CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms
Protocol Number:	MMED008
Compound Name:	MM-120 (D-lysergic acid diethylamide [LSD] D-tartrate)
Sponsor:	Mind Medicine, Inc.
Development Phase:	2
Regulatory Agency Identifying Number(s):	IND 151069
Version:	6.0
Effective Date:	26 July 2023

CONFIDENTIALITY STATEMENT

SUMMARY OF CHANGES

Version number: 6.0

Effective Date: 26 July 2023

Supersedes MMED008 V5.0 (31 March 2023)

MMED008 V5.0 was revised. Minor grammatical, wordsmithing, or formatting changes are not included in the summary below. New or revised text is shown in **bold font**, deleted text is shown as ~~strike-through text~~.

Table 1 Emergency Contact Information	Change of Primary Medical Monitor From Eric J Christopher to Christopher Perkins
Synopsis Number of Subjects Planned 4.2. Number of Subjects	Change in Number of Subjects Approximately ~~200~~**180**
Synopsis Study Design 4.1. Overall Study Design	Change in Number of Subjects The study will enroll approximately ~~200~~ **180** male and female subjects
Synopsis Exclusion Criterion #18 5.1.2 Exclusion Criterion #18	Clarification added regarding tapering …until End of Study**.** Note: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use. ***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.***
Synopsis Exclusion Criteria #26 g, 26 h, 26 i 5.1.2 Exclusion Criteria #26 g, 26 h, 26 i	Clarifications added related to blood pressure, heart rate, and orthostatic hypotension g. … after an additional approximately 5 minutes ~~relaxation~~**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.** ~~> 90 beats/minute, a second recording is allowed after an additional approximately 5-minute rest.~~ i. … following a change from a supine position to a standing position (measured within **1 to** 3 minutes of standing);
Synopsis Endpoints 3 Endpoints	Clarification to timing of assessments Change from Baseline to **Week 1, Week 2 (where applicable),** Week 4…
Synopsis Statistical Methods	Updated to account for the change in the number of subjects A total sample of ~~200~~ **180** subjects (~~40~~ **36** per dose arm and ~~40~~ **36** for the placebo arm) is required to ensure a mean power > ~~90~~**87**% for an MCP-Mod analysis rejecting the hypothesis…
Table 2: MMED008 Schedule of Activities	Updated to include measurement of weight, height, and BMI at the Screening Visit and revised footnote 'e' to describe collection of Vital signs e Vital signs should be performed prior to an ECG and/or a blood draw; **Screening and Baseline vital signs require sitting, lying, and standing vital signs in order to capture orthostatic vitals.**
3. Objectives and Endpoints	Addition of Exploratory Objective and Endpoints

	New Exploratory Objective: • **To assess response and remission across the 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A from Baseline to End of Study** New Exploratory Endpoints: • **HAM-A response (defined as ≥50% reduction in HAM-A Total Score) from Baseline to Weeks 1, 2, 4, 8, and End of Study.** • **HAM-A remission (defined as HAM-A Total Score of ≤7) at Weeks 1, 2, 4, 8, and End of Study**
4.1 Overall Study Design	Qualifications of Dosing Session Monitors clarified The lead monitor must be a licensed healthcare provider with **graduate-level** professional training and clinical experience. The lead monitor must be actively licensed to practice independently in the state of the study site location. Lead monitor acceptable professional credentials are as follows: Clinical or counseling psychologist (PhD or PsyD); Psychiatrist or other physician (MD or DO); Master **Level Clinician, such as of Social Work (Licensed Clinical Social Worker (-LCSW), Licensed Clinical Professional Counselor (LCPC), Licensed Marriage and Family Therapist (LMFT), or local state equivalent; Advanced Nurse Practitioner (NP/APRN) such as a Psychiatric Nurse Practitioner or local state equivalent.** ~~Masters-level Clinician (Licensed Professional Counselor – LPC, Licensed Professional Counselor Candidate – LPCC; Licensed Mental Health Counselor – LMHC, Licensed Marriage Family Therapist – LMFT, Licensed Professional Counselor – LPC, Licensed Clinical Professional Counselor – LCPC, Licensed Clinical Mental Health Counselor – LCMHC); Psychiatric Nurse Practitioner, Nurse Practitioner (NP), Advanced Practice Nurse (APRN) and Physician's Assistant (PA).~~ One of the DSMs must be appropriately trained to monitor vital signs **and administer the C-SSRS.**~~, including orthostatic blood pressure.~~ A site-designated licensed physician with prescribing rights or a qualified designee ~~can~~ **may** serve as the backup to either DSM if short breaks are needed.
5.2.2. Nicotine Use	Clarifications regarding the use of nicotine Due to the length of Day 1/Dosing Session **subjects are not permitted to smoke cigarettes/vape during the dosing session.** ~~and the~~**Due to the** possibility of nicotine withdrawal symptoms,
8.1.4. Eligibility Assessment	Clarification related to Vital Signs however, of the vital signs taken at Visit 3A ~~will not be~~**only temperature and blood pressure will be** used to confirm final eligibility
8.2.3 Vital Signs	Clarifications related to Vital Signs **Initial vital signs**~~Blood pressure~~ should be taken with the subject seated in a chair with back support and arms, feet flat on the floor, arm**s** supported by the arm rest. ~~a~~**A**fter an approximately 5-minute rest**, measure blood pressure**, ~~.~~**h**eart rate**,** and respiration rate**. If any of the first measurements are out of range, a second measurement can be taken after the subject has been allowed an additional approximately 5 minutes of rest.** ~~will be obtained after the subject has rested quietly in a supine position for approximately 5 minutes.~~ At Screening (Visit 1) and Baseline (Visit 2), ~~vital sign measurements will also include~~ measure ~~me nt of~~ orthostatic blood pressure. **This measurement is taken separately from the initial vital signs.** ~~For eligibility determinations at these 2 visits, the Oo~~ Orthostatic blood pressure should be measured **by: allowing the subject to rest in a supine position for approximately 5 minutes; the subject then stands; and heart rate and blood pressure are measured within in 1 to 3 minutes of standing.** ~~following a change from a supine position to a standing position (measured within 3 minutes of standing).~~ **If convenient, orthostatic blood pressure can be measured after the subject has been supine for the ECG.**
8.2.4. Weight	Clarifications related to timing of the measurement **Weight may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site to determine eligibility.**

	Body weight may be measured with the subject in street clothing with jacket/coat and shoes removed. ~~Weight may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site to determine eligibility.An estimated weight may be used during the optional Prescreen for sites that implement remote prescreening activities.~~
8.2.5. Height	Clarifications related to timing of the measurement **Height may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site.** Standing height will be measured without shoes at Screening (Visit 1) only **when** ~~Height may be estimated during a remote Prescreen session but should be physically measured once~~ **the subject is on-site to determine eligibility**~~.An estimated height may be used during the optional Prescreen for sites that implement remote prescreening activities~~.
9.1. Definition of an Adverse Event	Definition of adverse events updated Any change in clinical status ~~, ECGs, routine labs, physical examinations, etc.,~~ that is considered clinically significant by the PI should be documented. AEs occurring prior to randomization should be documented in medical history. AEs occurring after randomization should be documented in the AE log. Adverse events include any clinically significant changes not present prior to drug administration~~., or an already present event that worsens either in intensity or frequency following the treatment.~~ **An AE includes:** • **An unexpected worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.** • **A new condition detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.** • **Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately).** • **An investigational abnormality (e.g., laboratory parameter, vital sign, ECG) only if the abnormality which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, physical examinations, etc., that is considered clinically significant by the Investigator based on at least one of the following criteria:** - **Induces clinical signs or symptoms** - **Requires active intervention** • **Signs, symptoms, or the clinical sequelae of a suspected interaction.** • **Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.**
9.3. Adverse Events of Special Interest	Definition of adverse events of special interest updated for clarity The AE terms listed below are MedDRA Preferred Terms to be used in classifying Adverse Events of Special Interest (AESIs) related to abuse liability when deemed appropriate by the PI (or designee): • **Euphoria-related terms: Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect.** • **Terms indicative of impaired attention, cognition, and mood: Somnolence; Mood disorders and disturbances.** • **Dissociative/psychotic terms: Psychosis; Aggression; Confusion and disorientation.** • **Overdose-/ Misuse-related terms not captured elsewhere: Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders.** ~~• Euphoria~~ ~~• Disassociation~~

<table>
<tr><td></td><td>
~~• Impaired cognition and attention~~
~~• Psychomotor effects~~
~~• Inappropriate Affect~~
~~• Overdose/ Misuse~~
</td></tr>
<tr><td>Table 8: MMED008 Analysis Sets</td><td>
Updated to account for the change in the number of subjects
<table>
<tr><th>Analysis Set</th><th>Description</th></tr>
<tr><td>Randomized Set (RAN)</td><td>All subjects who received a randomization number, regardless of receiving trial medication. Subjects will be analyzed according to the treatment assigned.</td></tr>
<tr><td>Safety Set (SAF)</td><td>All subjects who received the double-blind study drug. Subjects will be analyzed according to actual treatment received.</td></tr>
<tr><td>Full Analysis Set (FAS)</td><td>All subjects in RAN ~~who were not mis randomized[a].~~with a valid Baseline HAM-A assessment and at least one valid post-baseline HAM-A assessment. Subjects will be analyzed according to the treatment assigned. ~~Following the intent-to-treat (ITT) principle, subjects are analyzed according to the treatment they have been assigned to at the randomization.~~</td></tr>
<tr><td>Per Protocol Set (PPS)</td><td>All subjects in FAS who ~~took the study medication and~~had no major protocol deviations deemed as impacting the primary endpoint[a]. Subjects will be analyzed according to the actual treatment received.</td></tr>
</table>
~~a— Mis-randomized subjects are those who have not been qualified for randomization and who have been inadvertently randomized into the study but have not received double-blind study drug.~~
An impact assessment will be performed prior to the unblinding of the study. The impact assessment will determine whether a major protocol deviation impacts the primary endpoint thereby leading to the removal of the respective subject(s) from the PPS.~~Major protocol deviations are those affecting the primary endpoint analyses and will be finalized prior to unblinding treatment codes for analyses.~~
</td></tr>
<tr><td>10.2.1. Patient Demographics and Other Baseline Characteristics
10.2.2.1 Primary Estimand Step 1</td><td>
Removal of geographical area from analysis of demographics
Summary statistics will be provided by treatment group for demographics and baseline characteristics, including sex at birth, self-identified gender, age, race, weight, height, BMI, systolic blood pressure, diastolic blood pressure, ~~geographical region,~~ medical history…
The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) model with the change from Baseline to Week 4 for HAM-A Total Score as a response variable, treatment (placebo and all MM-120 doses), and Baseline value of HAM-A Total Score, ~~- geographical region,~~
</td></tr>
<tr><td>10.2.2.1 Primary Estimand</td><td>
Added clarification of how the assessment of impact on the primary endpoint is conducted
• Handling of IEs prior to HAM-A assessment at Week 4:
- Intake or change in concomitant medications/therapies which have potential confounding effects per the impact assessment.
- Intake of prohibited medications/therapies assessed as “Yes” per the impact assessment.
</td></tr>
<tr><td>Statistical Methods & Analysis</td><td>
Correction of typographical error
• Sigmoid Emax (ED50, hill):
10, 1~~0~~
100, 5
100, 10
</td></tr>
</table>

<table>
<tr><td></td><td>150, 10</td></tr>
<tr><td>Step 2</td><td>Clarification of analysis population for the primary and key secondary endpoints
The MCP-Mod analysis will be performed on the ~~PPS~~ FAS population. It will also be performed on the PPS as a sensitivity analysis.</td></tr>
<tr><td>Handling of Missing/Potentially Biased Values</td><td>Clarifications related to impact assessment
- For intake or change in concomitant medications/therapies that have potential confounding effects per the impact assessment; or
- For intake of prohibited medications/therapies assessed as “Yes” per the impact assessment.</td></tr>
<tr><td>10.2.2.2. Sample Size Determination</td><td>Sponsor determination that 90% power was not necessary given the inherent power of the MCP-Mod analysis.
A total sample of ~~200~~ 180 subjects (~~40~~ 36 per dose arm and ~~40~~ 36 for the placebo arm) is required to ensure a mean power >~~90~~87% for an MCP-Mod Analysis
The analysis assumes 4 doses of active medication (25, 50, 100, and 200 µg freebase-equivalent) and placebo. The required sample size for each dose arm is ~~40~~ 36 subjects.</td></tr>
<tr><td>Table 9 Study MMED008 Power by Model</td><td>Updated based on N of 180 plus correction of typographical error
Sigmoid Emax (ED50, hill)
<table><tr><th>Model</th><th>Power (%)</th></tr><tr><td>Sigmoid Emax (ED50, hill)</td><td></td></tr><tr><td>10, 1~~0~~</td><td>84.5~~93.2~~</td></tr><tr><td>100, 5</td><td>90.7~~93.4~~</td></tr><tr><td>100, 10</td><td>91.0~~87.9~~</td></tr><tr><td>150, 10</td><td>89.9~~92.6~~</td></tr><tr><td>Emax (D50 = 100)</td><td>83.2~~86.6~~</td></tr><tr><td>Linear</td><td>85.0~~88.21~~</td></tr></table></td></tr>
<tr><td>10.2.2.4. Secondary Efficacy Endpoints</td><td>Clarifications to analyses of Secondary Endpoint
Change from Baseline to Week 1, Week 2 (as applicable), Week 4, Week 8 and End of Study (as applicable) in HAM-A, MADRS, CGI-S, CGI-I, PGI-S, PGI-C, SDS, EQ-5D-5L, PSQI and ASEX will be analyzed descriptively. Continuous outcomes will be summarized ~~reporting~~ by ~~dose~~: n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, maximum and ~~90~~95% Confidence Interval for the mean ~~and for the median~~. For the active doses similar statistics will be reported for the difference from placebo. Categorical measures will be summarized by the number and percentage of subjects within each category.</td></tr>
<tr><td>11.6. Safety Review</td><td>New Section providing guidance related to safety review of blinded data
The Sponsor’s Medical Monitor or designee will review blinded safety data listings monthly as detailed in the Medical Management Plan (MMP). Safety review meetings will review ongoing data for all subjects to identify trends in safety parameters. If necessary, the Sponsor will terminate the study if this blinded review process identifies significant intolerable safety signals based on either individual or aggregate blinded safety information that puts subjects in this study at unacceptable risk.</td></tr>
<tr><td>Appendix 1 Acceptable Highly Effective Methods of Contraception</td><td>Correction of typographical error
• Two barrier methods of contraception: condom ~~or~~ and occlusive cap (diaphragm or cervical/vault cap) with spermicide</td></tr>
<tr><td>Appendix 3. Rescue Medications</td><td>Clarifications that the study site physician will administer rescue medications
Rescue medications should only be considered after ~~other alternatives~~non-medical interventions have been exhausted. Under all circumstances, only the study site-designated physician will administer rescue medications in this study. The choice</td></tr>
</table>

	of rescue medications ~~are~~ **is** at the discretion of the ~~Investigator~~**study site designated-physician** and should be based **on** subject medical history and local standard of care. The ~~Investigator~~**study site-designated physician** must consider rescue medications and if they have been associated with lengthening QTc interval, which can lead to syncope, arrhythmia or sudden cardiac arrest.

SPONSOR SIGNATURE PAGE

Study Title: A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms

Protocol Number: MMED008

This protocol has been approved by Mind Medicine, Inc. The following signatures document this approval.

[redacted]
Chief Medical Officer

Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.
- I acknowledge that I will be making the application for a DEA Schedule I Researcher Registration and be in compliance with all Federal and State laws and regulations.

Principal Investigator Name (Printed)	Signature
Date	Site

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Sponsor's Address:	Mind Medicine, Inc. One World Trade Center, Suite 8500 New York, NY 10007
Primary Sponsor Contact:	[redacted] Chief Medical Officer Mind Medicine, Inc. **Email:** [redacted] **Phone**: [redacted]
Primary Medical Monitor:	[redacted] Senior Medical Director, Clinical Research PPD, part of Thermo Fisher Scientific **Email**: [redacted] **Phone**: [redacted]
Sponsor Medical Monitor:	[redacted] Director Clinical Development Mind Medicine, Inc. **Email**: [redacted] **Phone**: [redacted]
Contact for Serious Adverse Events or Adverse Events (SAEs or AESIs):	To report an SAE and/or AESI suggestive of abuse potential, please contact the [redacted] main Safety Management email / phone / fax (or your applicable country-specific toll-free numbers): **Email (preferred method)**: [redacted] **Phone (back-up method)**: [redacted]

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LIST OF ABBREVIATIONS

Term	Description
5D-ASC	5-Dimensional Altered States of Consciousness Rating Scale
5-HTP	5 hydroxytryptophan
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASEX	Arizona Sexual Experiences Questionnaire
AST	aspartate aminotransferase
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CIS	carcinoma *in situ*
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicidality Severity Rating Scale
C-SSRS – SLV	Columbia-Suicide Severity Rating Scale – Since Last Visit
CTCAE	Common Terminology Criteria for Adverse Events
DBS	deep brain stimulation
DEA	Drug Enforcement Agency
DMT	dimethyltryptamine
DSM	Dosing Session Monitor
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
EQ-5D-5L	EuroQol-5 Dimentions-5 Levels
FAS	Full Analysis Set
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid

Term	Description
GAD	generalized anxiety disorder
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GRAS	generally recognized as safe
HAM-A	Hamilton Anxiety Rating Scale
HCRU	health-care resource utilization
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IE	intercurrent event
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	integrated web response system
LDL	low-density lipoprotein
LS	least-squares
LSD	D-lysergic acid diethylamide
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAR	Missing at Random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP	multiple comparisons procedure
MCP-Mod	Multiple Comparison Procedure-Modelling
MCV	mean corpuscular volume
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MEQ30	Mystical Experience Questionnaire
MI	myocardial infarction
MINI	Mini-International Neuropsychiatric Interview
MM-120	Mind Medicine, Inc. compound code for D-lysergic acid diethylamide D-tartrate
MMP	Medical Management Plan
MNAR	Missing Not at Random
MPV	mean platelet volume

Term	Description
NCI	National Cancer Institute
NDA	new drug application
AESI	adverse events of special interest
PGI	Patient Global Impression
PGI-C	Patient Global Impression – Change
PGI-S	Patient Global Impression – Severity
PIND	pre-investigational new drug (application)
PPS	Per Protocol Set
PRO	patient-reported outcome
PSQI	Pittsburgh Sleep Quality Index
Q1	25th percentile
Q3	75th percentile
QTcF	QT interval corrected using Fridericia's formula
RAN	Randomized Analysis Set
RDW	red cell distribution width
SAE	serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Sheehan Disability Scale
SNDRI	serotonin–norepinephrine–dopamine reuptake inhibitor
SNRI	serotonin-norepinephrine reuptake inhibitor
SRC	Safety Review Committee
SSRI	selective serotonin reuptake inhibitor
T4	thyroxine
TCA	tricyclic antidepressant
TdP	Torsades de pointes
THC	tetrahydrocannabinol
TIA	transient ischemic attack
TMS	transcranial magnetic stimulation
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States (of America)
VAS	visual analogue scale
VNS	vagus nerve stimulation
WD	withdrawal
WHO	World Health Organization

Term	Description
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WOCBP	women of childbearing potential
β-HCG	beta human chorionic gonadotropin

1. SYNOPSIS

Study Title	A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms
Protocol Number	MMED008
Study Center Location(s)	United States
Number of Study Centers Planned	Approximately 20
Study Phase	2
Target Population	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	Approximately 180
Study Objectives	<u>Primary Objectives</u> • To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 4 <u>Key Secondary Objective</u> • To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 8 <u>Secondary Objectives</u> • To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to End of Study • To determine whether MM-120 (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: o Depressive symptoms o Anxiety symptoms o Functional disability o Quality of life o Sleep o Sexual function

	Safety Objective • To assess the safety and tolerability of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) after oral administration in subjects with anxiety symptoms
Study Design	This is a Phase 2, multi-center, randomized, double-blind, parallel-group, dose-finding study to assess the effect of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) for the treatment of anxiety symptoms in subjects diagnosed with GAD. The study will enroll approximately 180 male and female subjects 18 years to < 75 years of age at Screening who meet DSM-5 criteria for GAD and have a minimum HAM-A Total Score of 20. Potential subjects who have contraindicated medical or psychiatric conditions or who are 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 will be excluded from the study. Subjects on contraindicated concomitant medications, supplements or other therapeutics at Screening (Visit 1) will undergo 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 will be overseen by a psychiatrist based on acceptable local practice standards. Potential study subjects who provide informed consent will have 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 have the option of implementing a 'Prescreen' prior to Visit 1. Randomization will occur following the final assessment of eligibility on Day 1/Randomization (Visit 3A). Eligible subjects will be randomized in a 1:1:1:1:1 ratio to receive a single dose of either investigational drug (25, 50, 100 or 200 µg MM-120 freebase-equivalent) or placebo in a controlled clinical setting, which will be administered during the Dosing Session (Visit 3B) on Day 1. Prior to Day 1/Randomization & Dosing Session (Visits 3A & 3B), subjects will be given preparatory education about the planned intervention. Throughout the Dosing Session (Visit 3B) on Day 1, subjects will be supported by a team of appropriately trained and qualified Dosing Session Monitors who will be in the room with the subject at all times. A site-designated licensed physician will be available or on call and be able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency; events requiring intervention should be discussed with the Sponsor as soon as the situation permits, but implementation of the intervention should not be delayed. The Subject Education and Safety Management Framework for this study is included in the Dosing Session Monitor Manual, which provides 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 be met in order to release the subject from the clinic at the end of the Dosing Session (Visit 3B).

	After Day 1/Randomization & Dosing Session (Visits 3A & 3B), subjects will have 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).
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/kg^2 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, as defined in Appendix 1, 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: See Appendix 1 for definitions of WOCBP and highly effective methods of contraception and for information about unacceptable methods of contraception.* *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 [redacted] 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. [redacted]
11. [redacted]
12. Greater than [redacted] including microdosing. Any instance of psychedelic use in the [redacted] including microdosing (including use as part of a clinical trial)
13. History of illicit substance use in the past [redacted] 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 [redacted] before screening (including as part of a clinical trial); illicit use of ketamine [redacted]; or use of ketamine for treatment of an excluded condition (see exclusion criteria #4, #5, #6)

15. [redacted]
16. Current use at Baseline (Visit 2) or Day 1/Randomization (Visit 3A) of any prescribed psychotropic medication
    Note: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use.
17. Unwillingness or inability to discontinue prohibited concomitant medications, supplements or other therapeutics (prescription or over-the-counter)
    Note: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use; see Section 8.1.6 for information on medication tapering.
18. Any form of medicinal therapy should be [redacted] 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: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use. 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 [redacted] 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 m^2 at Screening (Visit 1), based on the Cockroft-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. [redacted]
Study Treatment	Subjects will be randomized 1:1:1:1:1 to receive a single dose of one of the following blinded treatments: • 25 µg (freebase-equivalent) of MM-120 (n ≈ 36) • 50 µg (freebase-equivalent) of MM-120 (n ≈ 36) • 100 µg (freebase-equivalent) of MM-120 (n ≈ 36) • 200 µg (freebase-equivalent) of MM-120 (n ≈ 36) • Placebo (n ≈ 36) All treatments will be administered orally. All subjects will receive a total of 8 capsules (combination of capsules containing MM-120 and/or placebo capsules, depending on their randomized dose), which are to be taken together as the subject's single dose of study drug.
Duration of Treatment	Subjects will receive a single dose of study drug during the trial. The trial duration will be 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 are 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) is expected to be approximately 18 months.
Endpoints/ Outcome Measures	<u>Primary Endpoint</u> • Change in HAM-A Total Score from Baseline to Week 4 <u>Key Secondary Endpoint</u> • Change in HAM-A Total Score from Baseline to Week 8

	Secondary Endpoints • Change in HAM-A Total Score from Baseline to End of Study • Change from Baseline to Week 1, Week 2 (where applicable), Week 4, Week 8, and End of Study in score for the following measures: o Montgomery-Åsberg Depression Rating Scale (MADRS) o Clinical Global Impression – Severity (CGI-S) Scale o Clinical Global Impression – Improvement (CGI-I) Scale o Patient Global Impression – Severity (PGI-S) Scale o Patient Global Impression – Change (PGI-C) Scale o Sheehan Disability Scale (SDS) o EuroQol-5 Dimentions-5 Levels (EQ-5D-5L) o Pittsburgh Sleep Quality Index (PSQI) o Arizona Sexual Experiences Questionnaire (ASEX) Safety Endpoints Safety will be 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	This study will utilize the Multiple Comparison Procedure-Modelling (MCP-Mod) approach to analyze the primary outcome measure (Bretz 2005, Pinheiro 2014). 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. A total sample of 180 subjects (36 per dose arm and 36 for the placebo arm) is 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 (MM-120 25, 50, 100, and 200 µg freebase-equivalent) and placebo.

Schedule of Activities

Table 2: MMED008 Schedule of Activities

STUDY PERIOD	Optional Prescreen	SCREENING	BASELINE & DOSING			FOLLOW-UP					
Visit	Prescreen	Screening[a]	Baseline	Day 1 Randomization (3A) & Dosing Session (3B)		Day 2	Week 1	Week 2	Week 4	Week 8	Week 12 (or Early WD)/EOS
Visit Number	N/A	1	2	3A	3B	4	5	6	7	8	9
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Administrative Procedures											
Prescreen Informed Consent	X										
Informed consent		X									
Demographics	X	X									
Eligibility assessment		X	X	X							
Medical psychiatric and medication history[d]	X	*Medical/psychiatric and medication history will be collected via interview at Screening [Visit 1] if information about the medical/psychiatric and medication history is learned during the course of the study, this will also be recorded, even if first learned after Screening [Visit 1].*									
Medication taper (if applicable)		X									
Concomitant medication & non-medicinal therapy collection	X	*Medications/non-medicinal therapies used at Baseline [Visit 2] or any time after, including those taken between visits, regardless of whether the subject is on the medication/therapy at the time of the site visit, will be recorded in the designated CRF. Medications/therapies stopped prior to Baseline [Visit 2] are recorded in medication history.*									
Randomization				X							
Clinical Procedures/Assessments											
Physical examination		X				X					X
Neuropsychiatric examination			X			X	X	X	X	X	X
Vital signs[e] (BP, heart rate, respiration rate, temperature)		X	X	X[f]	X	X	X	X	X	X	X
Weight	X[g]	X									
Height	X[g]	X									
BMI	X	X									
12-lead safety ECG		X	X			X					
Adverse event collection		*AEs are evaluated from the time informed consent is given until completion of the study and captured at each visit. Events occurring between signing of the informed consent form and dosing with study drug will be recorded on the medical history page of the eCRF. Events occurring from the time study drug is administered through EOS will be recorded on the AE page of the eCRF.*									

STUDY PERIOD	Optional Prescreen	SCREENING	BASELINE & DOSING			FOLLOW-UP					
Visit	Prescreen	Screening[a]	Baseline	Day 1 Randomization (3A) & Dosing Session (3B)		Day 2	Week 1	Week 2	Week 4	Week 8	Week 12 (or Early WD)/EOS
Visit Number	N/A	1	2	3A	3B	4	5	6	7	8	9
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Laboratory Procedures/Assessment											
Blood sample collection for biobanking (DNA)				X *If the subject gives informed consent to provide a pharmacogenomic sample, collect a sample once during the study, preferably at Day 1/Randomization [Visit 3A].*							
Blood sample collection for safety laboratory assessments		X	X			X	Opt[h]	Opt[h]	X	X	X
[redacted]		[redacted]	[redacted]			[redacted]					
Urine drug screen		X[i]	X[i]	X[i]			X[j]	X[j]	X[j]	X[j]	X[j]
Urine pregnancy test (if applicable)		X		X			X	X	X	X	X
Serum pregnancy test (if applicable)			X								
Screening and Efficacy Questionnaires											
Placebo Script Review			X						X	X	
MINI	X	X									
C-SSRS Baseline/ Screening Version		X									
C-SSRS- SLV Version			X	X	X[k]	X	X	X	X	X	X
HAM-A (central rater)		X	X				X	X	X	X	X
MADRS (central rater)		X	X				X	X	X	X	X
CGI-S		X	X			X	X	X	X	X	X
CGI-I						X	X	X	X	X	X
PGI-S		X	X			X	X	X	X	X	X
PGI-C						X	X	X	X	X	X
SDS		X	X				X	X	X	X	X
EQ-5D-5L			X				X	X	X	X	X
PSQI			X						X	X	X
ASEX			X				X	X	X	X	X
Drug Effect VAS						X					
MEQ30						X					
5D-ASC						X					
Treatment assignment / blinding question						X					

STUDY PERIOD	Optional Prescreen	SCREENING	BASELINE & DOSING			FOLLOW-UP					
Visit	Prescreen	Screening[a]	Baseline	Day 1 Randomization (3A) & Dosing Session (3B)		Day 2	Week 1	Week 2	Week 4	Week 8	Week 12 (or Early WD)/EOS
Visit Number	N/A	1	2	3A	3B	4	5	6	7	8	9
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Dosing-Related Activities[l]											
Administration of study drug					X						
Subject education / follow-up session with both DSMs			X	X		X	X	X			
Subject under observation by both DSMs					X						
Subject dosing day release from clinic/ Dosing Release Checklist					X						

5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; AE: adverse event; ASEX: Arizona Sexual Experiences Questionnaire; AUDIT: Alcohol Use Disorders Identification Test; BP: blood pressure; BMI: body mass index; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; C-SSRS (– SLV): Columbia-Suicide Severity Rating Scale (– Since Last Visit); DUDIT: Drug Use Disorders Identification Test; ECG: electrocardiogram; eCRF: electronic case report form; EOS: End of Study; ICF: informed consent form; MADRS: Montgomery-Åsberg Depression Rating Scale ; MEQ30: Mystical Experience Questionnaire; MINI: Mini-International Neuropsychiatric Interview; PGI-C: Patient Global Impression – Change; PGI-S: Patient Global Impression – Severity; PSQI: Pittsburgh Sleep Quality Index; SDS: Sheehan Disability Scale; HAM-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; THC: tetrahydrocannabinol; VAS, visual analogue scale; WD: Withdrawal

[a] Screening (Visit 1) assessments may be performed over multiple days

[b] If Baseline labs are needed, a minimum of 48 hours is required prior to Day 1 to allow for all eligibility assessment results to be reviewed to confirm subject eligibility

[c] If the Baseline occurs within 14 days of Screening, Baseline labs are not required, and Dosing Session day (Visit 3B) may occur within 24 hours of the Baseline Visit

[d] Sites should make an effort to obtain, at minimum, pharmacy records for subjects, and medical and /or psychiatric records

[e] Vital signs should be performed prior to an ECG and/or a blood draw; Screening and Baseline vital signs require sitting, lying, and standing vital signs in order to capture orthostatic vitals.

[f] On Day 1 (Visit 3A), the pre-dose vital signs (blood pressure, heart rate, respiration rate, and temperature) should be measured within 1 hour (+/- 15 mins) prior to study drug dosing. Note: Only BP and Temperature at Visit 3A will be used to confirm final eligibility against inclusion/exclusion criteria

[g] Weight and height may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site to determine eligibility

[h] Safety laboratory assessments are optional at Week 1 (Visit 5) and Week 2 (Visit 6) unless values at the prior visit were clinically significant and warrant follow up

[i] [redacted]

[j] [redacted]

[k] The Day 1/Dosing Session (Visit 3B) C-SSRS will be performed any time after 12 hours post dose and prior to the subject being released from the site

[l] Refer to section 8.6 and the Dosing Session Monitor Manual for full details of subject education and follow-up sessions with DSMs

2. INTRODUCTION

2.1. Background

Mind Medicine, Inc. is developing D-lysergic acid diethylamide (LSD) D-tartrate (MM-120) for the treatment of anxiety symptoms. MM-120 / LSD is a synthetic tryptamine belonging to the group of classic, or serotonergic, hallucinogens ("psychedelics").

There is an extensive body of literature on the nonclinical pharmacology/toxicology, clinical safety and efficacy and clinical pharmacology of LSD. LSD has previously been administered to hundreds of human subjects in recently conducted (i.e., since 2008) controlled clinical trials. These trials have demonstrated that LSD has an attractive safety profile and have provided preliminary evidence of efficacy in the target patient population when administered in controlled settings.

2.1.1. Disease Background and Unmet Need

There is a high unmet need to find new treatment options for patients with clinically significant anxiety, and it is an active area of research. Patients with anxiety disorders often experience substantial physical and emotional discomfort, functional impairment and reduced work productivity (Erickson 2009; Waghorn 2005), as well as increased rates of substance use and medical illnesses (Kariuki-Nyuthe & Stein 2015). With a 12-month prevalence rate of 18% in the United States (US), anxiety disorders are the most common psychiatric disorders, and there remains a significant need for novel treatments (Kessler 2005). Indeed, the course of anxiety disorders is often relapsing and chronic, with most patients remaining symptomatic decades after their initial diagnosis (Kessler 2001). The chronic and disabling nature of anxiety disorders is associated with substantial economic and social costs related to premature mortality, unemployment and reduced productivity (Bandelow & Michaelis 2015; Issakidis & Andrews 2004).

There are a number of medications approved to treat generalized anxiety disorder (GAD) – the target patient population for this study – but for many patients, they 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 (Gartlehner 2011). A meta-analysis of 21 placebo-controlled GAD trials from the world literature observed only modest treatment benefit from active medications: overall effect size (Cohen's d) = 0.39 (Hidalgo 2007). For adults with GAD, comparative effect sizes of the different agents were as follows: 0.5 for pregabalin, 0.45 for antihistamines, 0.42 for serotonin-norepinephrine reuptake inhibitors (SNRIs), 0.38 for benzodiazepines, 0.36 for selective serotonin reuptake inhibitors (SSRIs) and 0.17 for azapirones (buspirone). The practice of treating GAD patients with antidepressant treatments is fairly common, likely because patients with anxiety frequently have concurrent depressive symptoms. Gamma-aminobutyric acid (GABA) agonists, sedative-hypnotic drugs and antipsychotics have also been used off label for relief of insomnia or other common symptoms of anxiety disorders, but these drugs provide only symptomatic relief instead of disease modification.

2.1.2. Drug Background

LSD is a prototypical classic hallucinogen (reviewed in Nichols 2004; Passie 2008). The administration of LSD to humans was first reported in 1943 by Albert Hofmann (Hofmann 1979), after which Sandoz manufactured LSD (Delysid®) and distributed it for experimental use (Sessa 2011). In the 1950s to 1970s, LSD was initially used as an experimental tool to study psychotic-like states and model psychosis ("psychotomimetic") (Bercel 1956; Koelle 1958) and as an adjunct in "psycholytic (substance-assisted) psychotherapy". LSD became one of the best studied substances with several thousands of early scientific reports (reviewed in Hintzen & Passie 2010; Nichols 2004; Nichols 2016; Passie 2008). LSD has also been investigated for the treatment of alcoholism (Krebs & Johansen 2012), addiction (Savage 1973), anxiety associated with terminal illness (Gasser 2014; Grof 1973; Pahnke 1969), depression (Passie 2008) and different manifestations of headache (Schindler 2015; Sewell 2006).

Although regulatory restrictions implemented in the 1970s limited its distribution and led to a dearth of clinical research, the use of LSD for personal and recreational purposes continued. Among US residents, an estimated 32 million and 23 million people, respectively, reported using a hallucinogen and LSD at least once in their lifetime, based on data from a 2010 US population survey of individuals aged 12 years and older (Krebs & Johansen 2013a). Another report – based on 2015 results of repeated ongoing cross-sectional surveys of high school graduating classes since 1976 – estimated the adjusted lifetime usage of hallucinogens to range from 12-21% for younger groups (ages 21-30 years) and 26-30% for older groups (ages 35-50 years); in the same study, prevalence of LSD use was also reported for the younger age groups, which had an adjusted lifetime usage ranging from 8-10% (Johnston 2016). In Europe, the estimated prevalence for lifetime usage of LSD is lower than the US and varies by country, with most countries reporting a prevalence in the range of 1-5%, both among young adults (age 15-34 years) and all adults (age 15-64 years) (EMCDDA 2021). Thus, a significant proportion of the western society is familiar with the effects of hallucinogens, including LSD.

LSD is not associated with compulsive drug seeking (addiction), and there are relatively few medical emergencies and adverse effect (Nichols 2016). Use of LSD or psilocybin is not associated with mental health problems and may even be protective (Johansen & Krebs 2015; Krebs & Johansen 2013b). In a safe setting, no drug-related severe adverse effects have been observed after administration of LSD in healthy participants (Carhart-Harris 2015; Carhart-Harris 2016a; Dolder 2016; Gasser 2014; Schmid 2015). Beginning in 2008, the medical value of classic serotonergic hallucinogens has again been studied in several clinical trials (Baumeister 2014; Bogenschutz 2015; Davenport 2016; Gasser 2014; Gasser 2015; Grob 2011; Johnson 2014; Johnson 2017; Kupferschmidt 2014).

2.2. Study Rationale

Although there are a number of medications approved to treat anxiety disorders, for many patients, as noted in Section 2.1, anxiolytics (and antidepressants, which are sometimes prescribed off label for anxiety) may have unfavorable side effect profiles, contraindications or are ineffective. Thus, there remains a significant need for novel therapeutic approaches in treating anxiety disorders.

Classic serotonergic psychedelics such as LSD and psilocybin have shown promise in treating anxiety and depression (Carhart-Harris 2016b; Gasser 2014; Griffiths 2016; Grob 2011; Ross 2016). The potential clinical utility of LSD is complemented by a relatively safe physiologically profile that is further enhanced by the fact that a single administration may have both rapid-acting and long-lasting clinical effect.

Restrictions on LSD distribution and its subsequent illegalization led to a dearth of clinical research of LSD; however, following a four-decade hiatus, there has been a recent resurgence in clinical research studies of LSD. In the period since 2008, 12 clinical trials enrolling more than 200 subjects have been conducted investigating the safety, pharmacodynamics, pharmacokinetics and clinical activity of LSD. Evidence from both legacy and modern investigator-initiated studies support the safe use of LSD in controlled clinical settings, and preliminary evidence suggests a potential for clinical benefit in a variety of target indications and patient populations, including anxiety disorders. Robust clinical trial data are needed to confirm the clinical utility of LSD in treating anxiety disorders.

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. This randomized, double-blind, placebo-controlled study is designed to evaluate the safety, tolerability and efficacy of 4 doses of MM-120 compared to placebo in subjects with GAD. Specifically, it will examine the impact of single-dose treatment with MM-120 on anxiety symptoms as well as on other measures of function and quality of life.

2.2.1. Assessment of Efficacy in MMED008

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 (Ansseau 1996; Constantin 2020; Greiner 2020; Stein 2015; Stein 2018). 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 (Alaka 2014; Goodman 2005; Hartford 2007; Rynn 2008). 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.

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).

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.

2.2.2. Study Population Considerations

Eligibility for this study is based in part on a minimum HAM-A Total Score of 20. This is to target enrollment to a population of subjects who have significant anxiety that is sensitive to measurement by the HAM-A. A HAM-A Total Score of 17 and above has been consistently used as a cut-off for inclusion in clinical trials for GAD medications (Allgulander 2004; Lenze 2005; Llorca 2002; Rickels 2003; Sheehan & Sheehan 2008; Wan 2006). Additionally, to ensure that only subjects with relatively stable anxiety severity are enrolled, the HAM-A is completed at Screening (Visit 1) and Baseline (Visit 2) and the Total Score from both assessments must be at least 20 points; this exclusion criterion will help prevent enrolling subjects with transient anxiety related to daily stressors. These measures together will ensure that the study population consists of subjects with clinically significant anxiety that is sensitive to measurement by the HAM-A.

The sensitivity of the HAM-A to changes in the target patient population and disorder is also supported by results from past studies of other investigational drugs of the psychedelic drug class. In particular, Griffiths and colleagues found significant reductions in HAM-A scores following administration of psilocybin in cancer patients with distress (diagnoses included adjustment disorders, MDD, GAD and others) (Griffiths 2016). Following a single high dose of psilocybin, HAM-A scores in this study decreased from 25.73 (SD: 1.11) to 8.48 (1.16) at approximately 5 weeks post-dose, a reduction of approximately 67%.

The primary endpoint for the current study is change in HAM-A Total Score from Baseline to Week 4. Preliminary evidence suggests that LSD (along with other psychedelic therapies such as psilocybin) are rapid-acting, and that acute responses to treatment are predictive of intermediate and longer-term outcomes (Gasser 2014; Griffiths 2016; Ross 2016). To assess the durability of effect, the key secondary endpoint of change in HAM-A Total Score from Baseline to Week 8 will be used.

Bonson et al. found that chronic administration of antidepressants – including serotonergic antidepressants, monoamine oxidase inhibitors (MAOIs) and lithium – substantially attenuated the subjective effects of self-administered LSD, as evaluated using a standardized questionnaire (Bonson 1996a; Bonson & Murphy 1996b). Thus, in this study, subjects will be 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.

2.2.3. Summary

The use of LSD for anxiety in prior studies has yielded encouraging safety, tolerability and efficacious results. However, additional data from randomized, controlled clinical trials are needed. 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. The current study is designed to provide new data on the use of LSD in the treatment of anxiety symptoms in subjects with GAD.

2.3. Dose Rationale

Based on literature review, LSD has been safely administered in over 1000 subjects in studies with various levels of control and at doses up to 800 µg, including more than 200 subjects across 12 trials conducted since 2008. To date, however, full interrogation of the dose-response curve for LSD has not been established, and no prior dose-finding study has been completed for MM-120. The doses of 25, 50, 100 and 200 µg MM-120 (freebase-equivalent) used in the current study have been selected based on preliminary evidence of safety and clinical effect from prior, published studies of LSD. 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" (Holze 2021a), but doses within this range (and above) have been demonstrated to be safe.

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 (Bershad 2019; Holze 2021b; Hutten 2020) 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) (Holze, 2020; Holze 2021a; Passie 2008). 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).

The 4 individual dose levels of MM-120 in the current study have been selected to assess both: 1) the dose-response relationship over a wide dose range that has been previously shown to be safe in clinical trials; and 2) 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 3.

Table 3: Rationale for Selected MM-120 Doses

Dose of MM-120 (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 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"

Thus, the 4 doses of MM-120 administered in the current study are expected to have a dose-dependent response. Based on historical data in other patient populations, higher doses are expected to be associated with perceptual alterations including visual and auditory disturbances

(including hallucinations), emotional volatility and a dose-dependent autonomic stimulation (transient tachycardia, hypertension and pupillary dilation). The autonomic effects of LSD are typically mild and transient and rarely require intervention. The Sponsor concluded that no further dose increase beyond 200 µg (freebase-equivalent) would be required for predicted changes on HAM-A.

2.4. Benefit/Risk Assessment

Clinical data on the use of LSD in patients with anxiety disorder are limited. This is the first trial of oral MM-120, currently in development, in subjects with GAD, and thus, its safety profile for this patient population is unknown. Although to date there are no completed clinical trials with oral MM-120, expected safety signals of perceptual and autonomic effects may be detected and are considered as potential risks for oral MM-120 use.

The pharmacologic and toxicologic effects of LSD in various animal species has been extensively studied; published reports support the conclusion that LSD has a relatively benign safety profile (refer to the MM-120 Investigator's Brochure for details of nonclinical study findings). Monkeys (*M. mulatta*) have been injected with intravenous (IV) doses as high as 1 mg/kg without any lasting somatic effects (Evarts 1956). Although dose at first signs of toxicity is difficult to determine from the published literature, signs of toxicity described were at high mg/kg exposures in animal species whereas the current study uses µg doses (200 µg freebase-equivalent is the highest dose evaluated in the current study). The clinical relevance of these findings from the animal literature is not known.

Available human findings from historical published literature suggest that MM-120 or its active metabolites are not likely to cause clinically significant perceptual or physical adverse effects in a controlled clinical trial setting. LSD has been safely administered in controlled clinical trials to over 1000 persons aged 18-75 years, in doses ranging 5-800 µg. The most common adverse effects of LSD administration include visual and auditory disturbances (including hallucinations), emotional volatility and autonomic stimulation (transient tachycardia, hypertension and pupillary dilation). The autonomic effects of LSD are typically mild and transient and rarely require intervention. Physiological adverse reactions to LSD have been reported in common media in instances of illicit use outside of a controlled clinical setting; however, in a controlled clinical setting, adequate screening procedures, patient monitoring and psychological intervention (when warranted) have resulted in a low incidence of physiological AEs. Rare instances of serious adverse reactions (psychosis and seizure) have been reportedly precipitated by use of LSD in a clinical setting, but in these cases, the subjects had one or more pre-existing diagnoses or risk factors.

LSD is not associated with dependence. Hallucinogens are not self-administered by animals, and there is no human LSD dependence syndrome (Passie 2008). Patients with current substance use or a history [redacted] of other illicit substances are not included in the study.

Most available clinical research data on the use of LSD for relief of anxiety symptoms has been in the context of anxiety associated with life-threatening illness (Gasser 2014; Grof 1973; Pahnke 1969). However, findings from these studies have showed positive trends in reducing

anxiety, including the observation in one study of sustained benefits at a 12-month follow-up after finishing LSD psychotherapy (Gasser 2015). Subjects with GAD participating in this study may benefit from improvements to their well-being and functional ability.

Multiple procedures have been included in this study to enhance subject safety. Subjects will undergo repeated eligibility assessments at Screening (Visit 1), Baseline (Visit 2), and prior to dosing on Day 1 (Visit 3A) to ensure the subject is fit to receive study drug. Additionally, based on the pharmacological profile of LSD, which includes alterations of perception and consciousness and the potential for development of acute anxiety, subjects will be continuously monitored during the Dosing Session for psychological and physiological well-being. Two Dosing Session Monitors will support the subject, and subjects will be under their observation at all times during the Dosing Session (either both in the session room, or one in the session room and one via live remote monitoring on site in a separate room). Additionally, based on the known autonomic effects of MM-120, serial measurement of vital signs (heart rate and blood pressure) will be collected throughout the Dosing Session. A detailed Dosing Session Monitor Manual and Participant Education Session Manual has been developed to provide subjects across clinical sites with consistent education about what to expect and consistent, continual monitoring during the Dosing Session.

Overall, the benefit-risk profile of LSD at doses up to 200 µg (freebase-equivalent) is favorable and supports development based on its prior safe clinical use in over 1000 subjects, well-characterized pharmacokinetics, pharmacodynamics and manageable transient physiological and psychological effects. Inclusion of the 4 planned doses in this Phase 2 dose-finding study (see Section 2.3) will enable optimal dose selection for Phase 3 clinical trials, aid in interpretation of study results in the context of potential functional unblinding and will enable further characterization of the mechanism of action of MM-120 (i.e., whether psychedelic effects are necessary for clinical benefit).

Refer to the MM-120 Investigator's Brochure for additional risk-benefit information.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS/OUTCOME MEASURES
Primary	
• To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 4	• Change in HAM-A Total Score from Baseline to Week 4
Key Secondary	
• To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 8	• Change in HAM-A Total Score from Baseline to Week 8
Secondary	
• To determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to End of Study	• Change in HAM-A Total Score from Baseline to End of Study
• To determine whether MM-120 (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:	• Change from Baseline to Week 1, Week 2 (where applicable), Week 4, Week 8, and End of Study in score for the following measures:
o Depressive symptoms	o MADRS
o Anxiety symptoms	o CGI-S o CGI-I o PGI-S o PGI-C
o Functional disability	o SDS
o Quality of life	o EQ-5D-5L
o Sleep	o PSQI
o Sexual function	o ASEX

OBJECTIVES	ENDPOINTS/OUTCOME MEASURES
Safety	
• To assess the safety and tolerability of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) after oral administration in subjects with anxiety symptoms	• Adverse events • Vital signs (heart rate, blood pressure, respiration rate, temperature) • 12-lead safety ECG • Physical examination • C-SSRS • Safety laboratory evaluation
Exploratory	
• To assess response and remission across the 4 doses of MM-120 (25, 50, 100, or 200 µg freebase-equivalent) as measured by the change in HAM-A from Baseline to End of Study	• HAM-A response (defined as ≥50% reduction in HAM-A Total Score) from Baseline to Weeks 1, 2, 4, 8, and End of Study. • HAM-A remission (defined as HAM-A Total Score of ≤7) at Weeks 1, 2, 4, 8, and End of Study
• To explore dose response on drug effects, altered perception and mystical experience	• Score at Day 2 on the following questionnaires: o Drug Effect VAS o MEQ30 o 5D-ASC
• To explore the effect of MM-120 on direct and indirect health-care resource utilization (HCRU) and associated costs	• For later pharmacoeconomic analysis, the use of healthcare resources [redacted]
• To explore whether genetic polymorphisms are related to pharmacodynamics	• Pharmacogenomic sample
• To assess blind integrity and to examine whether guess rates are associated with outcomes such as AEs or mood/anxiety symptoms	• Score at Day 2 on Treatment Assignment/Blinding Question

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding clinical study that will assess the effect of 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) in comparison to placebo on anxiety symptoms in subjects diagnosed with GAD.

The study will enroll approximately 180 male and female subjects 18 years to < 75 years of age at Screening who meet DSM-5 criteria for GAD and have a minimum HAM-A Total Score of 20. Potential subjects who have contraindicated medical or psychiatric conditions or who are 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 will be excluded from the study. Subjects on contraindicated concomitant medications, supplements or other therapeutics at Screening (Visit 1) will undergo 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 will be overseen by the study site designated physician based on acceptable local practice standards.

Prescreening of potential study subjects to determine initial eligibility is a common strategy in the recruitment process. Sites will be provided with an IRB approved prescreening template which must be IRB approved for subjects to provide consent. The Prescreen process will determine if they are excluded based on the eligibility criteria before proceeding further. The Prescreening option is being offered to reduce unnecessary burdens on sites and potential study subjects and to further assess the subject's eligibility.

Potential study subjects who provide informed consent beyond the Prescreen stage will have eligibility evaluated/confirmed at 3 visits: 1) Screening (Visit 1); 2) Baseline (Visit 2), and 3) Day 1/Randomization (Visit 3A). Randomization will occur following the final assessment of eligibility on Day 1/Randomization (Visit 3A). Eligible subjects will be randomized in a 1:1:1:1:1 ratio to receive a single dose of either investigational drug (25, 50, 100 or 200 µg MM-120 freebase-equivalent) or placebo in a controlled clinical setting, which will be administered during the Dosing Session (Visit 3B) on Day 1.

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

Throughout the Dosing Session (Visit 3B) on Day 1, subjects will be supported by a team of appropriately trained and qualified Dosing Session Monitors. There will be two qualified monitors monitoring the subject at all times, and a site-designated licensed physician must be available or on call and be able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency; events requiring intervention should be discussed with the Sponsor as soon as the situation permits, but implementation of the intervention should not be delayed. The Participant Education Session Manual for this study is included in the Dosing Session Monitor Manual, which provides 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 be met in order to release the subject from the clinic at the end of the Dosing Session (Visit 3B).

At least one of the Dosing Session Monitors will be identified and qualified to serve as a 'lead monitor.' The lead monitor must be a licensed healthcare provider with graduate-level professional training and clinical experience. The lead monitor must be actively licensed to practice independently in the state of the study site location. Lead monitor acceptable professional credentials are as follows: Clinical or counseling psychologist (PhD or PsyD); Psychiatrist or other physician (MD or DO); Master Level Clinician, such as Licensed Clinical Social Worker (LCSW), Licensed Clinical Professional Counselor (LCPC), Licensed Marriage and Family Therapist (LMFT), or local state equivalent; Advanced Nurse Practitioner (NP/APRN) such as a Psychiatric Nurse Practitioner or local state equivalent.

The secondary monitor must have a bachelor's degree and at least one year of clinical experience in a mental health care setting. One of the DSMs must be appropriately trained to monitor vital signs and administer the C-SSRS. A site-designated licensed physician with prescribing rights or a qualified designee may serve as the backup to either DSM if short breaks are needed. This licensed physician must meet the criteria to be a lead monitor if they plan to step in as back up dosing session monitor to alleviate the lead or secondary monitor.

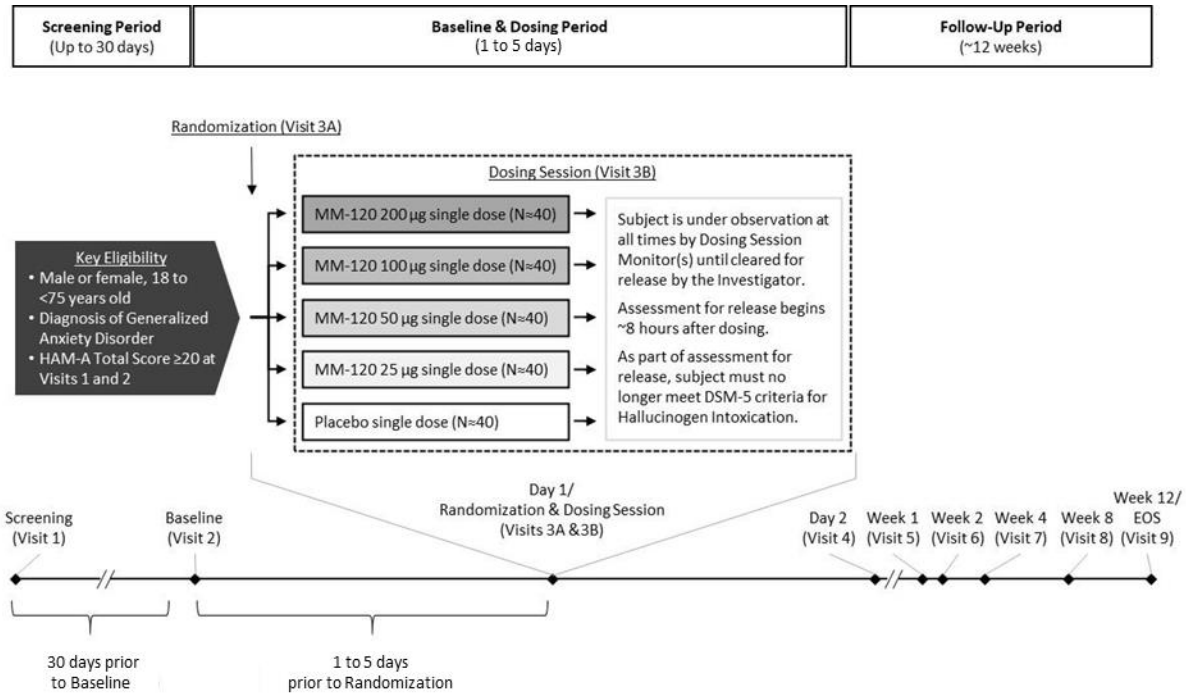
After Day 1/Randomization & Dosing Session (Visits 3A & 3B), subjects will have scheduled visits on Day 2 (Visit 4), Week 1 (Visit 5), Week 2 (Visit 6), Week 4 (Visit 7), Week 8 (Visit 8) and Week 12 (Visit 9). In the event that a subject withdraws early from the study (i.e., prior to Week 12), they should return to the clinic to complete an Early Withdrawal visit (same assessments/procedures as Week 12 [Visit 9]) or if the subject is at the site at the time of early withdrawal, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation.

At Week 4 (the study's primary endpoint), the efficacy of MM-120 in treating anxiety symptoms will be evaluated as the change from Baseline in the HAM-A Total Score. HAM-A and several additional questionnaires will be administered throughout the study, as outlined in the Schedule of Activities (Table 2), to further evaluate efficacy and/or the subjects' experiences taking study drug.

Subjects will be 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.

Figure 1 presents the design schema, and the study procedures/assessments at each visit are outlined in the Schedule of Activities (Table 2).

Figure 1: MMED008 Study Schematic



EOS = End of Study; HAM-A = The Hamilton Anxiety Rating Scale
Note: Doses of MM-120 are freebase-equivalent.

4.2. Number of Subjects

The target sample size for this study is approximately 180 subjects.

4.3. End of Study Definition

End of Study is defined as the date when the last subject has either completed the last study visit, has discontinued from the study, or is lost to follow-up (i.e., the site/Investigator is unable to contact the subject).

5. STUDY POPULATION

5.1. Eligibility

5.1.1. Inclusion Criteria

An individual will be eligible for participation in this study only if all the following inclusion criteria are met:

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/kg^2
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

5.1.2. Exclusion Criteria

An individual will be excluded from participation in this study if any of the following exclusion criteria apply:

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, as defined in Appendix 1, 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: See Appendix 1 for definitions of WOCBP and highly effective methods of contraception and for information about unacceptable methods of contraception.
   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 disorder 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. [redacted]
12. Greater than [redacted] of psychedelics use in the [redacted], including microdosing. Any instance of psychedelic use including microdosing in the [redacted] (including use as part of a clinical trial).
13. History of illicit substance use in the [redacted]
14. History of ketamine use including: ketamine therapy within the [redacted] before screening (including as part of a clinical trial); illicit use of ketamine [redacted]; or use of ketamine for treatment of an excluded condition (see exclusion criteria #4, #5, #6)
15. [redacted]

16. Current use at Baseline (Visit 2) or Day 1/Randomization (Visit 3A) of any prescribed psychotropic medication
    Note: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use.
17. Unwillingness or inability to discontinue prohibited concomitant medications, supplements or other therapeutics (prescription or over-the-counter)
    Note: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use; see Section 8.1.6 for information on medication tapering.
18. Any form of medicinal therapy [redacted] 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: See Section 6.10 for details of prohibited concomitant medications, supplements and other therapeutics and allowable conditions of use. 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 [redacted] 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 the 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 supine 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 m^2 at Screening (Visit 1), based on the Cockroft-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. [redacted]

5.2. Lifestyle Restrictions

5.2.1. Reproductive Concerns

There are mixed results from preclinical studies evaluating reproductive toxicity, chromosomal aberration and mutagenic studies (refer to the MM-120 Investigator's Brochure for details). Thus, to participate in this study, women of childbearing potential (WOCBP) (i.e., physiologically capable of becoming pregnant) must agree to use a highly effective method of contraception for the duration of the study, and non-sterilized men who are sexually active with a WOCBP must agree to use barrier contraception (e.g., condom with or without spermicidal cream or jelly). Subjects who do not agree to these conditions are not eligible to participate in the study.

Appendix 1 provides definitions of WOCBP, and highly effective methods of contraception as well as information about unacceptable methods of contraception. Subjects will be provided with information on methods of contraception as part of the informed consent process and by signing the consent form confirm that they understand the requirements for avoidance of pregnancy in the subject or the subject's sexual partner during the course of the study.

5.2.1.1. Additional Information for Female Subjects

WOCBP may participate in the study only if they have a negative urine pregnancy test result at Screening [Visit 1] and Day 1/Randomization [Visit 3A]), and a non-positive serum pregnancy test on Baseline [Visit 2], (see Section 8.3.4).

Subjects who are planning to donate eggs during the study period are excluded. If a subject is capable of producing egg and withdraws early from the study, they should be advised not to

donate eggs for at least 30 days after they received the single dose of study drug at Day 1/Dosing Session (Visit 3B).

Subjects who are currently or planning to become pregnant or breastfeed during the study period are excluded. If a subject who is physiological capable of becoming pregnant withdraws early from the study, they should be advised to continue use of a highly effective method of birth control for at least 30 days after they received the single dose of study drug at Day 1/Dosing Session (Visit 3B).

Because this is a single-dose study, if a subject becomes pregnant after Day 1/Dosing Session (Visit 3B), they are not required to withdraw from the study. The subject will be monitored for the outcome of the pregnancy, and reporting will occur as described in Section 9.10.

5.2.1.2. Additional Information for Male Subjects

Male subjects defined as subjects capable of producing sperm should be encouraged to advise any person of childbearing potential who are their sexual partners to use a highly effective method of contraception in addition to the subject's use of barrier contraception. A female condom and male condom should not be used together.

Subjects who are planning to donate sperm during the study period are excluded. If a subject is capable of producing sperm and withdraws early from the study, they should be advised not to donate sperm for at least 30 days after they received the single dose of study drug at Day 1/Dosing Session (Visit 3B). Additionally, male subjects who withdrawal early from the study should continue use of barrier contraception for a minimum of 30 days.

5.2.2. Nicotine Use

As changes in the consumption of nicotine may impact anxiety symptoms and/or mood, subjects should avoid starting, stopping or altering the use of these products from the time of providing informed consent until the End of Study. Due to the length of Day 1/Dosing Session, subjects are not permitted to smoke cigarettes/vape during the dosing session. Due to the possibility of nicotine withdrawal symptoms, subjects who are current users of nicotine products will be permitted to use nicotine replacement gum or patches. The dose and frequency of the nicotine replacement products will be determined by the subject's current level of dependence in accordance with the product's prescribing information.

5.2.3. Non-Medicinal Therapies

Any form of non-medicinal therapy should be stable 3 months prior to screening with no plans to start, stop or alter the use of non-medicinal therapies/activities (e.g., psychotherapy, acupuncture, hypnosis, or other similar therapy) from the time of providing informed consent until End of Study.

Non-medicinal therapies will be recorded in the eCRF, beginning at the time of ICF signing until End of Study (Week 12 [Visit 9] or Early Withdrawal).

5.3. Screen Failures

Screen failures are subjects who consent to participate in the clinical study but are never randomized.

Subjects excluded during screening should promptly be reported as a screen failure in the electronic data capture (EDC) system.

Subjects excluded during screening may be rescreened once in consultation with the Sponsor's Medical Monitor, when the reason for meeting an exclusion is likely to resolve (e.g., the subject had an exclusionary acute infection that is resolving, transient lab abnormalities, or a medication taper is taking longer than 30 days). Subjects who do not meet criteria for inclusion at screening or baseline on the HAM-A score are not permitted to rescreen. If a subject is rescreened, the subject must be reconsented to participate in the study, and all screening procedures should be repeated (unless the Investigator and Sponsor's Medical Monitor agree with re-using one or more original screening results).

6. STUDY DRUG AND CONCOMITANT THERAPY

6.1. Description of Study Drugs

For the purposes of this protocol, the term "investigational drug" refers to MM-120 (25, 50, 100 or 200 µg freebase-equivalent); the terms "study treatment" and "study drug" are interchangeable and refer to either MM-120 or matching placebo.

All study drugs will be supplied as a solid dosage form (capsules). Table 4 provides a description of the study drugs.

Table 4: MMED008 Study Drugs

Study Drug	Total Dose[a] (Freebase-equivalent)	Frequency; Route of Administration; Product Description	Use
MM-120	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

[a] Each subject will receive 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.

6.2. Directions for Administration of Study Drug

Study drug (MM-120 25, 50, 100 or 200 µg freebase-equivalent or placebo) will be administered under blinded conditions. To maintain the blind, all subjects will receive a total of 8 capsules, which will be a combination of active capsules each containing 25 µg MM-120 freebase-equivalent and/or placebo capsules, depending on the subject's randomized dose (see Table 4). All 8 capsules will be taken together as the subject's single dose of study drug. Administration of study drug will occur only during Day 1/Dosing Session (Visit 3B), as specified in the Schedule of Activities (Table 2).

Subjects will take the 8 study drug capsules orally with ad libitum water. Subjects will only have 15 minutes to swallow all 8 capsules. Administration of study drug will be witnessed by the Investigator and/or Dosing Session Monitor(s), and the subject will subsequently be monitored at all times until released from the clinic by the study site designated physician, as detailed in the Dosing Session Monitor Manual.

6.3. Randomization

Once final eligibility is confirmed at Day 1/Randomization (Visit 3A), subjects will be randomized centrally. The assigned randomization number will be used to identify the study drug to be dispensed to the subject and will be entered into the EDC system.

There are 5 treatment groups to which subjects will be randomized in a 1:1:1:1:1 ratio:

- Arm A: 25 µg (freebase-equivalent) of MM-120 (n ≈ 36)
- Arm B: 50 µg (freebase-equivalent) of MM-120 (n ≈ 36)
- Arm C: 100 µg (freebase-equivalent) of MM-120 (n ≈ 36)
- Arm D: 200 µg (freebase-equivalent) of MM-120 (n ≈ 36)
- Arm E: Placebo (n ≈ 36).

6.4. Blinding

A double-blind/masking technique will be used. All doses of MM-120 and placebo will be packaged identically so that treatment blind/masking is maintained. The subject, the Investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments.

At the end of the study and after medical/scientific review has been performed and data have been declared final and complete, the official, final database will be frozen and unblinded. The Sponsor will be granted access to the frozen and unblinded database in order to analyze the data.

6.4.1. Unblinding

In the event of a medical emergency where knowledge of subject's study drug assignment is necessary per the medical judgment of the Investigator, the Investigator may break the blind using the randomization system. If possible, the Sponsor's Medical Monitor should be notified before the Investigator breaks the blind to discuss the case. If not possible, the Sponsor's Medical Monitor should be notified as soon as possible after breaking a treatment code. The unblinding must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding.

Only the Investigator or delegate should be unblinded to the subject's code. Site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

Additionally, the Sponsor's delegate may unblind the treatment for an individual subject's serious adverse event (SAE) if needed to fulfill expedited regulatory reporting requirements, or the Safety Review Committee (SRC) may have access to the treatment code, if needed.

6.5. Dose Modification

This is a single-dose study. No dose modifications by the Investigator are permitted.

6.6. Encapsulation, Packaging and Labeling

Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed.

6.7. Handling/Storage/Accountability

The process for each site to abide by the security controls detailed by the Drug Enforcement Agency (DEA) surrounding Schedule I drugs is described in the DEA Site Security Agreement. The Investigator is responsible for ensuring compliance at the site with all procedures outlined in the DEA Site Security Agreement.

Additionally, details of drug handling, storage and accountability will be included in the Pharmacy Manual, which will provide information on tamper-proof dispensing, the maximum time period allowed between removal of drug from secured storage until dosing, tracking, control and return via reverse distributor, and prevention of unauthorized access.

Study drug should be stored in a secure (recommended double-locked and bolted to the floor/wall), limited-access location. Sites will ensure proper perimeter and internal physical security is in place to prevent any diversion or theft of study drugs.

At any time from the site's receipt of study drug until the final collection of study data, drug accountability discrepancies will be monitored as follows:

- The site will conduct drug accountability by site delegated team member and readily retrievable.
- Any time the site identifies a discrepancy or possible diversion, the Sponsor must be notified promptly. For any discrepancy that triggers a drug accountability check, the Investigator or designee must resolve it promptly and will complete the eCRF page and ensure state, federal and ethics committee reporting is accomplished. The triggering drug accountability discrepancies are as follows:
  - Compliance issues where 1 or more subjects' masked supplies are used more than the expected use, according to the drug accountability calculations
  - Missing masked supply capsule(s)
  - Evidence of tampering

The Investigator is required to indicate the level of certainty of the classification and enter this into the subject's eCRF for the trial. The Sponsor or their designee will review and confirm classified triggered cases and detail conclusions and recommendations (see Section 9.9 on Special Situations).

The Investigator is responsible for ensuring accurate records are kept of the study drug received from the Sponsor or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. Receipt and dispensing of study medication must be recorded by an authorized person at the study site.

Study drug may not be used for any purpose other than that stated in the protocol. DEA storage and dispensing procedures must be strictly followed to prevent the illegal distribution and/or abuse of study drug by subjects or site staff (i.e., diversion). In addition, study subjects must be administered study drug under the supervision of the study drug dispenser and dosing session monitors.

Each site will have a practitioner who is a Schedule I license holder.

6.8. Study Drug Compliance

All subjects will be dosed at the site and will receive study drug directly from the Investigator or designee under medical supervision; the study drug administration will be witnessed by the Investigator and/or Dosing Session Monitor(s). The date and time of study drug administration at the site will be recorded in the source documents and the eCRF.

The randomized study drug and study subject identification will be confirmed at the time of administration by a member of the study site staff other than the person administering the study drug. The study site personnel administering the dose will examine the subject's mouth and hands to ensure that the study drug was ingested.

6.9. Study Drug Overdose

Refer to Section 9.5 for the definition of overdose and overdose management and refer to Section 9.9 for information on overdose reporting.

6.10. Concomitant Therapies

All medications, therapies and supplements taken by the subject during the course of the study will be recorded. Upon entry into the study, subjects will be instructed to report the possible need for any prescription or nonprescription medications, therapies and supplements immediately (and before use) to the Investigator.

Subjects should remain on a stable regimen of all allowable medications from Baseline (Visit 2) until End of Study and will be excluded from the study if they plan to initiate, stop, or alter concomitant medication use during this time.

Medications and supplements to treat anxiety, depression or other mood disorders will be tapered prior to Baseline (Visit 2) (see Section 8.1.6 for information on medication tapering). As subject safety is paramount, any treatments considered necessary for the subject's welfare may be given during the study at the discretion of the Investigator. If the permissibility of the drug treatment is questionable, the Sponsor's Medical Monitor must be consulted.

6.10.1. Prohibited Medications, Supplements and Therapeutics

The use of medications, supplements and other therapeutics (over-the-counter or prescribed) for treating anxiety, depression or mood disorders are prohibited from Baseline (Visit 2) until End of Study (except if needed during Day 1/Dosing Session [Visit 3B], as noted in Table 5. Additionally, the use of other substances, supplements, etc. that may confound the results of the study are prohibited from Baseline (Visit 2) until End of Study (e.g., cannabis, cannabidiol [CBD], ginkgo biloba).

Subjects must also avoid starting, stopping or altering non-medicinal therapies from the time of providing informed consent until End of Study, as described in Section 5.2.3.

Any prohibited substance(s) being taken at the time of Screening (Visit 1) should be tapered prior to at Baseline (Visit 2), if safe for the subject, in the opinion of the Investigator; tapering

will be done with oversight from the study site designated physician and in accordance with information provided in Section 8.1.6.

Table 5 provides a listing of specific restrictions for concomitant therapy use during the course of this study, with any necessary washout periods or allowable conditions described. This table provides examples; however, it is not a comprehensive list of all restricted medications, supplements and other therapeutics. Consult the Sponsor's Medical Monitor or designee if there is any uncertainty regarding a subject's use of a particular drug, drug class, supplement or other therapeutic.

Subjects on prohibited medications, supplements or other therapeutics at the time of Screening (Visit 1) may taper off that substance (see Section 8.1.6) and participate in the study if the required washout conditions have been met. For prescribed medications to treat anxiety, depression or other mood disorders, the medication taper will be overseen by the study site designated physician based on acceptable local practice standards.

The final decision to continue or discontinue any medications/supplements/therapeutics that the subject is taking rests with the subject, the study site designated physician and/or the subject's primary care provider. However, the decision to have the subject receive study drug requires the mutual agreement of the Investigator, the Sponsor and the subject.

Table 5: Listing of Prohibited Medications, Supplements and Other Therapies

Drug Class or Drug Name	Washout Conditions/ Prohibition Period[a]	Allowable Conditions
Benzodiazepines	Last dose must have been taken at least 5 half-lives prior to Day 1/Randomization (Visit 3A)	To treat anxiety during Day 1/Dosing Session (Visit 3B), at Investigator's discretion[b]
Lithium	Last dose must have been taken at least 7 days prior to Day 1/Randomization (Visit 3A)	None
Monoamine oxidase inhibitors (MAOIs)[c]	Last dose must have been taken at least 3 weeks prior to Day 1/Randomization (Visit 3A)	None
Antipsychotics – traditional	Last dose must have been taken at least 5 half-lives prior to Day 1/Randomization (Visit 3A)	None
Antipsychotics – atypical		
Atypical agents (e.g., bupropion, mirtazapine)		
Barbiturates		
Selective serotonin reuptake inhibitors (SSRIs). NOTE: fluoxetine washout is 35 days		
Serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Serotonin–norepinephrine–dopamine reuptake inhibitors (SNDRIs)		
Serotonin modulators (e.g., vortioxetine, trazodone)		
Tricyclic antidepressants (TCAs)		
Stimulant (e.g., methylphenidate hydrochloride)		
Cannabis[d]	Prohibited from Baseline (Visit 2) through End of Study	None
Other medications, supplements, or therapeutics that affect serotonergic function (e.g., efavirenz, Kava, ginkgo biloba, St. John's Wort, 5-hydroxytryptophan [5-HTP], ayahuasca, dimethyltryptamine [DMT])	Last dose must have been taken at least 5 half-lives prior to Day 1/Randomization (Visit 3A)	None

Note: This table is not a comprehensive list of all restricted medications or supplements. Consult the Sponsor's Medical Monitor or designee with any questions about specific medications, supplements or therapeutics.

[a] Subjects on prohibited medications, supplements or other therapeutics at the time of Screening may taper off that substance(s) prior to Baseline (Visit 2) (see Section 8.1.6) and will be eligible to participate in the study if the required washout conditions have been met. Investigator must consider the half-life of active metabolites.

[b] Benzodiazepines should only be offered and administered if non-pharmacological interventions (e.g., reassurance, verbal communication) do not adequately address severe anxiety during the Dosing Session.

[c] Although the half-life of MAOIs is typically 1.5-4 hours (eliminated quickly), the irreversible inhibition of monoamine oxidase may persist for 2-3 weeks due to the requirement for *de novo* synthesis of new enzyme, which is a relatively slow process. Therefore, washout for any MAOI should be conservatively 3 weeks.

[d] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.10.3. Permitted Medications, Supplements and Therapeutics

Consult the Sponsor's Medical Monitor or designee if there is any uncertainty regarding a subject's use of a particular drug, drug class, supplement or other therapeutic.

6.11. Treatment after the End of the Study

Subjects will not receive any additional treatment with study drug from the Sponsor after completing the study. The Investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's mental health and physical health. Sites must refer subjects for ongoing psychiatric care at the end of the study.

7. WITHDRAWAL/DISCONTINUATION

7.1. Discontinuation of Study Drug

This is a single-dose study, and thus, discontinuation of study drug is not applicable.

7.2. Early Withdrawal from the Study

Subjects may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the Investigator should any untoward effect occur. A subject may be withdrawn by the Investigator or the Sponsor if enrollment into the study is inappropriate, the protocol is violated or for administrative and/or other safety reasons. The subject may be discontinued from further study participation after discussion between the Investigator and the Sponsor's Medical Monitor (or designee) if the subject requires therapy with any excluded medication (see Section 6.10.1). Every effort should be made to establish and document the possible reason(s) for withdrawal.

A subject must be discontinued from the study for any of the following reasons:

- The subject withdraws consent.
- The subject has a medical condition or personal circumstance that precludes the subject from attending future study visits, does not allow the subject to adhere to the requirements of the protocol or, in the opinion of the Investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial.

When a subject discontinues/withdraws prior to study completion (i.e., prior to Week 12 [Visit 9]), he/she should return to the clinic to complete an Early Withdrawal visit (same assessments/procedures as Week 12 [Visit 9]) or if the subject is at the site at the time of early withdrawal, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The Sponsor's Medical Monitor or designee should be notified within 24 hours if the withdrawal is due to an SAE and within 7 days if the withdrawal is due to another reason.

Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.

Once a subject is discontinued, the subject shall not be allowed to enroll again.

As this is a single-dose study, if a subject becomes pregnant after Day 1/Dosing Session (Visit 3B), they are not required to withdraw from the study. The subject will be monitored for the pregnancy outcome, and reporting will occur as described in Section 9.10.

Sites must refer subjects withdrawn early for ongoing psychiatric care.

Lost to Follow Up

Should a subject fail to attend a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the

subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 documented telephone calls and, if necessary, a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up". Efforts to establish the possible reason for discontinuation should be documented.

7.3. Early Study Termination

The study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study overall or at a particular study site may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, due to procedure-related problems or if the number of discontinuations for administrative reasons is too high. Sites must refer subjects for ongoing psychiatric care if the study is terminated early.

8. STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Activities (Table 2) summarizes the study assessments/procedures to be performed at each visit. Individual assessments and procedures are described below.

It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., testing for human immunodeficiency virus [HIV], hepatitis C virus [HCV], etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Sites may begin using the optional Prescreen assessments described within this protocol upon all regulatory approvals and Part 1 site activation.

Changes that may be implemented, if needed, due to the coronavirus disease 2019 (COVID-19) pandemic are described in Section 9.8.

8.1. Administrative Procedures

8.1.1. Informed Consent

For this study, the subject must be cognitively able to understand the requirements of the study and provide the informed consent to participate in the study; use of a legally authorized representative to provide consent to participate is not allowed.

Informed consent forms (ICFs), any subsequently revised written ICFs, and any written information provided to the subject must receive Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) approval in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised main ICF or addendum to the original ICF that captures the subject's dated signature.

The ICFs will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.1. Prescreen Informed Consent (Optional)

Informed consent must be obtained from each potential subject prior to the collection of any information about them during the Prescreen process. Prescreen consent may be obtained via a signed consent form or verbal consent over the phone per the standard practice of the individual site.

8.1.1.2. Main Informed Consent

Documented consent must be obtained from each potential subject prior to participating in study procedures. The subject will be given sufficient time to read the ICF(s) and the opportunity to ask questions. Consent must be documented by the subject's dated signature on

the ICF(s) along with the dated signature of the person conducting the consent discussion. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IRB.

A copy of the signed and dated ICF(s) should be given to the subject before participation in the study.

Subjects will be asked to inform their care provider(s) that they are considering taking part in the study to ensure that the subject's care providers are able to appropriately monitor the subject during the study including during any required tapering of prohibited concomitant medications.

8.1.1.3. Real World Evidence

At the beginning of the study participants will be invited to opt into a service which can link existing health data with the participant to enrich data collected in the study. In order to link traditional study data to Real World Data (RWD), a common, universal ID (herein named a "token") that is unique to each study subject, persistent, and also available in real-world datasets will be used. A token is a universal, de-identified key that can be used to reference participants across datasets, created based on elements of patient personal identifying information (PII) using privacy-preserving technology from vendor [redacted] The key features below make tokens a secure and consistent mechanism for linking real world healthcare data sources at the patient level while preserving the privacy of trial participants.

- Tokens are irreversible and blinded: Hashing by [redacted] technology destroys the input PII, which makes tokens de-identified. The input PII cannot be backward-engineered from the output token.
- Tokens are unique: Each token is unique to the input PII, avoiding false matches.
- Tokens are consistent: The same set of input PII will always create the same tokens. Tokens created in any dataset are compatible and can be matched to one another.
- Tokens are compliant with trial regulation: A participant's PII never leaves the site.
- Multiple tokens derived from different PII elements are created for each subject to enable accurate matching (avoiding false positives and limiting false negatives).

At the time trial participants are screened for enrollment into the study, participants will be offered the consent for tokenization and linking of their clinical trial data. Outside of tokenization and linking of their clinical trial data, no additional study procedures beyond what is outlined in this study protocol, would be completed as result of their participation. Participation in tokenization is optional and participants who decline to participate in the tokenization process will still be able to participate in the study. The trial participant's tokenized data will be available for linking to other future data indefinitely or until they withdraw their consent for future data linking. The participant will be instructed of the withdrawal consent process with information provided in the ICF.

8.1.2. Demographics

The following demographics will be recorded: year of birth, self-identified gender, sex at birth, race and ethnicity.

For the purposes of demographics, both sex at birth (e.g., male, female) and self-identified gender (e.g., male, female, non-binary) should be recorded. This is because normal ranges for some clinical laboratory and ECG parameters, scoring from some questionnaires and the ability to become pregnant are based on a binary male/female designation while other parameters such as baseline symptom scores for anxiety and depression are expected to correlate to gender identity. Further, selected dosing session monitors should be aligned with gender identity and not sex at birth.

8.1.3. Prescreen Assessment (Optional)

Per the Schedule of Activities (Table 2) limited activities are planned for the optional Prescreen. Verbal consent must be collected before any Prescreen information is collected (see Section 8.1.1.1). Sites that choose to participate in the optional Prescreen will be provided a checklist with detailed instructions including prompts for collecting demography, an abbreviated Medical History and Concomitant medication review. Sex at birth, age, weight and height will be collected (an estimate of weight and height can be made for a phone screen), and BMI will be determined via calculation. The MINI can also be administered by qualified site personnel at the Prescreen.

Note: Information captured during the Prescreening assessments will not be captured in the EDC.

8.1.4. Eligibility Assessment

All inclusion criteria (listed in Section 5.1.1) and exclusion criteria (listed in Section 5.1.2) will be reviewed by the Investigator or qualified designee at Screening (Visit 1), Baseline (Visit 2) and Day 1/Randomization (Visit 3A), prior to randomizing the subject, to ensure that the subject qualifies for the study, however, of the vital signs taken at Visit 3A only temperature and blood pressure will be used to confirm final eligibility against inclusion/exclusion criteria.

All inclusion criteria must be met and none of the exclusion criteria may apply for the potential subject to be eligible to participate in the study. No eligibility waivers (or other protocol waivers) will be granted.

Subjects found ineligible during review of inclusion/exclusion at any of these visits will not proceed through the remaining screening process, except in cases of rescreening as described in Section 5.3.

Eligibility at Visit 3a/Randomization includes:

1. Review medical, psychiatric, and medication history
2. Vital signs (BP, HR, RR, temperature) within 1 hour of dose administration; Temperature and blood pressure (only) will be used to determine eligibility at Visit 3a. Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg

(confirmed by 3 separate readings) will make the participant ineligible for dosing. Temperature over 37.78°C (100°F) would be indicative of an acute illness and would make the subject ineligible for dosing.

3. [redacted]

   [redacted]

   - A positive pregnancy test will make the participant ineligible for dosing.

4. C-SSRS-SLV version

   - Active suicidal ideation will make the participant ineligible for dosing as evidenced by a "Yes" in response to C-SSRS suicidal ideation question 4 or 5

8.1.5. Medical/Psychiatric and Medication History

Medical/psychiatric and medication history will be assessed during Screening (Visit 1) and recorded in the eCRF. However, if information about the subject's medical/psychiatric and medication history is learned during the course of the study, this will also be recorded in the eCRF, even if this history is learned after Screening (Visit 1).

The medical/psychiatric history will be obtained by the Investigator or qualified designee. Medical/psychiatric history will include all chronic, past and ongoing conditions, regardless of the year diagnosed. To confirm eligibility criteria, the medical/psychiatric history will include, but is not limited to, a review of the following: suicidal ideation or behaviors; neurological or psychiatric disorder(s); family history of relevant psychiatric and medical concerns; major traumas; surgeries; any clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, or musculoskeletal system; clinically significant immunological, endocrine, or metabolic diseases; infection with HIV, hepatitis B and hepatitis C. Sites should make an effort to obtain medical and/ or psychiatric records for subjects.

All therapies (prescription or over-the-counter medications, including vaccines, supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture), other than the study intervention will be assessed as part of the subject's medical and medication history. Medication history will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and reason for use. Sites should make an effort to obtain pharmacy records for subjects.

8.1.6. Medication Taper

Medication tapers will be required for any subject on a prohibited medication for the following reasons:

- to eliminate potential confounding efficacy in the statistical analysis,
- to mitigate the risk of serotonin syndrome, and
- to eliminate the pharmacologic effects of potent 2D6 inhibitors.

The study site designated physician must monitor study subjects throughout the taper and through the end of the study or early termination.

Any prohibited anxiolytics, antidepressants or other medications, supplements or therapeutics (over-the-counter or prescribed) used to treat anxiety, depression or other mood disorders, as well as any other substances, supplements etc. that may confound the results of the study (as described in Section 6.10.1) will be tapered prior to Baseline (Visit 2). Subjects on such prohibited medications/substances at the time of Screening (Visit 1) will undergo a medication taper prior to advancing to Baseline (Visit 2), if safe for the subject, in the opinion of the Investigator. Medication tapering will be done with oversight from the study site designated physician; for subjects on prescribed medications to treat anxiety, depression or other mood disorders, the medication taper will be overseen by the study site designated physician based on acceptable local practice standards.

The last dose of the substance being tapered must have been taken no closer to Baseline (Visit 2) or Day 1/Randomization (Visit 3A) than indicated by the prohibition period described in Table 5. If the medication taper is anticipated to require more time than is available in the subject's remaining screening period, the subject will need to be screen-failed, and will need to rescreen.

Confirmation of eligibility is required at Baseline (Visit 2) and Day 1/Randomization (Visit 3A), including confirmation of a negative urine dipstick drug screen at these 2 visits and confirmation that the subject is no longer taking any prohibited medications/substances.

Additionally, subjects must also avoid starting, stopping or altering non-medicinal therapies/activities from the time of providing informed consent until End of Study, as described in Section 5.2.3.

Note: It is not permitted to stop/taper medications being used to treat excluded conditions.

8.1.7. Concomitant Medication Review/Collection

Concomitant therapies will be recorded throughout the study, beginning at the time of ICF signing until End of Study (Week 12 [Visit 9] or Early Withdrawal).

Medications taken at Baseline (Visit 2) or any time after, including those between visits regardless of whether the subject is on the medication at the time of the site visit, will be recorded in the concomitant medication eCRF. Medications stopped prior to Baseline (Visit 2) are recorded in the medication history eCRF.

Non-medicinal therapies/activities (see Section 5.2.3) will also be recorded throughout the study, beginning at the time of ICF signing until End of Study (Week 12 [Visit 9] or Early Withdrawal).

8.2. Clinical Procedures/Assessments

Refer to the DSMM, SoA and Lab manual for specific information procedures/assessments, including any required order for conducting them and any particular timing between them that must be followed.

8.2.1. Physical Examination

The site-designated licensed physician (MD/DO) will conduct a comprehensive physical exam at Screening (Visit 1), Day 2 (Visit 4) and End of Study (Week 12 [Visit 9] or Early Withdrawal). The comprehensive physical examination should be based on local standard of care for a general physical and include general assessments: general appearance, head, eyes, ears, nose, throat, lungs, abdomen, heart, skin and extremities.

Although physical exams are not required at all visits, additional physical exams may be conducted if medically indicated in the opinion of the Investigator. Any physical exam finding judged by the Investigator to be a clinically significant change from the screening assessment should be entered as an AE and monitored to resolution in accordance with safety procedures described in Section 9.

8.2.2. Neuropsychiatric Examination

The site-designated licensed physician (MD/DO) will conduct the Neuropsychiatric Exam at Baseline (Visit 2), Day 1/Randomization (Visit 3B) and all subsequent visits including End of Study (Week 12 [Visit 9] or Early Withdrawal). The Neuropsychiatric Exam performed at Baseline (Visit 2) establishes a standard comparison for possible effects of the study drug, thus the site-designated licensed physician who completes the baseline exam should complete dosing session day Dosing Release Checklists. The exam will monitor for mental status and sensory motor abnormalities. Any abnormal findings should be documented in accordance with the protocol as described in Section 8.2.8 and 9.

Note: At Visit 3B, the Neuropsychiatric Exam is included as part of the Dosing Release Checklist and need not be repeated.

8.2.3. Vital Signs

For any visits which includes an ECG and/or blood draw, vital signs should be measured prior to those tests.

Vital signs measured will include blood pressure, heart rate, respiration rate, and temperature (oral or tympanic). Continuous HR/BP monitoring devices and temperature guns are not permitted.

Initial vital signs should be taken with the subject seated in a chair with back support and arms, feet flat on the floor, and arms supported by the arm rest. After an approximately 5-minute rest, measure blood pressure, heart rate, and respiration rate. If any of the first measurements are out of range, a second measurement can be taken after the subject has been allowed an additional approximately 5 minutes of rest.

At Screening (Visit 1) and Baseline (Visit 2), measure orthostatic blood pressure. This measurement is taken separately from the initial vital signs. Orthostatic blood pressure should be measured by: allowing the subject to rest in a supine position for approximately 5 minutes; the subject then stands; and heart rate and blood pressure are measured within in 1 to 3 minutes of standing. If convenient, orthostatic blood pressure can be measured after the subject has been supine for the ECG.

On Day 1/Randomization (Visit 3A), the pre-dose vital signs (blood pressure, heart rate, respiration rate, and temperature) should be measured within 1 hour (± 15 min) prior to study drug dosing. The only vital signs taken at Visit 3A used to confirm final eligibility against inclusion/exclusion criteria are blood pressure and temperature (see Section 8.1.4).

On Day 1/Dosing Session (Visit 3B), following administration of study drug, vital signs (blood pressure, heart rate, respiration rate, and temperature) will be monitored at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose. The time of vital sign assessments should be recorded in the study database. In situations in which the post-dose assessment of individual vital signs as specified in this section does not occur before the next post-dose vital signs assessment timepoint, the next temporal assessment should be recorded at the protocol-specified post-dose time. For example, if the 1.5-hour post-dose assessment does not occur before the 2-hour assessment, the 1.5-hour assessment should be skipped and recorded as missing, and the 2-hour assessment would proceed as specified in this section.

8.2.4. Weight

Weight may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site to determine eligibility.

Body weight may be measured with the subject in street clothing with jacket/coat and shoes removed.

8.2.5. Height

Height may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site. Standing height will be measured without shoes at Screening (Visit 1) only when subject is on-site to determine eligibility.

8.2.6. Body Mass Index

BMI will be calculated using the subject's weight and height recorded at Screening (Visit 1). BMI calculated during the optional Prescreen may be estimated and can be used to aid eligibility determinations, but the recorded value must come from Screening (Visit 1).

8.2.7. Electrocardiogram

For any visits in which there is an ECG and blood draw, the ECG should be performed prior to the blood draw.

ECG should be performed after 5 minutes of rest in a semi-recumbent position. A qualified designee at the investigative site is responsible for interpreting the ECG, and if needed, in consultation with a cardiologist. If an ECG finding is identified as abnormal and is a clinically significant change from the baseline assessment, then the finding should be entered as an AE and monitored to resolution in accordance with safety procedures described in Section 9.

8.2.8. Adverse Event Collection

AE collection (of all spontaneously-reported events or events described by the subject in response to site staff queries) will occur from the time informed consent (main consent) is given until completion of the study and will be recorded at each visit.

Events occurring between signing of the ICF and dosing with study drug at Day 1/Dosing Session (Visit 3B) will be recorded on the medical history page of the eCRF (see also Section 9.4.1). Events occurring from the time study drug is administered through End of Study (Week 12 [Visit 9] or Early Withdrawal) will be recorded on the AE page of the eCRF.

The Investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE or adverse event of special interest (AESI) suggestive of abuse potential. See Section 9 for details on AE definitions and reporting.

8.3. Laboratory Procedures/Assessments

8.3.1. Biobanking (DNA) Sample

For subjects who consent to provide a sample pharmacogenomic (DNA) sample, a single blood sample for biobanking will be collected from each subject during the study and stored for future analyses. It is preferable to collect the sample at Day 1/Randomization (Visit 3A); however, the sample may be collected at any time after this visit through End of Study (Week 12 [Visit 9] or Early Withdrawal). The blood sample should not be collected from the subject during Day 1/Randomization (Visit 3B) after being dosed with study drug.

All analyses of the biobanked samples will be conducted by the Sponsor's designee.

Information regarding the handling/shipping of specimens will be provided in the Laboratory Manual.

8.3.2. Safety Laboratory Assessments and Urinalysis

A central laboratory will perform all safety clinical laboratory assessments (blood chemistry panel and hematology) and urinalysis. (Note that the urine dipstick drug screen and pregnancy testing will be done locally; see Section 8.3.3 and Section 8.3.4, respectively). Additional testing may be required by the Sponsor based on emerging safety data. All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Table 2).

Safety clinical laboratory assessments and urinalysis tests to be performed by the central laboratory are listed in Table 6. The central laboratory will also provide estimated glomerular filtration rate (eGFR), calculated using the Cockroft-Gault formula.

Table 6: Required Laboratory Analytes

Serum Chemistry Panel	Hematology	Urinalysis

• Albumin
• Total protein
• Alkaline phosphatase
• ALT
• AST
• Bicarbonate
• Bilirubin, total
• Bilirubin, direct (if total bilirubin is > ULN)
• Blood urea nitrogen or urea
• Calcium
• Chloride
• Creatinine
• Creatinine clearance
• FSH[a] (Scr only; confirm postmenopausal)
• GGT
• Glucose
• Lactate dehydrogenase
• Lipid panel (cholesterol, HDL, LDL, triglycerides)
• Phosphorus
• Potassium
• Sodium
• TSH with reflex to free T4[b]
	Complete blood count, including:
	• Hemoglobin
	• Hematocrit
	• RBC indices
	  ○ MCV
	  ○ MCH
	  ○ MCHC
	  ○ RDW
	• Platelet count
	• MPV
	• Red blood cell count
	• White blood cell count
	
	Differential count, including:
	• Basophils
	• Eosinophils
	• Lymphocytes
	• Monocytes
	• Neutrophils
		• Protein
		• Glucose
		• Ketones
		• Bilirubin
		• pH
		• Nitrites
		• Specific gravity
		• Urobilinogen
		• Leukocytes
		• Microscopic (if positive for bacteria, leukocyte esterase, blood, protein or nitrites)
		• Red cell count
		• White cell count
		• Epithelial cells
		• Casts and crystals

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; GGT: gamma-glutamyl transferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPV: mean platelet volume; T4: thyroxine; RBC: red blood cell; RDW: red cell distribution width; TSH: thyroid-stimulating hormone; ULN: upper limit of normal

[a] FSH: Performed only at Screening (Visit 1) if needed to confirm a subject's post-menopausal status (> 40 mIU/mL)

[b] TSH and FT4: Performed only at Screening (Visit 1)

All laboratory tests considered clinically significant by the Investigator should be documented as AEs and repeated until the value returns to baseline or are no longer considered clinically significant by the Investigator or Sponsor's Medical Monitor or designee.

Information regarding the collection, processing and shipping of laboratory assessments is provided in the Laboratory Manual.

PI/Sub-I (if an MD/DO) or study site designated physician should review all lab values for clinical significance.

[redacted]

8.3.4. Urine/Serum Pregnancy Tests

As outlined in the Schedule of Activities (Table 2), all WOCBP will require a urine pregnancy test (performed at the site) at Screening (Visit 1) and a serum pregnancy test at Baseline (Visit 2). A negative β-HCG test result is required at Screening (urine) and a non-positive result is required at Baseline (serum); otherwise, the subject is not eligible to enroll or participate further in the study. Urine pregnancy tests (performed at the site) will be repeated at Day 1/Randomization (Visit 3A), Week 1 (Visit 5) and all subsequent follow-up visits including End of Study (Week 12 [Visit 9] or Early Withdrawal).

The results of each urine/serum pregnancy test will be recorded in the eCRF.

A pregnancy test is not required for persons of non-childbearing potential, defined as women meeting any of the following conditions (see also Appendix 1):

- Has undergone total hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation at least 2 months prior to Screening
- Has a congenitally absent uterus
- Is postmenopausal, confirmed as being age > 45 years with one of the following:
  - At least 1 year without menses prior to Screening
  - 6 months to < 1 year without menses prior to Screening and serum follicle-stimulating hormone [FSH] levels > 40 mIU/mL at Screening.

All persons who become pregnant or men with a female sexual partner who becomes pregnant during the study after Day 1 will be monitored for the pregnancy outcome, and reporting will occur as described in Section 9.10.

8.4. Screening and Efficacy Questionnaires

Questionnaires will be administered according to the timing/frequency indicated in the Schedule of Activities (Table 2). Information about the questionnaires is briefly summarized below.

The following instruments can be administered for sites that implement the optional Prescreen:

- MINI (see Section 8.4.1)

The following instruments will be administered during the screening process only:

- MINI (see Section 8.4.1)
- C-SSRS – Baseline/Screening Version (see Section 8.4.2)
- Placebo Script Review (see Section 8.4.11)

Additionally, the following instruments will be administered during the study to assess functionality and quality of life:

- HAM-A, performed by central rater (see Section 8.4.3)
- MADRS, performed by central rater (see Section 8.4.4)
- C-SSRS – SLV Version (see Section 8.4.2)
- CGI-S and CGI-I (see Section 8.4.5)
- PGI-S and PGI-C (see Section 8.4.6)
- SDS (see Section 8.4.7)
- EQ-5D-5L (see Section 8.4.8)
- PSQI (see Section 8.4.9)
- ASEX (see Section 8.4.10)

8.4.1. Mini-International Neuropsychiatric Interview (MINI)

The MINI will be administered at Screening (Visit 1) to help determine subject eligibility. The psychiatric interview using the MINI will be conducted by a certified site rater. DSMs may administer the MINI if qualified.

The MINI is a short structured diagnostic interview for the major psychiatric disorders in DSM-III-R, DSM-IV and DSM-5 and ICD-10. It was originally developed for the major psychiatric disorders in DSM-IV and ICD-10 to meet the need for a short, accurate structured psychiatric interview in various settings, including for multi-center clinical trials (Sheehan 1998). The standard MINI assesses the 17 most common disorders in mental health. It takes approximately 15 minutes to administer.

Note: The MINI will be used by sites that implement the optional Prescreen. The MINI must be repeated at Screening to confirm diagnosis.

8.4.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be 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 will be administered by the Investigator or designee at Screening (Visit 1) and will use recall periods of lifetime and over the past 3 months. The C-SSRS – SLV Version will be used at all other visits where the C-SSRS is to be administered, as described in the Schedule of Activities (Table 2).

For both versions, if the subject provides a "Yes" response in the Suicidal Behavior sections of the C-SSRS for Actual Attempt, Interrupted Attempt or Aborted Attempt, the site should inquire about the approximate date when the event occurred and record this in the source document and eCRF.

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) (Posner 2011).

Any positive findings or changes in the subject's suicidal ideation/behavior that are revealed by the subject's responses to the C-SSRS should be handled in accordance with local standard of care and at the Investigator's discretion. The Investigator may consult with the Sponsor's Medical Monitor on any questions related to treatment and/or follow-up of such findings.

The C-SSRS may be administered by certified site raters. DSMs may administer the C-SSRS if qualified.

8.4.3. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is being used as the primary outcome measure for this study for the evaluation of anxiety symptoms. It will be administered to determine eligibility at Screening (Visit 1) and Baseline (Visit 2) and will be administered at additional visits as described in the Schedule of Activities (Table 2). The HAM-A takes approximately 20 minutes to administer.

The HAM-A will be 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:

- Anxious mood
- Tension
- Fears
- Insomnia
- Intellectual
- Depressed mood

- Somatic (muscular)
- Somatic (sensory)
- Cardiovascular symptoms
- Respiratory symptoms
- Gastrointestinal symptoms
- Genitourinary symptoms
- Autonomic symptoms
- Behavior at interview (general)

The central rater must be appropriately trained/qualified to administer the HAM-A. The central rater will assess 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.

A central rater located remotely from the site will be 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 (see Section 8.4.4).

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.

The central raters will also complete a safety report risk assessment, and if any concerns are identified (e.g., possible suicide, homicide, abuse), the central rater will report this information to the site. If any such safety risks are identified, the Investigator is required to follow-up, including management and further reporting as needed, and will promptly notify the Sponsor's Medical Monitor.

Additionally, if the subject spontaneously reports any potential AEs to the central rater during an assessment, the central rater will notify the site after the interview session has concluded. It is the site's responsibility to determine whether this event qualifies as an AE, SAE or AESI suggestive of abuse potential and to report the event as described in Section 9.

If the central rater feels that there is an emergent risk to the safety of the subject, or to a third party, the site will be contacted immediately by the central rater to intervene in the subject assessment room. The central rater shall remain on the teleconference call with the subject until appropriate personnel from the clinical trial site arrive. The central rater will forward the complete report to the site. The Investigator retains responsibility for compliance with reporting requirements and to warn third parties of potentially harmful conduct by the subject.

8.4.4. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The MADRS takes approximately 15-20 minutes to administer.

An appropriately trained/qualified central rater located remotely from the site will be used to administer and score the MADRS, as was described for the HAM-A (see Section 8.4.3,

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 should be administered at approximately the same time of the day across each of the individual subject's study visits. The MADRS will be administered by the central rater after completion of the HAM-A.

The MADRS is used to assess depression severity and to detect changes due to antidepressant treatment (Montgomery & Åsberg 1979). 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 ≥ 50% indicates a response to treatment, and an actual score of ≤ 10 indicates a remission of symptoms.

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

The Clinical Global Impression (CGI) scales will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). Sites should make 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.

CGI-S: The CGI-S scale will be 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 (Guy 1976). 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.

CGI-I: The CGI-I scale will be 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.

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

The Patient Global Impression (PGI) scales will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The PGI-S/C are patient reported outcome measures.

The PGI scale is the patient-reported outcome counterpart to the CGI scale (Guy 1976), which was published in 1976 by the National Institute of Mental Health. 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).

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).

8.4.7. Sheehan Disability Scale (SDS)

The SDS will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The SDS is a patient reported outcome measure.

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 (Sheehan & Sheehan 2008).

The SDS will be used to assess the extent to which these 3 major domains in the subject's life are functionally impaired.

8.4.8. EQ-5D-5L

The EQ-5D-5L will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The EQ-5D is a patient reported outcome measure.

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 (Herdman 2011). The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS).

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.

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".

8.4.9. Pittsburgh Sleep Quality Index (PSQI)

The PSQI will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The PSQI is a patient reported outcome measure.

The PSQI assesses sleep quality and disturbances over the preceding month (Buysse 1989). This questionnaire includes 19 self-rated questions and 5 questions rated by the bed partner or roommate (if available).

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

- Subjective sleep quality
- Sleep latency
- Sleep duration

- Habitual sleep efficiency
- Sleep disturbance
- Use of sleeping medication
- Daytime dysfunction.

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.

8.4.10. Arizona Sexual Experiences Questionnaire (ASEX)

The ASEX will be administered during the study at the visits indicated in the Schedule of Activities (Table 2). The ASEX is a patient reported outcome measure.

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 (McGahuey 2000).

Possible total scores on the ASEX range of 5-30, with a higher score indicating more sexual dysfunction.

8.4.11. Placebo Response Reduction

A brief web-based script must be reviewed by the subject and the site personnel immediately before administering study assessments.

The purpose is to provide site staff and subjects straightforward information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies.

Placebo Response Reduction (PRR) training teaches the subject about the appropriate expectations of personal benefit while participating in a clinical trial (Erpelding 2020; Evans 2021).

The script is being implemented at 3 visits as follows; Baseline/Visit 2, Week 4/Visit 7 (primary endpoint), and Week 8/Visit 8 (key secondary endpoint) to reduce placebo response, and to balance subject and site burden.

8.5. Other Patient-Reported Outcomes

Other patient-reported outcomes (PROs) will be administered according to the timing/frequency indicated in the Schedule of Activities (Table 2). Information about these instruments is briefly summarized below.

The following instruments will be administered during the study to explore dose response on drug effects, altered perception and mystical experience:

- Drug Effect VAS (see Section 8.5.1)
- MEQ30 (see Section 8.5.2)
- 5D-ASC (see Section 8.5.3)

Additionally, the following instrument will be administered during the study to explore whether functional unblinding of study drug may have occurred:

- Treatment assignment/blinding question (see Section 8.5.4)

8.5.1. Drug Effect VAS

The Drug Effect VAS will be 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 will be 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".

8.5.2. Mystical Experience Questionnaire (MEQ30)

The MEQ30 will be 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.

The MEQ30 is a psychometrically validated instrument that includes 30 self-rated questions (Barrett 2015; Liechti 2017). The 30 items are combined into the following 4 subscales:

- Mystical (unity, noetic quality, sacredness)
- Positive mood
- Transcendence of time and space
- Ineffability

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 ≥ 60% of the maximum possible score is achieved on all 4 factor subscales.

8.5.3. 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

The 5D-ASC will be 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.

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 (Liechti 2017). The 94 items are combined into the following 5 subscales/dimensions (Dittrich 1998) with 11 lower-order scales defined for the first 3 subscales/dimension by Studerus et al. (Studerus 2010):

- 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.

8.5.4. Treatment Assignment/Blinding Question

On Day 2 (Visit 4), a 5-point Likert scale will be 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 will be 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.

8.6. Dosing Day Activities

8.6.1. Study Drug Dosing

Study drug will be taken as a witnessed dose as outlined in Section 6.2 and described in detail in the Dosing Session Monitor Manual.

8.6.2. Subject Education / Follow-up Session with Dosing Session Monitors

Refer to the Dosing Session Monitor Manual for details on the subject education that will be provided at 2 visits prior to dosing (i.e., at Baseline [Visit 2] and Day 1/Randomization [Visit 3A]) and for details on the follow-up sessions conducted at 3 visits following dosing (i.e., at Day 2 [Visit 4], Week 1 [Visit 5], and Week 2 [Visit 6]).

8.6.3. Subject Observation by Dosing Session Monitors

Following study drug administration on Day 1/Dosing Session (Visit 3B) until subject release from the clinic, subjects will be supported by two appropriately trained and qualified Dosing Session Monitors (DSMs) and will be under the observation of two DSMs at all times (both DSMs should be in the session room, however, one DSM can be in the session room and one in a separate room on site via live remote monitoring during breaks only). At least one of the Dosing Session Monitors will be identified and qualified to serve as a 'lead monitor.' A site-designated licensed physician must be available or on call and be able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency; events requiring intervention should be discussed with the Sponsor as soon as the situation permits, but implementation of the intervention should not be delayed.

The site-designated licensed physician with prescribing rights or a qualified designee can serve as the backup to either DSM if short breaks are needed. This licensed physician, or qualified designee, must meet the criteria to be a lead monitor.

Refer to the Dosing Session Monitor Manual for details on monitoring the subject from dosing of study drug until the subject is released from the clinic.

8.6.4. Subject Release on Dosing Day/ Dosing Release Checklist

Study subjects will be kept under continuous observation for a minimum of 12 hours following investigational drug administration.

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

In order to be eligible for release, subjects MUST:

- Self-report readiness for release (i.e., physical and mental readiness, and understanding of restrictions); and

- Be deemed eligible for safe release in the medical judgment of the study site-designated licensed physician as determined by the Dosing Release Checklist
- 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
- Display clinically significant abnormal mental status

Refer to the Dosing Session Monitor Manual and Dosing Release Checklist for further details on requirements that must be met in order for the subject to be released from the clinic at the end of Day 1/Dosing Session (Visit 3B).

9. SAFETY CONSIDERATIONS

9.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a research subject, whether or not considered drug related which occurs during the conduct of a clinical trial. Any change in clinical status that is considered clinically significant by the PI should be documented. AEs occurring prior to randomization should be documented in medical history. AEs occurring after randomization should be documented in the AE log. Adverse events include any clinically significant changes not present prior to drug administration.

An AE includes:

- An unexpected worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.
- A new condition detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately).
- An investigational abnormality (e.g., laboratory parameter, vital sign, ECG) only if the abnormality which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, physical examinations, etc., that is considered clinically significant by the Investigator based on at least one of the following criteria;
  - Induces clinical signs or symptoms
  - Requires active intervention
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.

All observed and subject reported AEs and SAEs will be recorded from time of randomization until the end of study. SAEs will be reported per FDA guidelines.

9.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death;
b. Is life-threatening;
   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization;

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity;
NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect;
f. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.3. Adverse Events of Special Interest

AESIs are a subset of AEs that are suggestive of abuse potential (including Central Nervous System-related and drug abuse-related) and any special situations defined in Section 9.9 that have an associated AE or drug accountability discrepancy (see Section 6.7).

The AE terms listed below are MedDRA Preferred Terms to be used in classifying Adverse Events of Special Interest (AESIs) related to abuse liability when deemed appropriate by the PI (or designee):

- Euphoria-related terms: Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect.
- Terms indicative of impaired attention, cognition, and mood: Somnolence; Mood disorders and disturbances.
- Dissociative/psychotic terms: Psychosis; Aggression; Confusion and disorientation.
- Overdose-/ Misuse-related terms not captured elsewhere: Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders.

9.4. Adverse Event Detecting and Reporting

The Investigator and site staff are responsible for detecting, documenting and reporting events that meet the definition of an AE, SAE or AESI suggestive of abuse potential.

The reporting of SAE and/or AESIs suggestive of abuse potential to regulatory authorities by the Sponsor is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the Investigator to report SAE and/or AESIs suggestive of abuse potential to their local IRB/IEC.

Care will be taken not to introduce bias when detecting AEs, SAEs and/or AESIs suggestive of abuse potential. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines since your last visit/contact?

Any abnormal exam finding(s) at Screening and Baseline should be entered once as medical history and as a physical exam finding (if applicable). The finding will only be considered an AE if there is a clinically significant change in signs or symptoms during the study, as judged by the Investigator. A medical history finding that worsens after randomization should be recorded as an AE. The term should match the recorded finding that has worsened.

The subject's responses in clinician reported outcome measures will not be used as a primary means to collect AEs, however any AEs indicated in these instruments should be queried by the study site personnel and the study monitors and recorded. Should the Investigator or site staff become aware of a potential AE through the information collected with these instruments, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

All subjects who experience an AE will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the Investigator and medical monitor will assess unresolved AEs and determine if additional follow-up is warranted.

All AEs, whether or not related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the subject's source documents. In addition, any AE resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the subject's source documents. AE terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the Investigator should record each sign and symptom as an individual AE.

AEs should be reviewed by a PI/Sub-I or Study Site Designated Physician.

Overdose and pregnancy in the subject or subject's partner will be reported as described in Section 9.9 and Section 9.10, respectively.

9.4.1. Period for Reporting Adverse Events

AE collection will occur from the time informed consent is given until completion of the study and will be recorded at each visit.

Any event occurring between signing of the ICF and dosing with study drug at Day 1/Dosing Session (Visit 3B) will be recorded as medical history in the eCRF and in the subject's clinical record for any subject who continues to meet eligibility criteria and proceeds to dosing with study drug.

Adverse events collected from the time study drug is administered through End of Study (Week 12 [Visit 9] or Early Withdrawal) will be recorded on the AE page of the eCRF. SAEs and/or AESIs suggestive of abuse potential will be collected from the signing of the informed consent form until the Week 12 (or Early Discontinuation) visit. SAEs and/or AESIs suggestive of abuse potential reported to the Investigator after the safety reporting period should be reported to the Sponsor if the Investigator assesses the event as related to the study drug treatment.

Reporting instructions for SAEs and/or AESIs suggestive of abuse potential are provided in Section 9.4.2.

9.4.2. Reporting Serious Adverse Events and Adverse Events of Special Interest Suggestive of Abuse Potential

All SAE and/or AESIs suggestive of abuse potential must be reported **within 24 hours of the study site personnel's knowledge of the event**, regardless of the Investigator's assessment of the relationship of the event to study drug. The events will be entered into the EDC and the narrative section provided in the drug safety database.

The minimum criteria for SAE and/ or AESI suggestive of abuse potential reporting are as follows: the event or outcome meets the definition of an SAE and/ or AESI suggestive of abuse potential (see Section 9.2 and Section 9.3); the event happens to an identifiable study subject; and the event is reported by an identifiable and qualified reporter (usually the Investigator or other qualified study site personnel).

A follow-up report to an SAE and/ or AESI suggestive of abuse potential should be prepared if any relevant change in the condition of the study subject occurs after the initial report. The follow-up report should be documented as an update to the initial report.

If the subject died, the report should include the cause of death as the event term (with death as the outcome) and whether or not the event leading to death was related to study drug, as well as the autopsy findings if available.

Do not delay reporting a suspected SAE and/ or AESI suggestive of abuse potential in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All SAE and/ or AESI suggestive of abuse potential will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All SAE

and/ or AESI suggestive of abuse potential continuing at the completion of the study must be assessed or followed to determine outcome.

SAE and/ or AESI suggestive of abuse potential that occur after End of Study (i.e., after Week 12 [Visit 9] or Early Withdrawal) should be reported if the Investigator feels that there is a reasonable possibility for the event to have been caused by the subject's participation in the study. The Investigator does not need to actively monitor subjects once the study has ended.

9.5. Study Drug Overdose Management

An overdose is defined as a known deliberate or accidental administration of a study drug, to or by a study subject, at a dose above that assigned to that individual subject according to the study protocol.

The Sponsor's Medical Monitor or designee must be contacted in the event of any study drug overdose.

For this study, any dose of more than 1 dose (i.e., 8 capsules) of study drug is an overdose. There is no known antidote for an overdose.

In the event of an overdose, the Investigator or treating physician should:

- Contact the Sponsor's Medical Monitor or designee immediately.
- Closely monitor the subject for adverse events and laboratory abnormalities.
- Report all overdose events as a Special Situation (see Section 9.9).
- If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the Sponsor's Medical Monitor or designee (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The Investigator, in consultation with the Sponsor's Medical Monitor or designee, will make decisions regarding subject status, based on the clinical evaluation of the subject.

9.6. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship plausible, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge), although information on drug withdrawal may be lacking or unclear.

Note: Re-administration/rechallenge is not applicable for this single-dose study; but the terminology has been left in the definition for completeness.

- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the subject's clinical record. In the event a subject is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

9.7. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious", which is based on subject/event outcome or action taken.

The Investigator must determine the severity of each adverse event according to the NCI CTCAE, version 5.0. For terms not specified within the CTCAE, the criteria in Table 7 should be used to determine the severity grade.

Table 7: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute Common Terminology Criteria for Adverse Events

Grade	Criteria
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
4	Life threatening consequences; urgent intervention indicated
5	Death related to adverse event

Note: The described grading is based on the National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the subject's source documents.

9.8. Urgent Safety Measures

All arrangements described in this section apply only to the extent that protocol requirements cannot be met because of restrictions due to a crisis, such as the COVID-19 pandemic. Study center visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as the crisis-related limitations permit.

Exceptional measures taken in response to a crisis (e.g., COVID-19) and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3 guidance.

In case any visit described in the Schedule of Activities (Table 2) cannot be conducted at the study center within the visit window due to restrictions related to COVID-19 or another such crisis, a telephone visit, home visit and/or video (central rater) call should be arranged.

The telephone visit should include all protocol assessments that can be performed remotely and should take place within the original visit window. The decision to replace the site visit with an alternate contact method will be made on a case by case basis with the Study Sponsor.

In addition to the remote visit, the Investigator should make reasonable efforts to complete the following assessments/procedures as soon as possible (if applicable to the study visit):

- Concomitant medication review/collection
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- 12-lead safety ECG
- Adverse event collection
- Chemistry and hematology
- Urine drug screening
- Urine pregnancy test (if applicable)
- HAM-A (central rater)
- C-SSRS – SLV Version

9.9. Special Situations

Special situations with study drug are defined as the following:

- Medication error or incorrect drug administration
- Overdose (exceeds the protocol-specified maximum; see Section 9.5 for the definition of overdose)
- Deliberate abuse
- Deliberate misuse
- Drug interaction
- Occupational exposure

- Breastfeeding with suspected infant exposure
- Drug accountability issue (e.g., diversion) if linked to an AE (see Section 6.7)

If any of these special situations with study drug occur, they will be reported on the special situations with study drug eCRF page, even if there is no accompanying AE. All clinical manifestations in relation to these special situations (as defined above) will be reported as an SAEs or AESIs at the same time using the corresponding section of the eCRF.

For example, if a medication error or interaction occurred, the Investigator will assess whether to consider an AE to have occurred, and if so, will assign the possible relationship to the study drug.

Additional information may be requested by the site including all AE information and all triggering drug accountability discrepancies.

9.10. Reporting of Pregnancy to the Sponsor

For all WOCBP, urine dipstick pregnancy testing will be done locally as described in Section 8.3.4 and outlined in the Schedule of Activities (Table 2). If any subject becomes pregnant prior to Day 1/Randomization (Visit 3A), the subject is not eligible to be randomized in the study.

As this is a single-dose study, if a subject becomes pregnant during the study after Day 1/Dosing Session (Visit 3B), she is not required to withdraw from the study.

If a female sexual partner of a male subject becomes pregnant (by the male subject) within 28 days after Day 1/Dosing Session (Visit 3B), and if the subject agrees, the subject's pregnant partner should be notified and requested to sign a Release of Information form, permitting transfer of information regarding the pregnancy and outcome to the Sponsor.

The Investigator must inform the subject of their right to receive treatment information. If the pregnant subject (or pregnant female partner of the subject) chooses to receive unblinded treatment information, the individual blind should be broken, and the treatment assignment provided to the subject/subject's partner. The study team will remain blinded to the subject's (partner's) treatment assignment. If she agrees, the Investigator should notify the subject's (partner's) primary care physician of the pregnancy and provide details of the subject's participation in the study and treatment (blinded or unblinded, as applicable).

Pregnancy is to be reported to the Sponsor **within 24 hours of awareness** by the study site personnel, using the pregnancy reporting forms and the contact information in Section 9.4.2. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data, etc. should be included in this information, as available.

The Investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the Sponsor.

10. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor.

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the MMED008 Statistical Analysis Plan (SAP) that will be finalized prior to unblinding of the study. The treatment code will be opened after the study database has been locked.

This study will utilize 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-ranging studies to find suitable dose(s) for confirmatory Phase 3 trials.

10.1. Analysis Sets

The following analysis sets will be defined for the statistical analysis. Subjects without valid written study informed consent will be excluded from all analysis sets.

Table 8: MMED008 Analysis Sets

Analysis Set	Description
Randomized Set (RAN)	All subjects who received a randomization number, regardless of receiving trial medication. Subjects will be analyzed according to the treatment assigned.
Safety Set (SAF)	All subjects who received the double-blind study drug. Subjects will be analyzed according to actual treatment received.
Full Analysis Set (FAS)	All subjects in RAN with a valid Baseline HAM-A assessment and at least one valid post-baseline HAM-A assessment. Subjects will be analyzed according to the treatment assigned.
Per Protocol Set (PPS)	All subjects in FAS who had no major protocol deviations deemed as impacting the primary endpoint[a]. Subjects will be analyzed according to the actual treatment received.

[a] An impact assessment will be performed prior to the unblinding of the study. The impact assessment will determine whether a major protocol deviation impacts the primary endpoint thereby leading to the removal of the respective subject(s) from the PPS.

10.2. Statistical Analyses

10.2.1. Patient Demographics and Other Baseline Characteristics

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including sex at birth, self-identified gender, age, race, weight, height, BMI, systolic blood pressure, diastolic blood pressure, medical history, baseline values for HAM-A Total Score, PSQI, MADRS, CGI-I, CGI-S, PGI-S and ASEX. These summaries will be performed for the FAS and PPS populations.

Continuous variables will be summarized using n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

10.2.2. Efficacy Analyses

10.2.2.1. Primary Estimand

The primary estimand quantifies the treatment effect of MM-120 at 4 weeks post-dose administration while accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to the 4-week assessment.

The following attributes describe the primary estimand:

- Population: As defined by the Inclusion/Exclusion criteria
- Endpoint: Change from Baseline to Week 4 in HAM-A Total Score
- Treatment of interest /the randomized treatment: 4 doses of MM-120 (25, 50, 100, or 200 µg free-base equivalent) or placebo as a single-dose treatment.
- Handling of IEs prior to HAM-A assessment at Week 4:
  - Intake or change in concomitant medications/therapies which have potential confounding effects per the impact assessment.
  - Intake of prohibited medications/therapies assessed as "Yes" per the impact assessment.
    Policy strategy: Available data recorded after the IE will be set to missing; such missing data will be imputed/substituted under a Missing Not at Random (MNAR) assumption by borrowing information from the placebo arm subjects (reference-based imputation).
  - IEs leading to study discontinuation due to other reasons.
  - IEs related to the COVID-19 pandemic
    Policy strategy: Available data will be used; missing data will be imputed under a Missing at Random (MAR) assumption, borrowing information from subjects in the same treatment arm.
- Summary measure: Identification of the dose-response curve and estimation of the target dose

Statistical Methods & Analysis

The MCP-Mod methodology (Bretz 2005; Pinheiro 2014) will be employed to assess the primary objective: to investigate the dose-response relationship for different doses of MM-120 versus placebo in change from Baseline in HAM-A Total Score at Week 4. An overview of the steps for the MCP-Mod methodology is given below.

Step 1

The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) model with the change from Baseline to Week 4 for HAM-A Total Score as a response variable, treatment (placebo and all MM-120 doses), and Baseline value of HAM-A Total Score. Centers will be pooled according to country and region as appropriate and as defined in the SAP prior to unblinding.

Missing or potentially biased data will be imputed as described in the following section on Handling of Missing/Potentially Biased Values. To account for the imputation uncertainty, this ANCOVA model will be repeated for each imputed dataset, which results in a set of least-squares (LS) mean estimates for all dose groups and the related covariance matrices. Rubin's rule will be used to combine the multiple sets of LS mean estimates and the related covariance matrices to a single set of LS mean estimates of change from Baseline to Week 4 for HAM-A Total Score for all dose groups and the related covariance matrix.

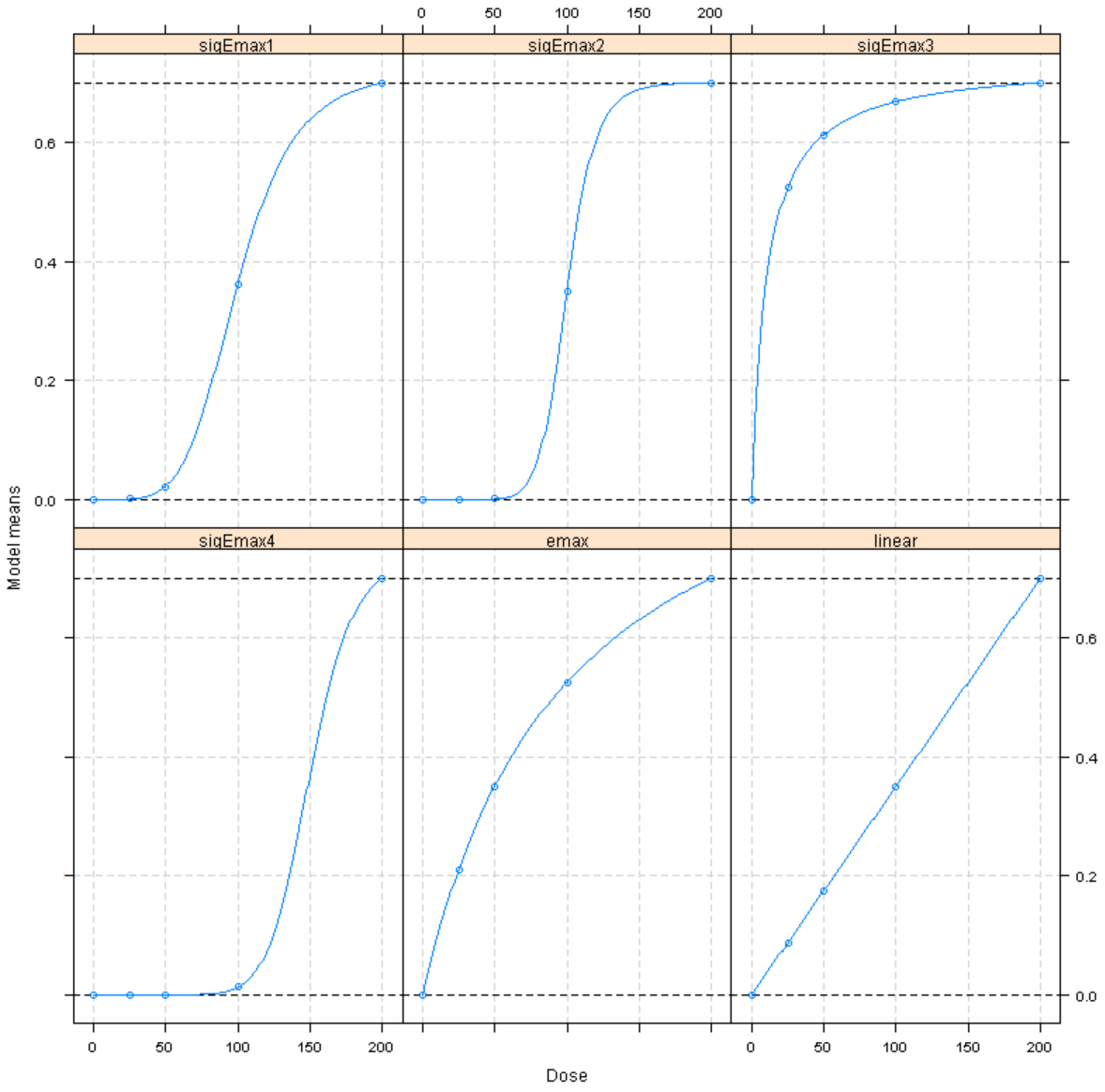
A range of possible dose-response relationships will be considered to take model uncertainty into account (see Figure 2). The following six candidate dose-response curves will be used to derive the optimal model contrasts for the multiple contrast tests:

- Sigmoid Emax (ED50, hill):
  - 10, 1
  - 100, 5
  - 100, 10
  - 150, 10
- Emax (D50 = 100)
- Linear

The optimal contrasts derived from the candidate model sets will be applied to the combined estimated dose means and covariance matrix to obtain the t-statistics for each candidate model and the common critical value $C_{0.05}$ derived from the reference multivariate t-distribution with the 6x6 correlation matrix induced by testing the candidate dose-range models with respect to comparing all MM-120 doses to the placebo group.

The null hypothesis will be rejected and the statistical significance of dose-response in change from Baseline to Week 4 for HAM-A Total Score will be established if the max (t_1, t_2, t_3, …, t_6) ≥ $C_{0.05}$.

Figure 2: Candidate Dose-response Curves



Step 2

The response data in each imputed data set, including relevant covariates, will be used to fit the models in the candidate set. The estimated dose-response will be derived by using model averaging methods on a subset of candidate models, for which the associated contrast tests are statistically significant. The ≤ 3 models with the largest t-statistics ≥ $C_{0.05}$ as calculated above will be selected as the basis for the model averaging.

Model averaging will be carried out for each imputed data set, and the resulting mean efficacy estimates, and confidence intervals will be derived using the combination variance that accounts for the uncertainty of the imputed data using Rubin's combination rules. Comparisons between MM-120 doses and placebo will be simultaneously derived for the model averaged estimates together with confidence intervals reflecting the imputation procedure applied. The

model-averaging-based estimates of the mean changes from Baseline to Week 4 for HAM-A Total Score within each dose group, and the mean differences between MM-120 and placebo and their confidence intervals will then be displayed.

Target dose selection will be based on the model change from Baseline to Week 4 for HAM-A Total Score over the dose range studied.

Detailed information about the algorithms including multiple imputation will be specified in the SAP that will be finalized prior to unblinding.

The MCP-Mod analysis will be performed on the FAS population. It will also be performed on the PPS as a sensitivity analysis.

Handling of Missing/Potentially Biased Values

Missing data will be imputed using a multiple imputation approach assuming that the missingness mechanism can be retrieved from observed data. The imputation model will include the longitudinal sequence of HAM-A Total Score.

For IEs, handling will depend on the IE causing the missing or potentially biased value as follows:

- The data recorded after the IE will be imputed/substituted under an MNAR assumption by borrowing information from the placebo arm subjects (reference-based imputation) for the following:
  - For intake or change in concomitant medications/therapies that have potential confounding effects per the impact assessment; or
  - For intake of prohibited medications/therapies assessed as "Yes" per the impact assessment.
- Missing data will be imputed under a MAR assumption, borrowing information from subjects in the same treatment arm for the following:
  - For IEs leading to study discontinuation due to other reasons than the above, including IEs related to the COVID-19 pandemic.

Centers will be pooled according to country and region as appropriate and as defined in the SAP prior to unblinding.

The full detailed information about the multiple imputation algorithms will be specified in the SAP.

10.2.2.2. Sample Size Determination

A total sample of 180 subjects (36 per dose arm and 36 for the placebo arm) is 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. The required sample size for each dose arm is 36 subjects.

The R package Dose Finding (https://CRAN.R-project.org/package=DoseFinding) has been used to estimate the sample size and the corresponding power. The power for each model is estimated as shown in Table 9.

Table 9: Study MMED008 Power by Model

Model	Power (%)
Sigmoid Emax (ED50, hill)	
10, 1	84.5
100, 5	90.7
100, 10	91.0
150, 10	89.9
Emax (D50 = 100)	83.2
Linear	85.0

10.2.2.3. Key Secondary Efficacy Endpoints

The change from Baseline to Week 8 in HAM-A Total Score will be analyzed using the same process as the primary endpoint. The outcome will be considered confirmatory, if in agreement with the primary endpoint outcome and provided that the null hypothesis is rejected for the primary outcome. This gatekeeping function of the primary outcome allows to avoid any adjustment for multiplicity of testing.

10.2.2.4. Secondary Efficacy Endpoints

Change from Baseline to Week 1, Week 2 (as applicable), Week 4, Week 8 and End of Study (as applicable) in HAM-A, MADRS, CGI-S, CGI-I, PGI-S, PGI-C, SDS, EQ-5D-5L, PSQI and ASEX will be analyzed descriptively. Continuous outcomes will be summarized by: n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, maximum and 95% Confidence Interval for the mean. For the active doses similar statistics will be reported for the difference from placebo. Categorical measures will be summarized by the number and percentage of subjects within each category.

10.2.3. Safety Analyses

No statistical inference on safety parameters is planned.

10.2.3.1. Adverse Events

The verbatim terms used in the eCRF by Investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset after the treatment phase or that are a consequence

of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between treatment groups will be provided as appropriate.

Summaries, listings, datasets, or subject narratives will be provided, as appropriate, for those subjects who die, or who experience an important medical event, SAE, and/or AESI suggestive of abuse potential.

10.2.3.2. Other Safety Parameters

Other safety outcomes, including vital signs, ECG parameters and abnormalities, C-SSRS scores, and laboratory parameter values, will be reported by treatment arm. All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by treatment/dose group at relevant timepoints. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment/dose group at relevant timepoints. Graphical presentations will be used as appropriate.

Where applicable, data will be summarized for the absolute value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each subject will be presented with abnormal or out-of-range values flagged. The percentage of subjects with values beyond clinically important limits will be summarized by frequency tables and shift tables.

Treatment-emergent ECG abnormalities will be summarized similarly to AEs.

10.2.4. Other Analyses

10.2.4.1. Treatments

A summary of subjects receiving or not receiving the single-dose treatment will be provided overall.

10.2.5. Interim Analyses

No interim analyses are planned.

11. STUDY GOVERNANCE CONSIDERATIONS

11.1. Financial Disclosure

Financial disclosure requirements are outlined by the United States Code of Federal Regulations Title 21, Part 54 (21 CFR 54), Financial Disclosure by Clinical Investigators. It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the Investigator's and sub-Investigator's responsibility to comply with any such request.

This is a “covered clinical study”, defined under 21 CFR 54 as “any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single Investigator makes a significant contribution to the demonstration of safety.” As such, all Investigators and sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-Investigator. The Investigator and sub-Investigator agree to notify the Sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

11.2. Pre-Initiation Visit

Sponsor personnel or designee(s) may visit the study site as necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, and reporting of adverse events with the site personnel.

11.3. Data Management

Subject data will be entered into a Sponsor-approved electronic database and combined with data from other sources in validated datasets then transmitted electronically to the Sponsor or designee.

Management of clinical data will be performed in accordance with applicable Sponsor-approved standards and data cleaning procedures to ensure data integrity (e.g., errors will be corrected, and inconsistencies clarified).

Adverse events and concomitant medications terms will be coded using the MedDRA and the World Health Organization Drug Dictionary Enhanced (WHO-DDE), respectively.

The Investigator will retain original source documents and the Sponsor will receive eCRF-required data as electronic datasets. Subject initials will not be collected or transmitted to the Sponsor.

11.4. Monitoring

This study will be monitored by the Sponsor (or designee) in accordance with current GCP regulations. By signing this protocol, the Investigator grants permission to the Sponsor (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to verify the accuracy of data collected in the eCRF,

the monitor will require direct access to original source documents (e.g., patient records, patient charts, and laboratory reports).

During the review of these documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries, and to meet with the Investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.5. Auditing or Inspections

Representatives of regulatory authorities, health authorities, the Sponsor or IRBs/IECs may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor immediately. By signing this protocol, the Investigator agrees to provide to appropriately qualified personnel from such groups, access to records, facilities and personnel for the effective conduct of any inspection or audit.

11.6. Safety Review

The Sponsor's Medical Monitor or designee will review blinded safety data listings monthly as detailed in the Medical Management Plan (MMP). Safety review meetings will review ongoing data for all subjects to identify trends in safety parameters. If necessary, the Sponsor will terminate the study if this blinded review process identifies significant intolerable safety signals based on either individual or aggregate blinded safety information that puts subjects in this study at unacceptable risk.

11.7. Protocol Modifications

Protocol modifications, except those made by the Investigator when intended to reduce immediate risk to subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The Investigator must not deviate from the protocol without first obtaining approval from the Sponsor and the IRB/IEC, if required. In medical emergencies, the Investigator will use medical judgment and will remove the subject from immediate hazard, then notify the Sponsor (or designee) and the IRB/IEC immediately regarding the type of emergency and the course of action taken. The Investigator must notify the Sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the informed consent form will be amended and approved by the IRB/IEC, and all subjects on treatment will again provide informed consent.

11.8. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the study subjects' interests.

11.9. Publications

After conclusion of the study and without prior written approval from the Sponsor, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation or publication will include the Sponsor's confidential information (see Section 11.10.5).

The Investigator will submit to the Sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with Sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

11.10. Investigator-Specific Responsibilities

11.10.1. Compliance with Regulations and Ethical Standards

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States investigational new drug application, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators", 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

The Investigator will also comply with financial disclosure requirements as described in Section 11.1.

11.10.2. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.10.3. Institutional Review Board/Independent Ethics Committee Requirements

The protocol, protocol amendments, informed consent form, Investigator's Brochure and any other relevant materials, including accompanying material to be provided to the subject (e.g., advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the following:

- Protocol number
- Protocol version
- Protocol date
- Documents reviewed
- Date on which the committee met and granted the approval.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, AESIs suggestive of abuse potential or other significant safety findings as required by procedures established by the IRB/IEC.

11.10.4. Obtaining Informed Consent

The Investigator (or Investigator's designee) is responsible for obtaining informed consent from each study subject. To help the individual make an informed decision about participating, the Investigator (or designee) shall discuss with the potential subject the purpose of the research, procedures, risks, benefits, alternative options to participating, confidentiality, how to contact study personnel and the subject's rights. Potential subjects must be informed that their participation is voluntary and must be given ample time to ask the Investigator questions and obtain clarifications regarding the study prior to providing consent.

The Investigator must utilize an IRB/IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the subject and the person obtaining consent.

As described in Section 11.6, subjects must be re-consented to participate in the study if a protocol amendment is made that substantially alters the study design or the potential risks or burden to subjects.

11.10.5. Confidentiality

The Investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC or laboratory. The Investigator must keep a screening log showing codes, names and addresses for all subjects screened and for all subjects enrolled in the study.

The Investigator agrees that all information received from the Sponsor, including but not limited to the protocol, Investigator's Brochure, eCRFs and other study forms, the investigational drug and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.10.6. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1. Investigator's study file. The Investigator's study file will contain the Investigator's Brochure, protocol/amendments, IRB/IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms and other appropriate documents and correspondence.
2. Subject clinical source documents. The required source data should include the following for each subject:
    - Subject identification (name, date of birth, gender)
    - Documentation that the subject meets eligibility criteria (e.g., history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria)
    - Participation in the study (including study number)
    - Study discussed and date of informed consent
    - Dates of all visits
    - Documentation that protocol-specific procedures were performed
    - Results of efficacy parameters, as required by the protocol
    - Dosing date of study drug
    - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the Investigator)
    - Concomitant medication (including start and end date)

- Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator's Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of study drug and study-related materials, documentation of financial aspects of the study, insurance statement, signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel and all correspondence pertaining to the conduct of the study.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

11.10.7. Electronic Case Report Forms

For each subject enrolled, an eCRF must be completed and signed by the Investigator or sub-Investigator (as appropriate) listed on Food and Drug Administration Form 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

11.10.8. Monitoring of Study Drug Accountability

The Investigator or approved Investigator's designee (e.g., pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition), subject dispensing records and returned or destroyed study drug. Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including lot number, date dispensed, Subject Identification Number and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with the Sponsor's requirements. Study drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final study drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor (or designee) for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.11. Sponsor-Specific Responsibilities

11.11.1. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

11.11.2. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins. Results will be posted as required.

REFERENCES

1. Alaka KJ, Noble W, Montejo A, Dueñas H, Munshi A, Strawn JR, Lenox-Smith A, Ahl J, Bidzan L, Dorn B, Ball S. Efficacy and safety of duloxetine in the treatment of older adult patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled trial. Int J Geriatr Psychiatry. 2014;29(9):978-86.
2. Allgulander C, Dahl AA, Austin C, Morris PL, Sogaard JA, Fayyad R, Kutcher SP, Clary CM. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry. 2004;161(9):1642-49.
3. Ansseau M, Bataille M, Briole G, Nayer A, Fauchère PA, Ferrero F, et al. Controlled Comparison of Tianeptine, Alprazolam and Mianserin in the Treatment of Adjustment Disorders with Anxiety and Depression. Hum Psychopharmacol Clin Exp 1996;11:293-8.
4. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test, Guidelines for Use in Primary Care, Second Edition. World Health Oranization, Department of Mental Health and Substance Dependence. WHO/MSD/MSB/01.6a. 2001. Available at https://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf?sequence=1&isAllowed=y [Accessed 15 February 2022].
5. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327-35.
6. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol. 2015;29(11):1182-90.
7. Baumeister D, Barnes G, Giaroli G, Tracy D. Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. Ther Adv Psychopharmacol. 2014;4(4):156-69.
8. Bercel NA, Travis LE, Olinger LB, Dreikurs E. Model psychoses induced by LSD-25 in normals. I. Psychophysiological investigations, with special reference to the mechanism of the paranoid reaction. AMA Arch Neurol Psychiatry. 1956 Jun;75(6):588-611.
9. Berman AH, Bergman H, Palmstierna T, Schlyter F. Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. Eur Addict Res. 2005;11(1):22-31. Available at: https://www.emcdda.europa.eu/drugs-library/drug-use-disorders-identification-test-dudit_en [Accessed 15 February 2022].
10. Bershad AK, Schepers ST, Bremmer MP, Lee R, de Wit H. Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers. Biol Psychiatry. 2019;86(10):792-800.
11. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015 Mar;29(3):289-99.

12. Bonson KR, Buckholtz JW, Murphy DL. Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. Neuropsychopharmacology. 1996a;14(6):425-36.

13. Bonson KR, Murphy DL. Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium. Behav Brain Res. 1996b;73(1-2):229-33.

14. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

15. Bruss GS, Gruenberg AM, Goldstein RD, Barber JP. Hamilton anxiety rating scale interview guide: joint interview and test-retest methods for interrater reliability. Psychiatry Res 1994;53:191–202.

16. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.

17. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016b;3(7):619-27.

18. Carhart-Harris RL, Kaelen M, Bolstridge M, Williams TM, Williams LT, Underwood R, Feilding A, Nutt DJ. The paradoxical psychological effects of lysergic acid diethylamide (LSD). Psychol Med. 2016a;46(7):1379-90.

19. Carhart-Harris RL, Kaelen M, Whalley MG, Bolstridge M, Feilding A, Nutt DJ. LSD enhances suggestibility in healthy volunteers. Psychopharmacology (Berl). 2015 Feb;232(4):785-94.

20. Constantin D, Dinu EA, Rogozea L, Burtea V, Leasu FG. Therapeutic Interventions for Adjustment Disorder: A Systematic Review. Am J Ther. 2020;27(4):e375-e386.

21. Davenport WJ. Psychedelic and nonpsychedelic LSD and psilocybin for cluster headache. CMAJ. 2016;188(3):217.

22. Dittrich A. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry. 1998;31 Suppl 2:80-4.

23. Dolder PC, Schmid Y, Müller F, Borgwardt S, Liechti ME. LSD Acutely Impairs Fear Recognition and Enhances Emotional Empathy and Sociality. Neuropsychopharmacology. 2016;41(11):2638-46.

24. EMCDDA (European Monitoring Center for Drugs and Drug Addiction). Statistical Bulletin 2021 — prevalence of drug use. Available at https://www.emcdda.europa.eu/data/stats2021/gps_en [accessed 15 February 2022].

25. Erickson SR, Guthrie S, Vanetten-Lee M, Himle J, Hoffman J, Santos SF, Janeck AS, Zivin K, Abelson JL. Severity of anxiety and work-related outcomes of patients with anxiety disorders. Depress Anxiety. 2009;26(12):1165-71.

26. Erpelding N, Evans K, Lanier RK, Elder H, Katz NP. Placebo Response Reduction and Accurate Pain Reporting Training Reduces Placebo Responses in a Clinical Trial on Chronic Low Back Pain. Clin J Pain. 2020;36(12):950-954.

27. Evans K, Colloca L, Pecina M, Katz N. What can be done to control the placebo response in clinical trials? A narrative review. Contemporary Clinical Trials. 2021;107:106503.

28. Evarts EV. Some effects of bufotenine and lysergic acid diethylamide on the monkey. AMA Arch Neurol Psychiatry. 1956;75(1):49-53.

29. Flockhart DA, Thacker D, McDonald C, Desta Z. [Internet]. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine (Updated 2021). Available from https://drug-interactions.medicine.iu.edu/MainTable.aspx [Accessed on 15 February 2022]

30. Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, Mager U, Thieda P, Gaynes BN, Wilkins T, Strobelberger M, Lloyd S, Reichenpfader U, Lohr KN. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772-85.

31. Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, Brenneisen R. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis. 2014;202(7):513-20.

32. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J Psychopharmacol. 2015;29(1):57-68.

33. Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord. 2005;87(2-3):161-7.

34. Greiner T, Haack B, Toto S, Bleich S, Grohmann R, Faltraco F, Heinze M, Schneider M. Pharmacotherapy of psychiatric inpatients with adjustment disorder: current status and changes between 2000 and 2016. Eur Arch Psychiatry Clin Neurosci. 2020;270(1):107-117.

35. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30(12):1181-1197.

36. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry. 2011;68(1):71-8.

37. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. Int Pharmacopsychiatry. 1973;8(3):129-44.

38. Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Clinical Global Impressions (CGI). 1976. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Alcohol Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, pp. 218–222.

39. Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, Walker D, Ball S, Dunayevich E, Dinkel J, Erickson J. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int Clin Psychopharmacol. 2007;22(3):167-74.

40. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

41. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol. 2007;21(8):864-72.

42. Hintzen A, Passie T. The pharmacology of LSD: a critical review. Oxford University Press: Oxford. 2010.

43. Hofmann A. How LSD originated. J Psychedelic Drugs. 1979;11(1-2):53-60.

44. Holze F, Liechti ME, Hutten NRPW, Mason NL, Dolder PC, Theunissen EL, Duthaler U, Feilding A, Ramaekers JG, Kuypers KPC. Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide Microdoses in Healthy Participants. Clin Pharmacol Ther. 2021b;109(3):658-666.

45. Holze F, Vizeli P, Ley L, Müller F, Dolder P, Stocker M, Duthaler U, Varghese N, Eckert A, Borgwardt S, Liechti ME. Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology. 2021a;46(3):537-544.

46. Holze F, Vizeli P, Müller F, Ley L, Duerig R, Varghese N, Eckert A, Borgwardt S, Liechti ME. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. Neuropsychopharmacology. 2020;45(3):462-471.

47. Hutten NRPW, Mason NL, Dolder PC, Theunissen EL, Holze F, Liechti ME, Feilding A, Ramaekers JG, Kuypers KPC. Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose-effect finding study. Eur Neuropsychopharmacol. 2020;41:81-91.

48. Issakidis C, Andrews G. Pretreatment attrition and dropout in an outpatient clinic for anxiety disorders. Acta Psychiatr Scand. 2004;109(6):426-33.

49. Johansen PØ, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol. 2015;29(3):270-9.

50. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017;43(1):55-60.

51. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol. 2014;28(11):983-92.

52. Johnston LD, O'Malley PM, Bachmann JG, Schulenberg JE, Miech RA. Monitoring the future, national survey results on drug use, 1975-2015: Volume 2. College students and adults ages 19-55. Ann Arbor: Institute for Social Research, The University of Michigan. 2016. Available at http://monitoringthefuture.org/pubs.html#monographs [Accessed 15 February 2022].

53. Kariuki-Nyuthe C, Stein DJ. Anxiety and Related Disorders and Physical Illness. In: Sartorius N, Holt RIG, Maj M (eds): Comorbidity of Mental and Physical Disorders. Key Issues Ment Health. Basel, Karger, 2015;179:81–87. Available at: https://www.karger.com/Article/Pdf/365538 [Accessed 15 February 2022].

54. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602.

55. Kessler RC, Keller MB, Wittchen HU. The epidemiology of generalized anxiety disorder. Psychiatr Clin North Am. 2001;24(1):19-39.

56. Koelle GB. The pharmacology of mescaline and D-lysergic acid diethylamide (LSD). N Engl J Med. 1958;258(1):25-32.

57. Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26(7):994-1002.

58. Krebs TS, Johansen PØ. Over 30 million psychedelic users in the United States. F1000 Res. 2013a;2:98.

59. Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. PLoS One. 2013b;8(8):e63972.

60. Kupferschmidt K. High hopes. Science. 2014;345(6192):18-23.

61. Lenze EJ, Mulsant BH, Shear MK, Dew MA, Miller MD, Pollock BG, Houck P, Tracey B, Reynolds CF 3rd. Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. Am J Psychiatry. 2005;162(1):146-50.

62. Liechti ME, Dolder PC, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology (Berl). 2017;234(9-10):1499-1510.

63. Llorca PM, Spadone C, Sol O, Danniau A, Bougerol T, Corruble E, Faruch M, Macher JP, Sermet E, Servant D. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002;63(11):1020-7.

64. Luethi D, Hoener MC, Krahenbuhl S, et al. Cytochrome P450 enzymes contribute to the metabolism of LSD to nor-LSD and 2-oxo-3-hydroxy-LSD: Implications for clinical LSD use. *Biochem Pharmacol* 2019;164:129-138.

65. Maier W, Buller R, Philipp M and Heuser I. The Hamilton Anxiety Scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affective Dis 1988;14:61-68.

66. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26(1):25-40.

67. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

68. Nichols DE. Hallucinogens. Pharmacol Ther. 2004;101(2):131-81.

69. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68(2):264-355.

70. Pahnke WN, Kurland AA, Goodman LE, Richards WA. LSD-assisted psychotherapy with terminal cancer patients. Curr Psychiatr Ther. 1969;9:144-52.

71. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther. 2008;14(4):295-314.

72. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014;33(10):1646-61.

73. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

74. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2003;160(4):749-56.

75. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z, Corby P, Schmidt BL. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30(12):1165-1180.

76. Rynn M, Russell J, Erickson J, Detke MJ, Ball S, Dinkel J, Rickels K, Raskin J. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. Depress Anxiety. 2008;25(3):182-9.

77. Savage C, McCabe OL. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. Arch Gen Psychiatry. 1973;28(6):808-14.

78. Schindler EA, Gottschalk CH, Weil MJ, Shapiro RE, Wright DA, Sewell RA. Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey. J Psychoactive Drugs. 2015;47(5):372-81.

79. Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, Brenneisen R, Müller F, Borgwardt S, Liechti ME. Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects. Biol Psychiatry. 2015;78(8):544-53.

80. Sessa B. The pharmacology of LSD: A critical review. British J Psych. 2011;199(3);258-9.

81. Sewell RA, Halpern JH, Pope HG Jr. Response of cluster headache to psilocybin and LSD. Neurology. 2006;66(12):1920-2.

82. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

83. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008;23(2):70-83.

84. Stein DJ. Etifoxine versus alprazolam for the treatment of adjustment disorder with anxiety: a randomized controlled trial. Adv Ther. 2015;32(1):57-68.

85. Stein DJ. Pharmacotherapy of adjustment disorder: A review. World J Biol Psychiatry. 2018;19(sup1):S46-S52.

86. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). PLoS One. 2010;5(8):e12412.

87. Vizeli P, Straumann I, Holze F, et al. Genetic influence of CYP2D6 on pharmacokinetics and acute subjective effects of LSD in a pooled analysis. *Sci Rep* 2021;11(1):10851.

88. Waghorn G, Chant D, White P, Whiteford H. Disability, employment and work performance among people with ICD-10 anxiety disorders. Aust N Z J Psychiatry. 2005;39(1-2):55-66.

89. Wan GJ, Zhang HF, Tedeschi MA, Hackett D. Estimation of symptom-free days in generalized anxiety disorder. Curr Med Res Opin. 2006;22(3):587-91.

APPENDIX 1. DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Definition of Women of Childbearing Potential (WOCBP)

A woman of childbearing potential (WOCBP) is defined as a person who is physiologically capable of becoming pregnant.

Subjects are considered to be not of childbearing potential if they meet at least one of the following conditions:

- Has undergone total hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation at least 2 months prior to Screening
- Has a congenitally absent uterus
- Is postmenopausal, confirmed as being age > 45 years with one of the following:
  - At least 1 year without menses prior to Screening
  - 6 months to < 1 year without menses prior to Screening and serum FSH levels > 40 mIU/mL at Screening.

Acceptable Highly Effective Methods of Contraception

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following highly effective methods of contraception are acceptable for use by WOCBP:

- Oral, injected or implanted hormonal methods of contraception
  - Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 3 months prior to Screening
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 3 months prior to Screening
- Established intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) (in place for at least 2 months prior to Screening)
- Surgical sterilization verified by either medical records (requires a medical release) or a progress note prior to randomization (hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal ligation or vasectomy at least 2 months prior to Screening)
- Sexual activity is limited to a male partner who has undergone effective surgical sterilization provided that partner is the sole sexual partner of the female study subject
- Sexual activity is limited to same sex partner

- Two barrier methods of contraception: condom and occlusive cap (diaphragm or cervical/vault cap) with spermicide

Unacceptable Methods of Contraception

Abstinence, periodic abstinence (calendar, "symptothermal," and post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhea method are not acceptable methods of contraception. A female condom and male condom should not be used together.

[redacted]

APPENDIX 3. RESCUE MEDICATIONS

Rescue medications should only be considered after non-medical interventions have been exhausted. Under all circumstances, only the study site-designated physician will administer rescue medications in this study. The choice of rescue medications is at the discretion of the study site-designated physician and should be based on subject medical history and local standard of care.

The unique pharmacologic properties of individual rescue medications (e.g., rapidity of onset, persistence of active drug or metabolite in the body) should be considered for rescue and considered along with a subject's sex, age, weight and/or comorbidities.

The study site-designated physician must consider rescue medications and if they have been associated with lengthening QTc interval, which can lead to syncope, arrhythmia or sudden cardiac arrest.

Other Considerations:

- Adjustment of doses for non-smokers versus moderate to heavy smokers.
- Concurrent use of IM and IV benzodiazepines and neuroleptics, individually or concomitantly, is not recommended outside of an emergency setting because of the need to monitor (e.g., a respiratory depression).
- If a rescue medication is considered, monitoring parameters include mental status/alertness, vital signs, neuropsychiatric signs and symptoms, delirium, fever, muscle rigidity, and/or autonomic instability, and risk of falling. Follow-up with ECG as needed.

Examples of acceptable rescue medications including benzodiazepines, neuroleptics, and antiemetics are shown in Table 10, Table 11, and Table 12. These tables are not meant to be exhaustive.

Table 10: Examples of Rescue Benzodiazepines: Dosing

Drug	Adult oral doses (mg)
Alprazolam	0.5 to 6
Clonazepam	0.5 to 4
Diazepam	4 to 40
Lorazepam immediate release	0.5 to 6 0.5 to 4 (hypnotic)

Table 11: Examples of Rescue Neuroleptics: Dosing

Agent	Initial oral dose range (mg)	Adjustment of oral dose in older subjects
Olanzapine	5 to 10	1.25 to 2.5 mg
Quetiapine	50 (immediate release) 300 (extended release)	25 to 50 mg
Risperidone	1 to 2	0.25 to 0.5 mg

Table 12: Examples of Medications for Nausea

Nausea is a known and tolerable effect of this compound. Supportive solutions are the best first line treatment, please refer to DSMM.

Drug	Dosing
Benzodiazepines	Refer to Table 10 for appropriate doses
Ondansetron	8 mg q12 hr
Promethazine	25 mg q12 hr

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