any time after 5 hours post-dose.

[000434] FIG. 14 is a graph of mean concentration versus time for d-LSD D-tartrate in capsule and ODT formulations showing a threshold of 0.5 ng/mL with a dashed line (overlaid on the graph of FIG. 10), i.e., the time to get exposure back below a given "threshold" concentration. It took on average 12 hours for capsule and ODT formulations to fall below the threshold of 0.5 ng/mL. All subjects fell below threshold after 24 hours. This is true both on average and for the time to all patients. This is important, because if this time were variable, that could mean more variability in the duration of

perceptual effects (i.e., longer AEs) which would require longer monitoring.

[000435] FIG. 15 is a graph of mean concentration versus time for d-LSD D-tartrate in capsule and ODT formulations showing a threshold of 1 ng/mL with a dashed line (overlaid on the graph of FIG. 10). It took on average 8 hours for capsule and ODT formulations to fall below the threshold of 1 ng/mL. All subjects fell below threshold after 12 hours for ODT formulation, while all subjects fell below threshold after 24 hours for capsule formulation. The time for all subjects to fall below threshold is lower for the ODT formulation compared to capsule formulation, because the ODT formulation PK is less variable. Higher variability in PK could mean more variability in the duration of perceptual effects (i.e., longer time that adverse events are present, in particular those that require monitoring by a healthcare practitioner) which would require longer monitoring. 1 ng/mL appears to be threshold of subjective VAS effects in Phase 1 dataset for majority of subjects who receive LSD (FIG. 16). The ODT formulation allows for faster time to reach clearance target/exposure below clinically relevant threshold. It should be understood that other threshold values can be desired or acceptable besides 1 ng/mL.

[000436] FIG. 17 is a graph of mean $\pm$ SE concentration versus time for OH metabolite PK in d-LSD D-tartrate in capsule and ODT formulations. The ODT formulation shows increased C_{max} and AUC of metabolite compared to the capsule formulation. The ODT formulation shows faster absorption of metabolite compared to the capsule formulation.

[000437] FIG. 18 shows a comparison of crossover results for PK of the ODT formulation relative to the capsule formulation. FIG. 19 is a graph showing crossover (incomplete block) results of PK of the ODT formulation relative to the capsule formulation.

[000438] FIGs. 20A-20C are graphs showing VAS profile for ODT and capsule formulation of mean $\pm$ SE versus, FIG. 20A shows any drug effect for period 1, FIG. 20B shows good drug effect for period 1, and FIG. 20C shows bad drug effect for period 1. FIG. 21 is a graph of DSRC times for the ODT and capsule formulation for period 1.

Discussion

[000439] The ODT formulation of d-LSD D-tartrate provides a faster time to absorption and bioavailability (within 5 minutes) than the capsule formulation which can take 15-20 minutes to reach the gut to start to be absorbed and become bioavailable. The ODT formulation has a faster time to maximum concentration which provides a faster time to desired clinical effects. Since the average concentration in the body is higher after administration of the ODT formulation, a lower dose of 92.3 μ g (or other doses such as 90 μ g instead of 100 μ g) with the ODT formulation than can be given than with the capsule formulation. There is also less variation in the elimination phase with the ODT formulation, which is important in determining when the acute perception- and consciousness-altering effects have concluded in a treatment session. These effects, while believed to be correlated with positive clinical efficacy, are treated as adverse events or side effects of the drug and may require continuous clinical monitoring by a healthcare practitioner. A blood test and/or a clinical assessment,

patient-completed assessment, or combinations thereof can be performed on an individual to check their exposure level of LSD, and if they are below a certain amount (such as 1 ng/mL), they can be cleared to be released from the treatment session/clinic because any acute effects or side effects have concluded or sufficiently resolved to enable release of the patient. While the time it takes to be below a certain exposure level can vary based on the dose of LSD given and the individual's physical characteristics, the fact that the ODT has reduced variability and faster absorption means that most patients will be clear of symptoms sooner and therefore monitoring time is reduced. It is important to be able to reach below the exposure level fast and at the same time for patients, which the ODT formulation is able to provide. [000440] The invention has been described in an illustrative manner and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

EQUIVALENTS

[000441] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

[000442] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

CLAIMS

What is claimed is:

1. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering lysergic acid diethylamide (LSD), or a salt thereof.
2. The method of claim 1, wherein the LSD salt is d-LSD D-tartrate.
3. The method of claim 1 or claim 2, wherein the LSD is administered as an orally disintegrating tablet.
4. The method of claim 3, wherein the orally disintegrating tablet comprises:
 - a. LSD, or a salt thereof;
 - b. a non-gelling matrix;
 - c. a binder;
 - d. a filler; and
 - e. solvent.
5. The method of claim 4, wherein the LSD salt is d-LSD D-tartrate.
6. The method of claim 4, wherein the non-gelling matrix is maltodextrin.
7. The method of claim 4, wherein the binder is hydroxypropyl methylcellulose.
8. The method of claim 4, wherein the filler is mannitol.
9. The method of claim 4, wherein the solvent is water.
10. The method of any one of claims 4-9, wherein the orally disintegrating tablet comprises:
 - a. d-LSD D-tartrate;
 - b. maltodextrin;
 - c. hydroxypropyl methylcellulose;
 - d. mannitol; and

e. water.

11. The method of any one of claims 4-10, wherein the orally disintegrating tablet stock solution comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 2% to about 10% maltodextrin;
- c. about 1% to about 5% hydroxypropyl methylcellulose;
- d. about 2% to about 10% mannitol; and
- e. water.

12. The method of any one of claims 4-10, wherein the orally disintegrating tablet comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

13. The method of any one of claims 4-10 or 12, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.

14. The method of any one of the preceding claims, wherein the LSD, or freebase equivalent of a salt thereof, is administered at a dose of about 25 µg to about 200 µg.

15. The method of any one of the preceding claims, wherein the LSD, or freebase equivalent of a salt thereof, is administered at a dose of about 25 µg, about 50 µg, about 100 µg, about 150 µg, or about 200 µg.

16. The method of any one of the preceding claims, wherein the LSD, or freebase equivalent of a salt thereof, is administered at a dose of about 100 µg.
17. The method of any one of claims 3-16, wherein the subject's serum d-LSD D-tartrate concentration is between about 2 ng/mL to about 2.5 ng/mL within about four hours after administration of the orally disintegrating tablet.
18. The method of any one of the preceding claims, wherein the generalized anxiety disorder is severe generalized anxiety disorder.
19. The method of any one of the preceding claims, wherein the generalized anxiety disorder is moderate generalized anxiety disorder.
20. The method of any one of the preceding claims, wherein the symptom of generalized anxiety disorder is feeling nervous, having a sense of impending danger, panic, increased heart rate, rapid breathing, sweating, trembling, gastrointestinal problems, restlessness, fatigue, difficulty concentrating, irritability, muscle tension, a sleep disturbance, or sexual dysfunction.
21. The method of any one of claims 3-20, wherein the symptom of generalized anxiety disorder is reduced or eliminated between about 6 hours to about 12 hours after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
22. The method of any one of claims 3-21, wherein the symptom of generalized anxiety disorder is reduced or eliminated for about 12 weeks or greater after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
23. The method of any one of claims 3-22, wherein the subject has a Hamilton Anxiety Scale (HAM-A) improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
24. The method of any one of claims 3-23, wherein the subject has an about 20-point HAM-A improved score within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.

25. The method of any one of the preceding claims, wherein the subject is not administered a second agent for the treatment of generalized anxiety disorder or depression.
26. The method of any one of claims 3-25, wherein the subject has a reduction in Clinical Global Impressions – Severity (CGI-S) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
27. The method of any one of claims 3-26, wherein the subject has an about 1.8-point reduction in CGI-S within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
28. The method of any one of the preceding claims, wherein the subject has depression.
29. The method of any one of claims 3-28, wherein the subject has a reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
30. The method of any one of claims 3-29, wherein the subject has an about 18-point reduction in MADRS within about 12 weeks after administration of the orally disintegrating tablet comprising LSD, or a salt thereof.
31. The method of any one of the preceding claims, wherein the LSD, or salt thereof, is administered one to four times per year.
32. The method of any one of the preceding claims, wherein the LSD, or salt thereof, is administered once every about 12 weeks.
33. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet one to four times per year, wherein the orally disintegrating tablet comprises:
- a. d-LSD D-tartrate;
 - b. maltodextrin;
 - c. hydroxypropyl methylcellulose;

- d. mannitol; and
- e. water.

34. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering an orally disintegrating tablet once every about 12 weeks, wherein the orally disintegrating tablet comprises:

- a. d-LSD D-tartrate;
- b. maltodextrin;
- c. hydroxypropyl methylcellulose;
- d. mannitol; and
- e. water.

35. A method of treating a symptom or preventing a symptom of generalized anxiety disorder in a subject, comprising administering a dose of about 100 µg lysergic acid diethylamide (LSD), or a salt thereof.

36. The method of claim 35, wherein the LSD, or a salt thereof, is administered as an orally disintegrating tablet.

37. The method of claim 35 or claim 36, wherein the LSD, or a salt thereof, is administered one to four times per year.

38. The method of claim 35 or claim 36, wherein the LSD, or a salt thereof, is administered once every about 12 weeks.

39. The method of any one of claims 33-38, wherein the orally disintegrating tablet stock solution comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 2% to about 10% maltodextrin;
- c. about 1% to about 5% hydroxypropyl methylcellulose;
- d. about 2% to about 10% mannitol; and
- e. water.

40. The method of any one of claims 33-38, wherein the orally disintegrating tablet comprises:

- a. less than about 1% d-LSD D-tartrate;
- b. about 15% to about 77% maltodextrin;
- c. about 8% to about 38% hydroxypropyl methylcellulose;
- d. about 15% to about 77% mannitol; and
- e. less than 10% water.

41. The method of any one of claims 33-38 or 40, wherein the orally disintegrating tablet stock solution comprises:

- a. less than 1% d-LSD D-tartrate;
- b. about 6% maltodextrin;
- c. about 2% hydroxypropyl methylcellulose;
- d. about 5% mannitol; and
- e. about 87% water.