MPKF
Clinical Study Protocol
IND 063384

A Phase 1, single center, open label, randomized sequence, 2-period cross-over study to determine the effect of food on the relative bioavailability of 3,4-methylenedioxymethamphetamine (MDMA) oral formulation in healthy volunteers

COMPOUND	3,4-methylenedioxymethamphetamine (MDMA)
BRIEF TITLE	MDMA food effects in healthy volunteers
STUDY PHASE	Phase I
STUDY NUMBER	MPKF
SPONSOR NAME	Multidisciplinary Association for Psychedelic Studies (MAPS)
SPONSOR DESIGNEE	Amy Emerson Chief Executive Officer MAPS Public Benefit Corporation
REGISTRY ID	[NCT ID, TBD]
VERSION AND DATE	Version 1, 29 November 2021
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Disclaimer: This protocol version is for public viewing. Some information has been removed to maintain the integrity of this ongoing study.

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List of Abbreviations

°C	Degrees Celsius
ACE	Adverse Childhood Experiences Questionnaire
ADHD	Attention Deficit/Hyperactivity Disorder
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	American Heart Association
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
AxMP	Auxiliary Investigational Medicinal Product
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
BP	Blood Pressure
BTD	Breakthrough Therapy Designation
BUN	Blood Urea Nitrogen
CAPS-4	Clinician-Administered PTSD Scale for DSM-4
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
%CDT	%Carbohydrate-deficient Transferrin
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl/F	Apparent Clearance
C_{max}	Peak Concentration
CMC	Chemistry Manufacturing and Control
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatinine Phosphokinase
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CRU	Clinical Research Unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DID	Dissociative Identity Disorder
dIGPP	Cohen's d Independent Groups Pre-test Post-test
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSUR	Development Safety Update Report
EAT-26	Eating Attitudes Test
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
ED	Emergency Department

EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ePRO	Electronic Participant Reported Outcome
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human Chorionic Gonadotropin
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability
HPA	Hypothalamic-pituitary-adrenal
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IPF	Inventory of Psychosocial Functioning
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
kg	Kilogram
LAM	Lactational Amenorrhea Method
LAR	Legally Authorized Representative
LTFU	Long-term Follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MPBC	MAPS Public Benefit Corporation
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
mg	Milligram
mITT	Modified Intent-to-Treat
mmHg	Milligrams of Mercury
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
NDA	New Drug Application
NIMP	Non-Investigational Medicinal Product
PABP	Person Able to Become Pregnant
PAC	Premature Atrial Contractions
PBC	Public Benefit Corporation

PK	Pharmacokinetic
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PVC	Premature Ventricular Contractions
RA	Regulatory Agency
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SE	Subjective Effects
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SIB	Suicidal Ideation and Behavior
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SRNU	Self-reported Nicotine Use
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Half-life of drug
TAS-20	Toronto Alexithymia Scale
TBI	Traumatic Brain Injury
TdP	Torsade de pointes
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to peak concentration of the drug
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal
U.S.	United States
VA	U.S. Department of Veterans Affairs
VAS	Visual Analog Scale
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1.0 Protocol Summary

1.1 Synopsis

Protocol Title

A Phase 1, single center, open label, randomized sequence, 2-period cross-over study to determine the effect of food on the relative bioavailability of 3,4-methylenedioxymethamphetamine (MDMA) oral formulation in healthy volunteers

Brief Title

MDMA food effects in healthy volunteers

Rationale

The sponsor has completed a Phase 3 study of MDMA-assisted therapy for individuals diagnosed with severe PTSD demonstrating the safety and efficacy of this treatment. However, the effect of food intake on the absorption and bioavailability of orally administered MDMA is not yet well characterized.

This protocol is a Phase 1 open-label study with a primary purpose to evaluate the food effect of a high calorie meal as compared to fasting conditions on the relative bioavailability of oral MDMA capsules in healthy volunteers. In addition, an increase in heart rate is anticipated following MDMA administration. Therefore, the secondary purpose of this study is to evaluate the effect of food on the safety and tolerability of oral MDMA, as well as MDMA effects on ECG. Directly comparing the pharmacokinetics of MDMA and its active metabolite, 3,4-methylene-dioxyamphetamine (MDA) in a within-subject crossover study will allow for assessment of any impacts of food and inform product labeling.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of a high fat (high calorie) meal as compared to administration in the fasted state on the relative bioavailability of oral MDMA capsules in healthy volunteers.	PK parameters determined for MDMA and its active metabolite MDA: area under the concentration-time curve from dosing time to last measurement time (AUC_{0-t}), area under the concentration-time curve from dosing time to infinity ($AUC_{0-\infty}$), and peak concentrations (C_{max}).
Safety	
To characterize the cardiac-related effects of MDMA by collecting supportive ECG data.	Mean change from baseline QT interval corrected for heart rate.
To observe the rates of treatment emergent adverse events of special interest that would reflect a serious arrhythmia or suggest the potential for such an arrhythmia.	The rates of the following events: • Torsade de pointes (TdP) • Sudden death • Ventricular tachycardia • Ventricular fibrillation and flutter • Syncope of cardiovascular etiology
To evaluate the effect of MDMA and its active metabolite MDA, on hemodynamic parameters compared to baseline when administered to healthy volunteers.	Change from baseline in basal (resting) hemodynamic parameters: heart rate (HR) systolic blood pressure (SBP), diastolic blood pressure (DBP).

To further evaluate the safety and tolerability of MDMA in both fed and fasted states.	Incidence of adverse events, clinical laboratory test results, and vital sign measurements (body temperature).
Exploratory	
Further characterize the subjective effects of MDMA.	Change in subjective effects (self-reported VAS) from pre-dose to multiple timepoints post-dose.

Overall Design

This phase I, open-label, randomized sequence, multi-dose, 2-period crossover pharmacokinetic (PK) study assesses the effect of food on the relative bioavailability of MDMA.

Potential participants will be identified by the clinical site and invited to phone screen for the study. Following informed consent, potential study participants will undergo screening examinations to assess eligibility for inclusion in the study. Participants can enroll in this study after meeting all inclusion criteria without meeting any exclusion criteria.

Participants will be randomized to receive one of two conditions before the other:

- **Fasted Treatments**: 10 hours of fasting followed by IMP administration with 240 mL water.
- **Fed Treatments**: A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal will be consumed within 30 minutes of IMP administration.

Participants will be confined at the Clinical Research Unit (CRU) for each Dosing Session from the time of check-in on the night before dosing until discharge 48 hours after dosing. IMP will be administered on Day 1 following the treatment sequence to which the participant has been randomized. Concentration-time profiles of MDMA will be determined in the time interval 0-72 hours post-dose, according to the expected PK profiles of MDMA and its metabolites [1]. Participants will remain at the CRU for at least 36 hours after administration of study drug for collection of serial blood samples for PK analysis and safety monitoring. An additional outpatient visit will occur 72 hours after dosing to collect a final PK sample and perform safety assessments.

The washout period between Dosing Sessions will be at least 14 days. Participants that experience emesis within 4 hours after a drug dose may be withdrawn from the study and replaced with a new participant.

An End of Study Visit will be performed 2-10 days after the completion of the final Dosing Session.

An informal interim analysis may be performed after approximately 5 participants have completed at least one Dosing Session to confirm the PK parameters are reported as expected based on existing literature.

Number of Participants and Study Duration

Published trials in patient populations from the sponsor have a post-ICF ineligibility rate of ~62% for MDMA-assisted therapy. To ensure a healthy-control population, eligibility criteria are more narrow than those in patient population studies and therefore the sponsor anticipates a potentially higher screen fail rate. Therefore, the protocol will permit ICF and screening of up to 50

participants to achieve 12 participants enrolled to study intervention. If a participant withdraws prematurely, they may be replaced at the discretion of the study sponsor.

Study details include:

- The study duration will be approximately 10 weeks for each participant (including a screening period of 4 weeks).
- Two Dosing Sessions will occur, with a washout period of at least 14 days between treatments.
- Participants will stay at the Clinical Research Unit (CRU) starting the night prior to each Dosing Session and then remain in the CRU until 48 hours after dosing. An outpatient visit will occur 72 hours after dosing.
- After both Dosing Sessions have been completed, an End of Study Visit will occur 7-14 days after final Dosing Session visit.

Intervention Groups

Participants who are enrolled in the study will be randomized to 1 of 2 dosing regimens, both of which receive the same intervention in opposite order. Group 1 receives a Fasted Treatment followed by a Fed Treatment, while Group 2 receives a Fed Treatment followed by a Fasted Treatment.

Fasted Treatments: Following an overnight fast of at least 10 hours, participants will be administered 100 mg MDMA (equivalent to 120 mg MDMA HCl) with 240 mL of water. No food should be allowed for at least 4 hours post-dose.

Fed Treatments: A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal will be used as a test meal for food-effect evaluation. Following an overnight fast of at least 10 hours, participants will start the recommended meal 30 minutes prior to administration of the drug product. Participants will eat this entire meal in 30 minutes or less. 100 mg MDMA (equivalent to 120 mg MDMA HCl) will be administered 30 minutes after start of the meal with 240 mL of water.

Data Monitoring/Other Committee

A Data Monitoring Committee (DMC) will not be used for this open-label study.

2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy in patients with posttraumatic stress disorder (PTSD). MAPS-sponsored studies are implemented through MAPS' wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (PBC), a small or medium-sized enterprise organization.

Controlled Phase 1 studies, nonclinical studies, Phase 2 and Phase 3 studies and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA under the U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) #063384. MDMA-assisted therapy is an FDA Breakthrough-Designated treatment for PTSD based on the potential for substantial improvement over available medications.

2.1 Study Rationale

The sponsor has completed a Phase 3 study of MDMA-assisted therapy for individuals diagnosed with severe PTSD demonstrating the safety and efficacy of this treatment. However, the effect of food intake on the absorption and bioavailability of orally administered MDMA is not yet well characterized.

This protocol is a Phase 1 open-label study with a primary purpose of evaluating the food effect of a high calorie meal as compared to fasting conditions on the relative bioavailability of oral MDMA capsules in healthy volunteers. In addition, increases in heart rate are anticipated following MDMA administration. Therefore, the secondary purpose of this study is to evaluate the effect of food on the safety and tolerability of oral MDMA, as well as MDMA effects on ECG. Directly comparing the pharmacokinetics of MDMA and its active metabolite MDA, in a within-subject crossover study will allow for assessment of any impacts of food and inform product labeling.

2.2 Background

2.2.1 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by Merck pharmaceutical company in 1912 [2, 3]. MDMA binds to monoamine transporters, enhancing synaptic levels of serotonin and norepinephrine, and to a lesser extent dopamine, by vesicular carrier-mediated release and reuptake inhibition of these neurotransmitters [4-10]. MDMA increases levels of affiliative neurohormones oxytocin and vasopressin, which is associated with increased trust and attenuation of reactivity to threatening cues, and cortisol and prolactin. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, which would treat the core psychopathology of PTSD for a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the dose. Effects of the dose last 3 to 6 hours. The pharmacokinetics of MDMA in humans has been characterized using oral doses of up to 150 mg MDMA, and its disposition follows nonlinear pharmacokinetics [11]. Metabolism of MDMA results in N-demethylation to the active metabolite 3,4-methylenedioxyamphetamine (MDA). Orally administered MDMA has a half-life of 7 to 9 hours and its metabolite MDA has a half-life of 10 to 12 hours, resulting in the elimination of both drugs within 72 hours in humans [1]. Unlike

approved PTSD medications, therapeutic effects of MDMA have a rapid onset, and do not require daily dosing or a steady state in the blood to be effective. Thus, the effects of MDMA are distinct from and work through different mechanisms than anxiolytics and SSRIs. Despite being a Schedule I controlled substance, there is no evidence that limited doses of MDMA in controlled clinical settings creates a physical dependence or drug seeking behavior. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (unregulated material represented as containing MDMA) [12, 13]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [14]. Hence, MDMA is said to have low abuse potential in clinical settings.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MDMA is provided in the Investigator's Brochure (IB).

2.2.2 Previous Clinical Experience with MDMA

MDMA-assisted therapy is a novel treatment package that combines therapeutic techniques with the administration of MDMA as a pharmacological adjunct intended to enhance certain aspects of therapy. In the 1970s, psychotherapists used MDMA-assisted therapy [15]. Legal therapeutic use continued until its placement on the U.S. list of Schedule 1 [16-18]. An estimated 500,000 doses of MDMA were administered during therapy [16, 19].

Controlled human studies for clinical development of MDMA commenced in the mid-1990s with a MAPS-funded investigator-initiated Phase 1 dose-response safety study [20, 21]. Starting in 2000 in Spain, MAPS funded a Phase 2 investigator-initiated dose-response effect and safety pilot study in participants with PTSD that was terminated early due to political pressure. This study enrolled six participants, with four receiving a single session of MDMA-assisted therapy without any safety concerns and with some PTSD symptom reduction [22]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS IND with FDA.

MAPS initiated an international series of Phase 2 clinical trials to develop the medical use of MDMA-assisted therapy for patients with chronic, at least moderate PTSD (CAPS-4 score: 50+), with at least 6 months of symptoms. Intent-to-treat (ITT) analysis of primary efficacy and safety data from six MAPS-sponsored MDMA PTSD Phase 2 clinical trials worldwide (MP1, MP2, MP4, MP8, MP9, MP12) consisting of 107 blinded participants with chronic PTSD was completed in 2016 [23]. In these studies, PTSD, independent of cause, appears treatable with a two- to three-session treatment package of MDMA-assisted therapy, as assessed by difference in CAPS-4 severity scores from baseline to 1 to 2 months after the final experimental session. Large placebo-subtracted effect sizes (Cohen's d=0.9), initial indications of efficacy, and favorable safety outcomes led to the approval of MDMA for the treatment of PTSD as a Breakthrough Therapy Designation (BTD) by the FDA in 2017 for expedited drug development [24]. Improvements were durable at least 12 months after the last Experimental Session in 91 participants who received a therapeutically active dose of MDMA in these Phase 2 studies with 67% not meeting PTSD diagnostic criteria per CAPS-4 assessment [25].

MAPS completed a pivotal Phase 3 clinical trial (MAPP1) in 2020, further demonstrating the efficacy and safety of MDMA-assisted therapy for treatment of PTSD [26]. In a randomized, double-blind, placebo-controlled study, 90 participants with severe PTSD (CAPS-5 score: 35+ with at least 6 months of symptoms) were treated across 15 sites. Similar to Phase 2 results, PTSD symptoms were significantly attenuated by MDMA-assisted therapy. Manualized therapy in conjunction with MDMA (divided-doses of 80+40 mg or 120+60 mg MDMA HCl) was statistically superior for PTSD treatment in CAPS-5 severity scores from Baseline to 2 months

after three blinded experimental sessions in comparison to an inactive placebo ($p<0.0001$). At the primary endpoint, 67% of participants in the MDMA group no longer met diagnostic criteria for PTSD, compared to 32% of the placebo group. Based on the successful completion of MAPP1, a confirmatory Phase 3 clinical trial (MAPP2) is currently underway to encompass a larger sample of participants with moderate to severe PTSD.

As of October 01, 2020, with 341 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1,434 participants in MDMA research studies conducted without sponsor support (for a total of at least 1,775 individuals), the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted therapy.

A comprehensive review of MDMA research can be found in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MDMA may be found in the IB, Informed Consent Form (ICF) and/or development safety update report (DSUR).

2.3.1 Risk Assessment

Potential risks, summaries, rationale, and mitigation strategy can be found in Table 1: Risk Assessments. For more information, see Investigator's Brochure, section 7.4 Risk Assessment and Mitigation.

Table 1: Risk Assessments

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of IMP		
Cardiovascular and Cerebrovascular Events	MDMA transiently increases heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes typically last no more than 8 hours. Most people do not experience elevations in cardiovascular parameters that exceed those seen after moderate exercise. An examination of safety data drawn from Phase 2 and Phase 3 studies of MDMA-assisted therapy detected a dose-dependent increase in SBP and to a lesser extent DBP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.	• Triplicate ECGs and a 1-minute rhythm strip will be completed at screening to assess for undiagnosed cardiac conduction abnormalities. • Before and after IMP administration, site staff will monitor vital signs and perform triplicate ECGs. Site staff will attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction (AMI) after IMP administration. Any symptoms such as chest pain, shortness of breath, neurological deficit or confusion or other potential indicators of end organ effects will prompt additional vital sign measurements, and intervention if appropriate. Site staff will notify the investigator for evaluation if this occurs, see Section 7.1.1 QTc Stopping Criteria.

Negative Psychological Impact	Psychological distress from MDMA could arise from the onset of MDMA effects until the last effects have dissipated, or even later. Anxiety or distress during the session may also occur. In addition, psychological distress could arise following a Dosing Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In clinical studies treating participants with moderate or severe PTSD, these symptoms have been self-limiting and have responded well to reassurance from the research team, with occasional use of benzodiazepines for anxiety. These effects are not expected to occur in this healthy volunteer population.	• Provision of a preparation session to describe the potential psychological effects of MDMA. • Provision of an optional post-dose Integration Session to facilitate the processing of any issues which may have arisen for the participant while experiencing the effects of MDMA. • Site staff will be trained on psychological effects of MDMA and trained on how to support participants if they experience difficult or challenging emotions. • Participants will remain confined (inpatient) until at least 48 hours post-dose, by which time all effects of MDMA will have dissipated.
Thermoregulatory Events	Epidemiological reports of Ecstasy (unregulated material represented as containing MDMA) use have documented cases of hyperthermia resulting in rhabdomyolysis. In MAPS-sponsored Phase 2 and Phase 3 studies, MDMA administered in a controlled setting produces only a slight increase in body temperature (up to approximately 1° C).	• During IMP administrations, ambient temperature will be kept at a comfortable level during IMP administration. If a participant's temperature rises more than 1° C or the participant states that they feel hot, attempts will be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. • If body temperature rises more than 1.5° C above baseline despite these efforts, the site physician will be consulted.
Osmolarity Changes	Epidemiological reports of Ecstasy use indicate that combining Ecstasy with increased consumption of water and permissive factors, such as strenuous exercise in warm ambient temperatures, can cause in changes in osmolality resulting in hyponatremia.	• Participants will be limited to a maximum of 3 liters of fluid consumption during experimental sessions.

Reproductive and Developmental Risks	MDMA has been demonstrated to be negative for genotoxicity, both *in vitro* and *in vivo*, with and without metabolic activation. Consistent with this, despite very high doses of MDMA being tested in preclinical studies, none have reported carcinogenic effects. However, there is no data on the use of MDMA in pregnant individuals.	• Participants who are pregnant or breast feeding will be excluded from participation. • Urine pregnancy tests will be conducted during screening and immediately prior to any Dosing Session, and at the end of systemic exposure. • Participants who are able to become pregnant will be required to adhere to contraceptive measures with a <1% failure rate, as described in Appendix 2: Contraceptive and Barrier Guidance.
Abuse Potential	Despite its classification as a Schedule I drug (U.S.), there have been no AESIs reported and MAPS-sponsored Phase 2 and Phase 3 studies which could be suggestive of abuse potential among research participants treated with MDMA.	• MDMA is only administered under supervision and no take-home doses are administered. MDMA administration and handling follows all regulations pertaining to the use of controlled substances within research studies.
Risk of Other Study Procedures		
Discomfort with Medical Assessments	Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress.	• Medical examinations and blood sampling are required to establish eligibility and measure the primary endpoint and cannot be omitted from the protocol.
Other		
Suicide and Risk of Self-Harm	MDMA is a CNS-active intervention and therefore there is a theoretical risk of suicidal ideation and/or thoughts related to self-harm.	• Changes in suicidal ideation will be monitored throughout the study using the C-SSRS.

2.3.2 Benefit Assessment

There is no direct benefit to participants in this study. It is hoped that the data generated will enable significant insight into the bioavailability of MDMA in both fed and fasted states.

2.3.3 Overall Benefit Risk Conclusion

Based on the previously reported data and the current state of scientific knowledge, the data generated this study will provide an important contribution to development of MDMA-assisted therapy for PTSD.

Across Phase 2 and Phase 3 studies, the overall rates of AEs and reactions are low and generally self-limiting. In addition, there was an absence of AEs supporting drug dependence, intentional drug misuse, and substance abuse, and one participant to date has reported experiencing hallucinations that reflect acute intoxication in PTSD patients in a controlled therapeutic setting. Proper preparation, testing, monitoring, and follow-up support is expected to mitigate the potential risk for cardiovascular events or psychologically distressing events that have been noted as medium-level safety risks. Risk mitigation mechanisms have been incorporated into the study design and will reduce the difficulties that participants might have with adverse reactions as described in Table 1: Risk Assessments. This Phase 1 study is intended to assess the effect of food on the pharmacokinetics of MDMA and its active metabolite, MDA.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with MDMA administration are justified by the anticipated benefits that may be afforded in the future to patients.

3.0 Objectives and Endpoints

The overall objective of this pharmacokinetic study is to assesses the effect of food on the relative bioavailability of MDMA in healthy volunteers.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of a high fat (high calorie) meal as compared to administration in the fasted state on the relative bioavailability of oral MDMA capsules in healthy volunteers.	PK parameters determined for MDMA and its active metabolite MDA: area under the concentration-time curve from dosing time to last measurement time (AUC_{0-t}), area under the concentration-time curve from dosing time to infinity ($AUC_{0-\infty}$), and peak concentrations (C_{max}).
Safety	
To characterize the cardiac-related effects of MDMA by collecting supportive ECG data.	Mean change from baseline QT interval corrected for heart rate.
To observe the rates of treatment emergent adverse events of special interest that would reflect a serious arrhythmia or suggest the potential for such an arrhythmia.	The rates of the following events: • Torsade de pointes (TdP) • Sudden death • Ventricular tachycardia • Ventricular fibrillation and flutter • Syncope of cardiovascular etiology
To evaluate the effect of MDMA and its active metabolite MDA, on hemodynamic parameters compared to baseline when administered to healthy volunteers.	Change from baseline in basal (resting) hemodynamic parameters: heart rate (HR) systolic blood pressure (SBP), diastolic blood pressure (DBP).

To further evaluate the safety and tolerability of MDMA in both fed and fasted states.	Incidence of adverse events, clinical laboratory test results, and vital sign measurements (body temperature).
Exploratory	
To further characterize the subjective effects of MDMA.	Change in subjective effects (self-reported VAS) from pre-dose to multiple timepoints post-dose.

4.0 Study Design

4.1 Overall Design

This phase I, open-label, randomized sequence, multi-dose, 2-period crossover pharmacokinetic (PK) study assesses the effect of food on the relative bioavailability of MDMA.

Potential participants will be identified by the clinical site and invited to phone screen for the study. Following informed consent, potential study participants will undergo screening examinations to assess eligibility for inclusion in the study. Participants can enroll in this study after meeting all inclusion criteria without meeting any exclusion criteria.

Participants will be randomized to receive one of two conditions before the other:

- **Fasted Treatments**: 10 hours of fasting followed by IMP administration with 240 mL water.
- **Fed Treatments**: A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal will be consumed within 30 minutes of IMP administration.

Participants will be confined at the Clinical Research Unit (CRU) for each Dosing Session from the time of check-in on the night before dosing until discharge 48 hours after dosing. IMP will be administered on Day 1 following the treatment sequence to which the participant has been randomized. Concentration-time profiles of MDMA will be determined in the time interval 0-72 hours post-dose, according to the expected PK profiles of MDMA and its metabolites [1]. Participants will remain at the CRU for at least 36 hours after administration of study drug for collection of serial blood samples for PK analysis and safety monitoring. An additional outpatient visit will occur 72 hours after dosing to collect a final PK sample and perform safety assessments.

The washout period between Dosing Sessions will be at least 14 days. Participants that experience emesis within 4 hours after a drug dose may be withdrawn from the study and replaced with a new participant.

An End of Study Visit will be performed 2-10 days after the completion of the final Dosing Session.

An informal interim analysis may be performed after approximately 5 participants have completed at least one Dosing Session to confirm the PK parameters are reported as expected based on existing literature.

4.2 Scientific Rationale for Study Design

This protocol is for a Phase 1 open-label study with a primary purpose of evaluating the effect of food on the pharmacokinetics of MDMA and its active metabolite MDA.

In addition, an increase in heart rate is anticipated following MDMA administration. Therefore, the secondary purpose of this study is to evaluate the effect of food on the safety and tolerability of oral MDMA, as well as MDMA effects on ECG.

4.3 Justification for Dose

A dose of 100 mg MDMA (equivalent to 120 mg MDMA HCl) was selected as it represents the proposed maximum single clinical dose of MDMA. Similar MDMA doses to the proposed dose in this study have been safely used in previous Phase 2 and Phase 3 studies sponsored by MAPS. This dose is expected to produce all commonly reported effects of MDMA.

In both Fasted Treatment and Fed Treatment Dosing Sessions, the total administered dose of MDMA will be 100 mg MDMA (equivalent to 120 mg MDMA HCl).

Table 3: Dose Regimen of MDMA

Group 1		**Group 2**	
Dosing Session	**MDMA Dose**	**Dosing Session**	**MDMA Dose**
1 (Fasted)	100 mg	1 (Fed)	100 mg
2 (Fed)	100 mg	2 (Fasted)	100 mg
Total Cumulative Dose	**200 mg**	**Total Cumulative Dose**	**200 mg**

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all periods of the study including the last visit.

The sponsor has the right to discontinue this study at any time. If the study is prematurely terminated, the investigator is to promptly inform participants and ensure any final safety assessments are completed. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with country regulations.

5.0 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Be 18 to 65 years of age inclusive at the time of signing the informed consent.

Type of Participant and Characteristics

2. Be considered generally healthy upon completion of medical history, physical examination, ECG and rhythm strip, and biochemical investigations as judged by the investigator.
3. Able to swallow pills.

Weight

4. Body weight of at least 48 kilograms (kg) and body mass index (BMI) within the range 18 – 30 kg/m^2.

Sex and Contraceptive/Barrier Requirements

5. For participants assigned female sex at birth:

   - A participant is eligible to participate if not pregnant or breastfeeding, and one of the following conditions applies:
     - Is not able to become pregnant as defined in Appendix 2: Contraceptive and Barrier Guidance.

   OR

     - Is a person able to be pregnant (PABP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 2: Contraceptive and Barrier Guidance, during the study intervention period and for at least 7 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
   - All PABP must have a negative highly sensitive pregnancy test (urine test) at screening and before each session receiving IMP.
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have evidence or history of significant medical disorder or illness that, in the opinion of the investigator, might pose risk in administering the study drug to the participant.
2. Have a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds [ms] corrected by Bazett's formula).

Other Exclusions

3. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with study participation.
4. Are unable to fast or consume the food provided in the study.

5.3 Lifestyle Considerations

All participants must agree to the following lifestyle modifications at time of signing the ICF and throughout the study.

Participants are eligible to enroll in the study if they:

- Are willing to complete all activities described in the ICF, which includes two MDMA Dosing Sessions and all related activities.
- Agree to not participate in any other interventional clinical studies during the duration of this study, without prior approval of the Medical Monitor.
- Agree not to take any new or prohibited medications or recreational drug substances during the course of the study without first discussing with the investigator in consultation with the Medical Monitor.
- Agree to inform the investigator of any changes in health during the course of the study (including both mental and physical health changes).

5.3.1 Meals and Dietary Restrictions

Participants must:

- For **Fasted Treatment** sessions, agree to fast overnight for at least 10 hours prior to drug administration. The drug product will be administered with 240 mL of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration, at a paced intake.
- For **Fed Treatment** sessions, agree to fast overnight for at least 10 hours and then consume a high-fat/high-calorie meal for food-effect evaluation. Agree to start consuming the recommended meal 30 minutes prior to administration of the drug product and finish the meal within 30 minutes. No additional food will be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour after drug administration, at a paced intake.
- Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice, from 7 days before the start of study intervention until the end of the final Dosing Session.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants must:

- Agree not to use caffeine for at least 12 hours prior to the Dosing Session.
- Refrain from all nicotine-containing products from 7 days before the first dosing session and throughout the duration of the study.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if approved by the investigator in consultation with the Medical Monitor. Rescreened participants should be assigned a new screening number for every screening/rescreening event and should sign a new copy of the ICF.

5.4.1 Pre-Dosing Early Termination

'Pre-Dosing Early Terminations' are defined as participants who were deemed eligible and enrolled in the study but are deemed ineligible prior to the first IMP administration. These participants may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to the first IMP administration. All enrolled participants, even Pre-Dosing Early Terminations, will be maintained in the Electronic Data System (EDC). Pre-Dosing Early Terminations are not considered evaluable.

Pre-Dosing Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. At any time prior to first IMP administration, if a potential participant is deemed to be ineligible, classify as a Pre-Dosing Early Termination, notify the potential participant that they are not eligible for the study, and do not schedule additional assessments. Do not perform the next visit.

6.0 Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Medications

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA as a hydrochloride salt (HCl). Refer to the IB for a comprehensive review of the pharmacology, effects, and proposed mechanisms of action of the Investigational Medicinal Product (IMP).

Table 4: Study Medication Intervention Administered

Intervention Label	Active Intervention
Intervention Name	3,4-methylenedioxymethamphetamine (MDMA) as a hydrochloride salt (HCl)
Intervention Description	100 mg MDMA, two 50 mg capsules (equivalent to 120 mg MDMA HCl), per Dosing Session
Type	Drug
Dose Formulation	capsules
Unit Dose Strength(s)	50 mg MDMA (equivalent to 60 mg MDMA HCl)
Dosage Level(s)	100 mg MDMA, two 50 mg capsules (equivalent to 120 mg MDMA HCl), per Dosing Session with a washout period of at least 14 days between sessions.
Route of Administration	Oral
Use	Experimental
IMP and NIMP/AxMP.	IMP
Sourcing	Provided centrally by sponsor.

Packaging and Labeling	The IMP is packaged in 50 mg MDMA (equivalent to 60 mg MDMA HCl) blister strips. Blister strips are packaged in cartons and labeled with a unique container number, protocol number, IMP name, lot number, sponsor contact information and a statement that the IMP is restricted to clinical study use only. All labels will comply with local, state/provincial, and federal regulations. This will include the following: *Caution: New Drug-Limited by Federal (or United States) law to investigational use.*

Table 5: Study Arms

Arm Title	**Group 1: Fasted/Fed**	**Group 2: Fed/Fasted**
Arm Type	Experimental treatment sequence of Fasted state followed by Fed state.	Experimental treatment sequence of Fed state followed by Fasted state.
Arm Description	Participants will receive 100 mg of MDMA (equivalent to 120 mg MDMA HCl) while in a Fasted state during their first inpatient session. During their second inpatient session, participants will receive 100 mg of MDMA (equivalent to 120 mg MDMA HCl) 30 minutes after consuming a high fat (high calorie) meal.	Participants will receive 100 mg of MDMA (equivalent to 120 mg MDMA HCl) 30 minutes after consuming a high fat (high calorie) meal during their first inpatient session. During their second inpatient session, participants will receive 100 mg of MDMA (equivalent to 120 mg MDMA HCl) while in a Fasted state.

6.1.1.1 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP, and any discrepancies are reported and resolved before use of the study IMP.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual.

6.2 Therapy and Emotional Support

This study does not include formal therapeutic sessions or therapy during MDMA Dosing Sessions.

A MAPS-trained study team member may be present during the Dosing Sessions to offer psychological support as necessary. Team members present during the Dosing Session may offer a grounded, empathic presence and support in the form of sitting next to the participant, listening

to the participant discuss thoughts or feelings which are emerging during the session, or holding the participant's hand if requested. They will not provide therapy to the participant and will engage in conversation only if initiated by the participant.

6.2.1 Preparation and Integrative Support

A Preparation Session will occur prior to the first Dosing Session, in which a MAPS-trained therapist will work with the participant to prepare for the psychological effects of MDMA, see Section 8.2 Preparation Session.

Additionally, following the Dosing Session an optional Integrative Session will be offered to the participant, facilitated by a MAPS-trained therapist, see Section 8.3.5 Integration Session.

All MAPS-trained therapists are extensively trained in a training program prior to the study to ensure all participants are treated in a similar manner. The largely non-directive therapeutic method is described in detail in the Treatment Manual. In Preparation Sessions, therapists address participants' questions and concerns and prepare them for the potential psychological and emotional effects of MDMA. In Integrative Sessions, therapists are present to answer any questions the participant may have, as well as to offer support and encouragement as the participant processes their experience of the MDMA session and any resulting challenges, emotional responses, or new perceptions.

6.3 Measures to Minimize Bias

Participants, site staff, and the sponsor will be aware that each participant will be receiving open-label MDMA with no blinding at the site level. The order of the fed and fasted treatments will be randomized for each participant.

Type of Study	**Description**
Open-label, no blinding at site level, with randomized treatment order	This is an open-label pharmacokinetic study. Participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the 2 arms of the study, according to the randomization schedule generated prior to the study by the study biostatistician. Each participant will be assigned to the first treatment (fed or fasted) and then crossed over to the alternate treatment.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study IMP directly from the investigator or designee. The date and time of each dose administered will be recorded in the source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. The person administering the IMP will confirm the participant has swallowed the IMP by checking the oral cavity, including under the tongue, once the participant has finished drinking the water to administer the IMP.

6.5 Dose Modification

There is no planned dose modification proposed in this study.

6.6 Continued Access to Study Intervention after the End of the Study

After completion of the study, no further access to the study intervention (IMP) will be provided.

6.7 Treatment of Dosing Errors

For this study, any dose of MDMA greater than intended dose of study intervention within a 24-hour time period will be documented as a dosing error.

In the event of a dosing error, the investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the dosing error.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Psychiatric Medications

Psychiatric medications are not permitted during the study.

6.8.2 Permitted Concomitant Medications

The site physician may prescribe necessary and appropriate medications in accordance with local country regulations during the study to treat AEs.

All psychoactive medications, herbal supplements, non-prescription medications, and prescription medications must be reviewed by the Medical Monitor. Failure to comply with protocol requirements for concomitant medications may result in withdrawal from treatment, depending on the investigator and Medical Monitor judgment.

6.8.2.1 Acutely Prescribed Medications

Acutely prescribed medication may be considered necessary if the participant experiences severe, persisting emotional distress, anxiety, or insomnia that is not resolved via empathetic listening or diaphragmatic breathing. The study site will supply acutely prescribed medication that will be obtained locally if prescribed by the site physician.

The name, dosage regimen, and date of the acutely prescribed medication administered will be recorded.

Although the use of acutely prescribed medications is allowable at any time during the study, this may alter the primary outcome PK results being collected. Therefore, if a participant requires acutely prescribed medication they may be withdrawn from the study and referred to further medical care if necessary. The site staff will make every effort to follow-up until the symptoms are resolved.

6.8.3 Prohibited Medications

To be enrolled in the study participants must:

- Be willing to comply with all medication requirements per protocol.

7.0 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of the site or study as a whole is detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study Dosing Sessions. If the Dosing Sessions are permanently discontinued, the participant may remain in the study and continue with the optional Integration Session. If the investigator determines it is in the participant's best interest to completely withdraw from the study, an early discontinuation visit should be conducted, defined as all the procedures included in the End of Study Visit.

7.1.1 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets either bulleted criterion based on multiple ECG readings will be withdrawn from study intervention.

- QTc >500 ms OR Uncorrected QT >600 ms
- Increase from baseline of QTc >60 ms

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, defined as all the procedures included in the End of Study Visit.
- The participant will be permanently discontinued from the study intervention and the study at that time.

- If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Site, affects the safety of the participant, the participant will not receive any additional IMP but will complete the remaining procedures in that Dosing Session, and an End of Study Visit.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (e.g., three telephone calls or emails). In addition, site shall reach out to the contact person (relative, spouse, close friend, or other support person) provided by the participant. Finally, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8.0 Study Assessments and Procedures

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria.

8.1 Screening Period

Prospective participants may be pre-screened by telephone to ascertain if they meet basic eligibility criteria. Data from potential participants who do not pass telephone screening will not be entered in the eCRF, but reason of ineligibility will be documented on a Telephone Screening Log.

Participants who are preliminarily eligible following the telephone screen will be invited to screen for the study. Site staff (preferably a member of the team who would be treating this potential participant) will explain and obtain written (or electronic) informed consent using the IRB-approved ICF. Written consent must be obtained prior to performing any tests or evaluations for the study. The signature may be obtained using an electronic 21 CFR Part 11 compliant system due to COVID-19. Discussion about the ICF may take place over a telemedicine visit or at the first in-person visit. If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

All individuals who are screened should be assigned a Screening Number and recorded on the Screening Log.

At any time during Screening, if a potential participant is deemed ineligible, they will be classified as a Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments. Participants who are eligible by pre-screening will be invited to undergo the informed consent process, either in-person or via telemedicine as allowed per local and study site regulations.

Screening may take place over multiple visits and will be completed in-person, via tele-assessment, or over the telephone. Medical records, if available, should be requested from the participant's general practitioner to ensure a comprehensive medical history has been obtained.

8.1.1 Enrollment

Participants who meet all eligibility criteria and are randomized to a treatment assignment will be considered enrolled in the study. Participants who meet all eligibility criteria but who are subsequently not randomized will be classified as screen failures.

8.2 Preparation Session

Participants will undergo one 90-minute Preparation Session via telemedicine prior to the first Dosing Session. During this session, a MAPS-trained individual will work with the participant to prepare for the psychological effects of MDMA, promote a safe set and setting for confronting any unexpected memories, emotions, and thoughts, and introduce and offer the optional post-dose Integration Session.

8.3 Dosing Period

8.3.1 Dosing Sessions

There will be two open-label Dosing Sessions. Procedures for each dosing session are the same, except for the meal during the fed treatment. Participants will be randomized to first treatment. Dosing Sessions must be at least 8 hours long, measured from 30 minutes prior to IMP administration. At both Dosing Sessions, a dose of 100 mg MDMA (equivalent to 120 mg MDMA HCl) will be administered.

Study team will call participants 7 days prior to CRU check-in to remind them to stop any smoking or use nicotine containing products, if applicable.

8.3.1.1 Check-in to CRU

Participants will arrive at the CRU the night prior to IMP administration.

- The site team will ensure the participant fasts for at least 10 hours prior to IMP administration and agrees to comply with all other requirements per Section 5.3 Lifestyle Considerations.
- The site team will inquire about any possible changes in health and concomitant medications to ensure the participant continues to meet all eligibility requirements and record AEs, as described in Section 8.7.5 Method of Detecting AEs and SAEs.
- The site team will complete symptom-directed physical exam, urine drug screen, urine nicotine/cotinine screen, alcohol screen, pregnancy test (for PABP only), and concomitant medication review.
- The site team will measure blood pressure, body temperature, and pulse.
- The site team will administer Since Last Visit C-SSRS.
- A symptom-directed physical examination, or additional vital signs measurements, may be conducted at any time if clinically indicated.

8.3.1.2 Pre-IMP administration

Prior to each Dosing Session:

- The site team will inquire about any possible changes in health and concomitant medications to ensure the participant continues to meet all eligibility requirements and record AEs, as described in Section 8.7.5 Method of Detecting AEs and SAEs.
- The site team will review procedures for the Dosing Session with the participant and some of the commonly experienced effects of MDMA.
- The site team will administer Since Last Visit C-SSRS.
- Ninety minutes to two hours prior to IMP administration, the site team will collect baseline measures:
    - Collect PK samples
    - Measure blood pressure, body temperature, and pulse
    - Administer a 12-lead ECG (in triplicate)
    - Administer the Subjective Effects VAS
- Thirty minutes prior to IMP administration, for Fed Treatments only:
    - Participants will begin eating a high-fat and high-calorie meal, see Section 8.3.2 Pre-IMP Meal.

8.3.1.3 During the Dosing Session

During each Dosing Session:

- The site team will administer the study IMP with 240 mL of water.
- The participant will sit or recline on comfortable furnishings. Participants will be encouraged to bring items to each dosing session which will provide comfort while under the effects of MDMA. This may include comfortable clothes, a personal pillow, soft blanket, music, art supplies, or other supplies to engage in light recreational activities. Eyeshades and a program of music will be provided for the participant if they wish to use them.
- Water will be provided throughout the session at a paced intake, not to exceed three liters overall.

- The site team will collect the following measures at the following timepoints after IMP administration: 30 minutes, 1, 2, 4, 6, 8, 12 hours.
    - Collect PK samples
    - Measure blood pressure, body temperature, and pulse
    - Administer a 12-lead ECG (in triplicate)
    - Measure Subjective Effects VAS
- **Note**: when multiple assessments are scheduled at the same timepoint, the above order of assessments should be observed, so that the PK sample is collected as close to the exact timepoint as possible.
- No food should be allowed for at least 4 hours post-dose. A mid-day meal may be offered at least 4 hours after medication administration, and an evening meal may be offered 4 hours later.
- A member of the site team will remain available to the participant throughout the Dosing Session, see Section 8.3.3 Psychological Support During Dosing Session.

8.3.1.4 End of Dosing Session

Following the final Day 1 Assessments at 12 hours, the site team will complete end of dosing procedures.

- The site team will record AEs and concomitant medications.
- The session may be ended if all medical and psychiatric parameters are acceptable, elevations in vital signs have resolved to pre-IMP levels, the participant is alert, ambulatory, and emotionally stable.

8.3.1.5 Post-Dosing Sessions

Participants will stay in the CRU for at least 36 hours following Dosing Session.

- An optional Integration Session will be offered 24 hours post-IMP to the participant, see Section 8.3.5 Integration Session.
- Following collection of samples and assessments 48 hours post-IMP, participant will be discharged from CRU.
- Participants will return on 72 hours post-IMP for sample collection and assessments.
- The site team will collect the following measures at the following timepoints after IMP administration: 24 hours post-IMP, 48 hours post-IMP, and 72 hours post-IMP.
    - Collect PK samples
    - Measure blood pressure, body temperature, and pulse
    - Administer a 12-lead ECG (in triplicate)
    - Administer Since Last Visit C-SSRS
- Meals are not restricted after the Dosing Sessions.

8.3.1.6 Washout Period and Second Dosing Session

The washout period between Dosing Sessions will be at least 14 days.

- Participants will be reminded not to smoke or use nicotine containing products during the washout period.
- Participants will cross over to the second study arm such that participants initially fasted will be fed and those initially fed will be fasted and repeat the procedures outlined above. The Pre-IMP Meal will only be administered in the “Fed” arm.

8.3.2 Pre-IMP Meal

A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal will be used as a test meal for food-effect evaluation. The targeted macronutirent allocation for the calories of this test meal is as follows: protein (150 calories), carbohydrates (250 calories), and fats (500-600 calories). Following an overnight fast of at least 10 hours, participants will start the recommended meal 30 minutes prior to administration of the drug product. Participants will eat this entire meal in 30 minutes or less.

- An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar number of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

The start and stop time of the start of the high-fat high-calorie pre-dose meal must be recorded. The percent of the total meal consumed by the end of the 30-minute eating period should be recorded. This percentage may be estimated by the study staff.

8.3.3 Psychological Support During Dosing Session

A MAPS-trained study team member will be present during the Dosing Sessions to offer psychological support as necessary. This may be in the form of sitting next to the participant and discussing thoughts or feelings which are emerging for the participant during the session. They will not provide therapy to the participant.

8.3.4 Night Attendant

A night attendant will accompany the participant during the overnight stay. The night attendant's primary function is to ensure the participant is comfortable and has a meal, to provide minimal support, and to alert qualified site staff in case of need expressed by the participant or determined by observation. All night attendants are interviewed, trained, and approved by the site team to ensure they are comfortable providing the necessary support and know whom to call if medical support is needed.

8.3.5 Integration Session

After Day 1 of each Dosing Session, an optional Integration Session will be offered to the participant. The purpose of this session will be to process any thoughts or feelings which emerged as a result of the MDMA and will be facilitated by a MAPS-trained therapist via telemedicine. If necessary, the facilitator will help the participant to reduce any residual psychological distress they are experiencing. The facilitator will be supportive, validate the experience, facilitate understanding and emotional clearing, and offer referral resources for further support as needed.

8.4 Study Termination Follow-up Period and Study Termination

8.4.1 End of Study Visit

An End of Study Visit will take place 2-10 days after day 4 of the second Dosing Session.

After all End of Study Visit procedures are completed, the participant is considered terminated from the study.

8.5 Study Assessments

8.5.1 Primary Outcome Measure

8.5.1.1 PK Blood Sampling

PK samples to determine the bioavailability of MDMA and its metabolites will be collected.

Blood samples will be collected for the determination of plasma concentrations and PK. Additionally, at the occurrence of an SAE, unscheduled blood samples should be collected as soon as possible relative to the event. Blood samples will be collected via a saline flush catheter or by direct venipuncture.

At each timepoint, approximately 2 mL of blood will be collected for the analysis of plasma MDMA and MDA concentrations. Samples will be collected in blood collection tubes containing EDTA K_2 anticoagulant, inverted several times, and immediately placed in an ice bath. The clock times of all blood draws will be recorded and reported for each subject. All tubes will be labeled with a bar code. When scanned, the bar code will provide the SUBJID, protocol ID, anticipated blood draw time point, and actual collection time. Samples should be stored at -20/70° C until it will be transported to the lab for analysis.

The total volume of blood collected for MDMA and MDA PK analysis is approximately 22 mL (11 samples over a period of 72 hours).

Blood samples for determination of plasma concentrations of study drug/metabolite will be analyzed at off-site contract laboratories designated by the sponsor. Samples will be analyzed using a validated bioanalytical method.

When multiple assessments are scheduled at the same timepoint, the following order of assessments should be observed, so that the PK sample is collected as close to the exact timepoint as possible:

1. PK or blood sample
2. Vital Signs
3. ECG

A detailed document providing standard operating procedures for PK sample collection, processing, storage, and shipment will be provided by the sponsor.

8.5.2 Exploratory Measures

8.5.2.1 Subjective Effects (SE)

The subjective effects (SE) chosen are based on literature reviews of subjective effects of MDMA among healthy volunteers in controlled studies [27, 28]. Subjective effects will be collected using the visual analog scale (VAS) on 14 items: negative mood, body perception changes, confusion, difficulty concentrating, compassion for self, compassion for others, positive mood, intellectual efficiency, social, calmness, talkative, open to new experiences, meaningful experience, emotional distress. VAS items are rated on a series of 100 mm long lines, marked from ‘not at all’

on the left to 'extremely' on the right. The SE measure takes approximately 10 minutes to complete.

8.6 Safety Assessments

Additional visits or repeat assessments (in person, at home, by telephone, or via tele-assessment) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential participant.

8.6.1 Suicidal Ideation and Behavior Risk Monitoring

Participants will be monitored appropriately and observed closely for increases in suicidal ideation and behavior (SIB) or any other unusual changes in behavior. Participants who experience increases in SIB should undergo a risk assessment.

Baseline assessment of suicidal ideation and behavior/intervention-emergent suicidal ideation and behavior will be monitored during the study using the MAPS Adapted C-SSRS.

8.6.1.1 MAPS Adapted Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical study [29]. It consists of a Baseline/Screening version and a Since Last Visit version that assess suicidal ideation, ideation intensity, and behavior. The C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The Baseline/Screening version will only be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. Participants who are discontinuing medications to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS Intensity scale obtained a Cronbach's alpha of 0.94 for the Since Last Visit form, and Last Visit MAPS-adapted C-SSRS severity scores were positively correlated with the BDI "suicide thoughts" item [30]. The MAPS Adapted C-SSRS was developed utilizing Dr. Kelly Posner's Columbia Suicide Severity Scale. The MAPS Adapted C-SSRS maintains the content and flow of the standard C-SSRS. The scale was adapted to modify formatting and add additional administrative guidance to reduce rater and data entry errors. The MAPS Adapted C-SSRS has been approved by Dr. Posner for use in MAPS Research and is referred to throughout the protocol as C-SSRS. The MAPS Adapted C-SSRS takes approximately 10 minutes to complete.

8.6.2 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, integumentary, and neurological systems. Traumatic Brain Injury (TBI) assessment with residual neurological signs or symptoms should be included as part of this exam. Height and weight will also be measured and recorded, which will be used to calculate Body Mass Index (BMI). A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.6.3 Vital Signs

Vital signs will be measured after 5 minutes of rest in a semi-supine position and will include temperature, systolic and diastolic blood pressure, and pulse.

8.6.4 Electrocardiograms

12-lead ECG(s) will be obtained after 5 minutes of rest in a semi-supine position. ECGs will be collected in triplicate using an ECG machine that automatically calculates the heart rate and measures PR, QRS, RR, QT intervals and morphological changes. A 1-minute rhythm strip will also be obtained to screen out participants with arrhythmias at baseline.

12-lead triplicate ECGs will be reviewed by an independent (blinded) reviewer for the purposes of assessing the safety endpoints of mean change from baseline QT interval corrected for heart rate , and any adverse events of special interest that would reflect a serious arrhythmia or suggest a potential for such arrythmia.

8.6.5 Clinical Safety Laboratory Tests

Laboratory assessments, detailed in Table 6: Protocol-required Safety Laboratory Tests, with the exception of urine pregnancy and drug tests, will be performed at the site clinical laboratory. Certificates and normal ranges will be stored in the site's Investigator Site File (ISF).

The site physician will confirm laboratory assessments gathered in screening for assessing eligibility. The site physician will use the list of normal ranges to conclude whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values after consultation with the Medical Monitor.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- If follow-up clinical labs are collected, record any clinically significant changes occurring during the study as an AE.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Table 6 Protocol-required Safety Laboratory Tests must be conducted in accordance with the Laboratory Manual.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

An additional blood collection will be performed at the End of Study visit, which will only repeat Hematology, Clinical Chemistry, Routine Urinalysis and CPK. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology [A]	• Hematocrit • Hemoglobin

	• Red Blood Cell (RBC) indices:
	  ○ RBC count
	  ○ Percentage and absolute differential counts
	  ○ Red cell distribution width (RDW)
	  ○ Mean corpuscular volume (MCV)
	  ○ Mean corpuscular hemoglobin (MCH)
	  ○ Mean corpuscular hemoglobin concentration (MCHC)
	  ○ % Reticulocytes
	• White blood cell (WBC) indices:
	  ○ RBC count
	  ○ Percentage and absolute differential counts
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils

Clinical chemistry [A]	• Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Albumin, serum • Albumin:Globulin (A:G) ratio • Alkaline phosphatase [B] • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Bilirubin, total and direct • Blood urea nitrogen (BUN): creatinine ratio • Calcium, serum • Carbon dioxide • Chloride, serum • Creatine phosphokinase (CPK) • Creatinine, serum and eGFR (calculated using CKD-EPI equation) • Globulin, total • Glucose • %CDT • Potassium, serum • Protein, total, serum • Sodium, serum
Routine urinalysis	• Specific gravity, color, appearance • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
Pregnancy testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for people able to become pregnant) [B]
Other screening tests	• Cytochrome P450 Genotyping Panel [A] • Thyroid Stimulating Hormone (TSH) with reflex free T3 and T4 • Urine drug screen • Urine or breath alcohol screen • Urine Nicotine/Cotinine screen
[A] All screening and repeat samples may be taken in the non-fasted state. [B] Local urine testing will be standard for the protocol.	

Investigators must document their review of each laboratory safety report.

8.6.6 Pregnancy Testing

- Pregnancy testing is required for participants that are a person able to become pregnant (PABP) as defined in Appendix 2: Contraceptive and Barrier Guidance.
- Pregnancy testing should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.7 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE) and remain responsible for following up on all AEs.

AEs will be reported by the participant (or by a caregiver, surrogate, or the participant's legally authorized representative, when appropriate).

8.7.1 AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

8.7.1.1 Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of any underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected dosing error of either study intervention or a concomitant medication. A dosing error will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

8.7.1.2 Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition or meet other prespecified reporting criteria.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure may fit the criteria for an AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Expressions of emotion or other emotional descriptions which are consistent with what would be expected during a typical IMP administration session with healthy volunteers, unless participant reports effects interfere with daily activities.
    - Limited examples of this include positive mood, compassion for self, compassion for others, intellectual efficiency, calmness, talkative, open to new experiences, and meaningful experience.

8.7.2 SAE Definition

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

1. Results in death.
2. Is life threatening.
    - The term *life threatening* in the definition of SAE refers to an event in which the participant 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.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    - In general, hospitalization signifies that the participant has been admitted (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 outpatient 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.
4. Results in persistent or significant disability/incapacity.
    - 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect.
6. Other situations:

    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

8.7.3 Adverse Events of Special Interest (AESI)

In accordance with the guidance Clinical Safety Data Management Definitions and Standards for Expedited Reporting ICH Topic E2A: Guidance for Industry or FDA Safety Reporting Requirements for INDs and BA/BE Studies, the sponsor will pay special attention to a subset of AEs. These AEs will be marked in the eCRF with the denotation "Adverse Event of Special Interest" (AESIs) whether serious or non-serious.

A subset of AEs will be collected in order to assess signals of cardiovascular risk for the IMP in the intended patient population that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, non-postural syncope, and seizures.

A subset of AEs involving suicide risk will be collected as AESIs whether serious or non-serious. These AESI terms include:

- Suicides
- Suicide attempts
- Self-injurious behavior associated with suicidal ideation
- Suicidal ideation judged to be serious or severe in the opinion of the investigator

In order to assess signals of abuse potential for the IMP in the intended patient population:

- AESIs involving the terms of Behavioral addiction, Drug abuser, Substance abuser, Dependence, Intentional product misuse, Overdose (accidental, intentional, or prescribed), or Drug diversion in cases that are related to MDMA or "Ecstasy" (unregulated material presented as MDMA) will be collected and coded as AESIs in the eCRF.
- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs;
- Qualitative urine drug test data will be collected prior to each Dosing Session. Any positive findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the Medical Monitor to assess compliance with ongoing eligibility criteria and for presence of AESIs.

If an AESI is a SAE or if it involves suicide risk, it should be reported via the eCRF within 24 hours of the site's awareness of the event.

8.7.4 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the study termination visit.

All AEs will be collected from initial study enrollment (in participants who meet eligibility criteria following screening) until the study termination visit.

Medical occurrences that begin prior to randomization but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.7.5 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.7.6 Recording and Follow-Up of AE and/or SAE

8.7.6.1 AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor, RA, or EC. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.7.6.2 Assessment of Severity

The investigator will assess severity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: No limitation in normal daily activity.
- **Moderate**: Some limitation in normal daily activity.
- **Severe**: Unable to perform normal daily activity.

8.7.6.3 Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The relationship of study treatment to an AE will be determined by the investigator based on the following definitions:

1. "Not Related": The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e., there are no facts, evidence, or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

2. "Related": The administration of the investigational product and AE are considered reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE or is the most likely cause of the AE. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- Following an initial report, the investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.7.6.4 Further Evaluation of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up, as defined in Section 7.3 Lost to Follow-up.

8.7.7 Reporting of SAEs

8.7.7.1 SAE Reporting via Paper Data Collection Tool

- Email transmission of the electronic SAE Form (paper data collection tool) is the preferred method to transmit this information to the Medical Monitor or study CRA. A scanned copy of a printed SAE form may be accepted if the electronic form cannot be submitted.
- In rare circumstances and in the absence of email equipment, notification by telephone is acceptable with a copy of the SAE Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Form within the designated reporting timeframes.
- Contacts for SAE reporting can be found on the title page of this document (the Medical Monitor) or in the sponsor contact list provided separately.

8.7.8 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator (within 24 hours of becoming aware of the event) to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authorities, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.7.9 Pregnancy

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.7.8 Regulatory Reporting Requirements for SAEs. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Any PABP who becomes pregnant while participating in the study will be withdrawn from the study and followed up for safety as stated above.

8.7.10 Disease-related Events and/or Disease-related Outcomes

This healthy volunteer study does not define any disease-related events.

8.7.11 Interruptions and Arrangements Due to COVID-19 Pandemic or Any Other Unforeseen Emergency at Clinic Locations

This clinical study may be impacted by the Coronavirus Disease 2019 (COVID-19) global pandemic. Special arrangements may be required for study continuation and participant and study site staff safety due to this or any other unforeseen emergency in the future. The following accommodations in the protocol will be allowed, captured, and noted in the Clinical Study Report as COVID-19 deviations when applicable:

- Delaying the start of the first inpatient arm after enrollment
- Delaying the second inpatient assessment window

For any participant with COVID-19 related illness, continued study participation after full recovery of the disease may be appropriate after discussion between the site physicians and Medical Monitors on a case-by-case basis.

8.8 Other Assessments

8.8.1 Pharmacokinetics

PK parameters are collected in this study as a Primary Outcome measure as per Section 8.5.1.1 PK Blood Sampling.

8.8.2 Genetics

This study may perform a Cytochrome P450 Genotyping Panel to assess variants in genes that code CYP isozymes that may influence pharmacokinetics and may predict or explain non-standard dose requirements, therapeutic failure, or adverse reactions.

8.8.3 Biomarkers

Biomarkers are not evaluated in this study.

8.8.4 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8.5 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9.0 Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and includes a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and safety endpoints.

9.1 Statistical Hypotheses

The primary objective is to analyze change in exposure measurements in participants with and without food. Thus, the null hypothesis to be tested is that food will have no effect on exposure of MDMA.

9.1.1 Multiplicity Adjustment

No adjustments are planned for controlling overall type I error as it is not relevant for this type of study.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	All randomized participants. Participants will be included in the analyses according to the intervention they actually received.
Safety analysis set	All participants who are exposed to IMP. Participants will be included in the analyses according to the intervention they actually received.
PK analysis set	All participant who have sufficient timepoints for evaluable PK and do not vomit within 4 hours of dosing.

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive and summary statistics will be performed, as appropriate. Statistics will include number of observations, mean, standard deviation, median, range, and inter-quartile range for continuous variables, and the number and percent for categorical variables; 95% or 90% confidence intervals will be presented where appropriate. Additional statistics such as geometric mean and coefficient of variation (CV%) may be calculated as warranted. Demographics and baseline characteristics (e.g., age, sex, race, ethnicity, body weight) will be summarized using descriptive statistics.

The reasons for all discontinuations will be tabulated and grouped by treatment group and major reason. All deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be described.

9.3.2 Primary Endpoint Analysis

The primary objective is to compare bioavailability under fasted vs. fed administration conditions, as measured by PK parameters of MDMA and its active metabolite MDA. These relationships will be sought using linear and nonlinear models.

Plasma PK parameters for MDMA and its active metabolite will be calculated using non-compartmental and/or compartmental methods as appropriate using actual sample collection times post-dose. Individual subject PK parameters will be listed and descriptive statistics will be

calculated for both cohorts. Mean and individual subject plasma concentration-time profiles will be presented on rectilinear and semi-logarithmic scales.

Plasma concentrations of MDMA and its active metabolite MDA will be listed for each individual subject and descriptive statistics will presented for each time point. As warranted, PK data will be presented in tables and graphical displays with time "0" assigned to the dosing time of each treatment.

The statistical analysis will be performed on log-transformed peak MDMA concentrations (C_{max}), time to peak concentration of the drug (T_{max}), delay in achieving T_{max} (t_{lag}), terminal elimination half-life of the drug ($t_{1/2}$), apparent clearance (Cl/F), apparent volume of distribution (Vd/F), area under the concentration-time curve from dosing time to last measurement time (AUC_{0-t}) and area under the concentration-time curve from dosing time to infinity ($AUC_{0-\infty}$). The 90% confidence interval (CI) for the ratio of population geometric means between fasted and fed conditions will also be provided for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The same analysis will be performed for the active metabolite MDA. An absence of a food effect on bioavailability is established if the 90% CI for the ratio of the population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80-125 percent for $AUC_{0-\infty}$ (AUC_{0-t} when appropriate) and C_{max}.

Correlations between PK parameters and safety may be explored graphically and if relationships are observed, exploratory analyses may be performed. Additional exploratory analyses may be conducted and will be described in detail in a separate analysis plan.

9.3.3 Safety Analyses

Safety and tolerability will be evaluated. Safety analyses include change from Baseline blood pressure, pulse, and temperature values at specified time points. All laboratory results and vital sign measurements will be summarized using appropriate descriptive statistics.

Adverse event (AE) data will be descriptively evaluated. Descriptive statistics (e.g., number of observations, means, standard deviations, medians, maximum and minimum values) will be used to summarize continuous variables. Frequencies, proportions, and the exact 95% confidence intervals (CI), when appropriate, will be used to summarize categorical variables. Subject listings will also be provided.

Suicidal ideation and behavior will be summarized according to suggestions made in the C-SSRS Scoring and Data Analysis Guide. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by treatment group and time period (lifetime, screening, baseline, each Dosing Session (pre- and post-IMP), Integrative Sessions, and endpoints). Frequency and incidence of positive or serious ideation and suicidal behavior will be presented using descriptive statistics in tabular format.

ECG analysis: Mean of the triplicate ECGs at each nominal time point will be used for all reporting and analysis; however, individual values will be used to calculate the correction coefficient (γ) for the individual correction QTc (QTcI). Individual correction coefficient, γ, will be estimated using linear regression of log QT on log RR for each subject using all baseline ECG assessments collected before Day 1 dosing within a subject.

The QTc corrections will be individual correction by $QTcI = QT/RR^{\gamma}$, Fridericia's by $QTcF = QT/RR^{0.33}$, and Bazett's by $QTcB = QT/RR^{0.5}$.

Change from baseline (ΔQTcI) will be calculated as the average of the three predose assessments on Day 1 subtracted from the value (i.e., QTc) on Day 1 at a given time t. The effect of MDMA on cardiac repolarization will be assessed, as measured by the time point with the largest upper one-sided 95% confidence limit for the ΔQTcI. The relationship between ΔQTcI (dependent variable) and MDMA or MDA concentrations (independent variable) will be determined using a linear mixed-effects model.

Additional safety analyses other than those described in this section may be performed if deemed appropriate and will be described in detail in a separate analysis plan.

9.3.4 Other Analyses

Additional exploratory analyses will be outlined in the SAP.

9.4 Interim Analysis

An informal interim analysis may be conducted after 5 participants have completed at least one Dosing Session. This will allow for any issues with the pharmacokinetic assay to be identified as early as possible in the study.

ECGs may also be sent to the independent reviewer for analysis at this time, if requested by the sponsor.

9.5 Sample Size Determination

Approximately 50 participants will sign an ICF and be screened to achieve 24 enrolled, to yield 18 evaluable and at least 12 participants who complete both study periods. The sample size for this study is determined per FDA guidance on *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*.

Note: Enrolled means a participant, or their legally acceptable representative, has agreed to participate in the clinical study following completion of the informed consent process and eligibility screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered as enrolled if the informed consent is not withdrawn prior to participating any study activity after screening.

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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 participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- 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 or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The study record must include documentation that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative (LAR).
- Participants who are rescreened are required to sign a new ICF.
- If applicable, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Ongoing Safety Data Review Committee

- Participant safety will be continuously monitored by the sponsor's internal Medical Science and Safety team.
- In addition, an aggregated safety data review that includes safety signal detection will be performed as part of the sponsor's standard operating procedure for the MDMA development program, per the sponsor's SOP.
- For trials with a Data Monitoring Committee, safety review will occur per the DMC charter and applicable sponsor SOP.

Dissemination of Clinical Study Data

Study data and results will be posted in accordance with applicable local regulations (e.g., 42 CFR, Part 11.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in a separate document.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Data Safety and Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous or current medical records or transfer records, depending on the study.
- Definition of what constitutes source data and its origin can be found in the source data acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or clinical trial agreement, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included in the study completed earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to participants enrolled in a study and therefore, encourage publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In that case, it is intended that the first publication of the study's primary clinical data be co-authored by designated participating centers and the sponsor or designated representatives. Inclusion of Clinical Investigators in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the Study.
- All publications will follow International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, unless other guidelines are required by the journal. It is understood by the Clinical Investigators that the information generated in this study will be used by the sponsor in connection with the development of the IMP and therefore may be disclosed to government agencies in various countries.
- To allow for the use of information derived from the study, it is understood that the investigators are obliged to provide the sponsor with complete test results, all study data, and access to all study records.
- It is mandatory that all data analysis is done on the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician and follows the SAP where applicable.

- Any results of medical investigations with the sponsor and/or publication/lecture/manuscripts based thereon shall be exchanged and discussed by the investigator and sponsor prior to submission for publication or presentation.
- Due regard shall be given to the sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating, and maintaining submissions to health authorities, and coordinating with other ongoing studies in the same field.
- The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.

Appendix 2: Contraceptive and Barrier Guidance

Participants in the following categories are considered a person able to become pregnant (PABP), i.e., fertile:

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - PABP on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance

Contraceptive use by either partner should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods of contraception are defined as those with a failure rate of <1% per year when used consistently and correctly.

Refraining from sexual activity periodically (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

Contraceptives Allowed During the Study Include:

Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [A] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) [A] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) [B]
Highly Effective Methods That Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [A]
  o Oral
  o Intravaginal
  o Transdermal
  o Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation [A]
  o Oral
  o Injectable
• Refraining from engaging in sexual activities that lead to pregnancy [C]

[A] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. [B] Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note**: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. [C] This is considered a highly effective method only if defined as occurring over the entire period of risk associated with the study intervention. Reliability needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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