Protocol and Synopsis MED1
IND #142908

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An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Psychotherapy for Eating Disorders

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USE  In conjunction with relevant U.S. Food and Drug Administration (FDA) and Health Canada (HC) guidance

Disclaimer: This protocol version is for public viewing. Some information has been removed to maintain the integrity of this ongoing study.
Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor researching 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy for Anorexia Nervosa restricting subtype (AN-R) and Binge Eating Disorder (BED). AN-R and BED will be the focus of this pilot study due to the great need for effective treatments. Anorexia nervosa (AN) among adults with more chronic symptomology is often resistant to recommended treatments and associated with poor outcomes [1]. Furthermore, completion rates for existing AN treatments are often low (e.g., 60.0% reported by Byrne and colleagues [2]). Among adults with BED, approximately 41 to 60% of individuals who receive treatment for BED continue to experience binge-eating symptoms after treatment [3]. While new and innovative treatments are also needed for Anorexia Nervosa binge-purge subtype and Bulimia Nervosa, medical complications related to serious patterns of purging may increase the risk of interaction with the drug and therefore this study will first explore the safety and feasibility of a MDMA-assisted psychotherapy protocol with AN-R and BED.

Study Design Summary

This Phase 2, open-label, multi-site study will enroll 12 participants who meet the Diagnostic Statistical Manual for Mental Disorders Edition 5 (DSM-5) criteria for Anorexia Nervosa, Restricting-Type (AN-R), and 6 participants who meet DSM-5 criteria for Binge Eating Disorder (BED), for a total of 18 participants with an eating disorder.

Only persons assigned female at birth will be included in the study due to the biological sex bias in prevalence rate, the significant differences that exist between sexes with respect to treatment response, as well as the fact that some eating disorder (ED) measures have not been validated among sufferers who are assigned male at birth. A supportive caregiver (i.e., parent or partner) to each participant will also be recruited to participate in the study and will receive non-drug psychotherapy support. Therefore, 36 participants (12 AN-R, 6 BED, and 18 caregivers) will be enrolled in the study. Any ED participant who drops out before the third Experimental Session may be replaced. Dropout rates will be recorded. Participants who do not have a supportive caregiver or whose caregiver is unwilling to participate in the study will be excluded. Data will be collected on the psychological effects of MDMA-assisted psychotherapy to treat AN-R and BED. The study’s specific aims are to assess the safety and feasibility of MDMA-assisted psychotherapy and adjunctive caregiver involvement in the treatment of individuals with AN-R and BED.

For each participant, the study will consist of:

- **Pre-Screening Period:** Pre-screening of potential participants according to a script approved by the Institutional Review Board (IRB) or Ethics Committee (EC) in order to ascertain if basic eligibility criteria is met
- **Screening and Enrollment Period:** Informed consent, phone screen, Independent Rater assessment, eligibility assessment by investigator and the sponsor Medical Monitor, and enrollment of eligible participants
- **Preparatory Period:** Medication tapering (if applicable), Preparatory Sessions, and Baseline assessments
- **Treatment Period:** 3 Experimental Sessions (for the Eating Disorder Participant [ED-P] only), and associated Integrative Sessions over ~9 weeks
• **Study Termination**: Approximately 1 week after the last Integrative Session visit both the ED-P and Caregiver Participant (CG-P) will complete their final study visit.

### Study Design Overview

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Eating Disorder Participant (ED-P)</th>
<th>Caregiver Participant (CG-P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>ED-P and CG-P Screening Period (~1-3 Weeks Prior to Visit 1) &amp; Enrollment</td>
<td></td>
</tr>
<tr>
<td><strong>Preparatory Period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>90-minute ED-P + CG-P Required Dyadic On-Site Preparatory Session</td>
<td></td>
</tr>
</tbody>
</table>
| 2     | 2    | 90-minute ED-P Individual Preparatory Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V3 is conducted on-site.* | (No CG-P Session) |
| 3     | 3    | 90-minute ED-P Individual Preparatory Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V2 was conducted on-site.* | 60-minute CG-P Individual Preparatory Session  
*May be conducted remotely via telemedicine.* |
| **Treatment Period** | | | |
| 4     | 4    | 8-hour On-Site ED-P Experimental Session 1 | (No CG-P Session) |
| 5     | 4    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 6     | 5    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
| 7     | 6    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 8     | 7    | 8-hour On-Site ED-P Experimental Session 2 | (No CG-P Session) |
| 9     | 7    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 10    | 8    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
| 11    | 9    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 12    | 10   | 8-hour On-Site ED-P Experimental Session 3 | (No CG-P Session) |
| 13    | 10   | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 14    | 11   | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
Visit | Week | Eating Disorder Participant (ED-P) | Caregiver Participant (CG-P)
--- | --- | --- | ---
15 | 12 | 90-minute ED-P + CG-P Required Dyadic Integrative Session *May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | 

**Study Termination**

16 | 13 | ED-P + CG-P Required Dyadic On-Site Study Termination Visit |

All ED-P sessions (individual and dyadic) will be facilitated by a two-person therapist team. CG-P individual sessions may be led by one of the study therapists. The therapists and ED-Ps will have discretion regarding the appropriateness of the Visit 6, 10, and 14 Dyadic Integrative Sessions. These visits may be conducted as individual sessions for both the ED-P and the CG-P. Visit 15 is a required Dyadic Integrative Session since it is the last session before the Study Termination Visit.

**fMRI Investigator Initiated Sub-Study**

To understand the neural circuitry that underlies the therapeutic effect of MDMA in AN-R in particular, a pilot functional magnetic resonance imaging (fMRI) Investigator Initiated Sub-Study (IIS) will be conducted using a select cohort of AN-R ED participants at pre-selected study sites in efforts to identify neuroimaging biomarkers of treatment response. This IIS will be conducted by the Hartford Hospital/Institute of Living in Hartford, Connecticut with Dr. Mirjana Domakonda as Clinical Investigator. Details regarding this IIS are listed separately in the fMRI IIS protocol.

**Dose Selection**

This study will examine the safety and feasibility of three open-label Experimental Sessions of psychotherapy assisted by flexible doses of MDMA for ED-Ps along with associated non-drug preparatory and integrative psychotherapy. Similar MDMA doses to those proposed in this study have been safely used in previous studies sponsored by MAPS.

**Dose Regimen of MDMA for ED-Ps Weighing 48 kg or Higher**

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Initial Dose</th>
<th>Supplemental Dose*</th>
<th>Min-Max Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
<tr>
<td>2</td>
<td>80 mg or 120 mg</td>
<td>40 mg or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
<tr>
<td>3</td>
<td>80 mg or 120 mg</td>
<td>40 mg or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
</tbody>
</table>

**Total Cumulative Dose** 240 mg to 480 mg

*A supplemental dose will be administered unless contraindicated or refused by the ED-P. Observed response, safety, and tolerability of the previously administered dose, and discussion with the participant will all be taken into consideration as potential contraindications to the supplemental dose, and when considering escalating the initial dose in the 2nd and 3rd Experimental Sessions.

**Dose Regimen of MDMA for ED-Ps Weighing ≥ 45 kg and < 48kg**

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Initial Dose</th>
<th>Supplemental Dose*</th>
<th>Min-Max Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
<tr>
<td>2</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
<tr>
<td>3</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
</tbody>
</table>

**Total Cumulative Dose** 240 mg to 360 mg

*A supplemental dose will be administered unless contraindicated or refused by the ED-P. Observed response, safety, and tolerability of the previously administered dose, and discussion with the participant will be taken into consideration as potential contraindications to the supplemental dose.
Protocol Objectives

The overall objective of this study is to use standard clinical measures to explore the safety and feasibility of open-label MDMA-assisted psychotherapy with a flexible dose of MDMA and adjunctive caregiver support in reducing eating disorder and associated symptoms for participants with AN-R or BED.

Primary Objective

The primary objective of the study is to evaluate the feasibility of MDMA-assisted psychotherapy for the subgroups of AN-R and BED based on a comparison of Eating Disorder Examination (EDE) results at Baseline to Visit 16 (Study Termination).

Secondary Objective

The secondary objective of the study is to assess differences for readiness of change among individuals with eating disorders based on a comparison of Readiness and Motivation Questionnaire (RMQ) results at Baseline to Visit 16 (Study Termination).

Exploratory Objectives

Exploratory objectives of this study are as follows:

- To further review the treatment modality method and develop a manual specifically for the eating disorders patient population by collecting impressions on this from the study therapists after the study.
- To assess changes in eating disorder-related thoughts/symptoms and physiological markers for ED participants based on a comparison of the following standard clinical measure results:
  - From Baseline to Visit 11:
    - Eating Disorder Examination-Questionnaire (EDEQ)
  - From Baseline to Visit 15:
    - Eating Disorder-15 (ED-15)
  - From Baseline to Visit 16 (Study Termination):
    - Body mass index measures (BMI, calculated with height and weight)
    - Eating Disorder Inventory (EDI-3)
- To assess the numbers and types of adverse childhood experiences for ED participants based on the Adverse Childhood Experience Questionnaire (ACE) at Baseline.
- To assess ED participant perceptions about satisfaction of treatment received using a feedback questionnaire (FQ) at Visit 16 (Study Termination).
- To assess emotional breakthrough as a distinct component and possible therapeutic mechanism of psychedelic experiences based on The Imperial Emotional Breakthrough Inventory (EBI) at Visit 5, Visit 9, and Visit 13.
- To assess changes in psychological functioning, family functioning, and quality of life for both ED and CG participants based on a comparison of the following standard clinical measure results from Baseline to Visit 16 (Study Termination):
  - ED-P Exploratory Outcome Measures:
    - Attachment Style Questionnaire-Short Form (ASQ-SF)
    - Beck Depression Inventory-II (BDI-II)
    - Clinical Impairment Assessment (CIA)
Safety Objectives

The overall safety objective is to assess severity, incidence, and frequency of adverse events (AEs), Treatment Emergent AEs (TEAEs), AEs of special interest (AESIs), and serious adverse events (SAEs) in both ED-P subgroups: AN-R and BED. Concomitant medication uses and vital signs will also be assessed in ED-Ps. Changes in electrocardiogram (ECG) parameters will be assessed with QTcF in AN-R participants only. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy in a clinical practice setting:

- Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Medicinal Product (IMP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
- Assess incidence of AEs by severity.
- Assess incidence of TEAEs by severity reported during an Experimental Session, 1 day and 2 days after IMP administration.
- Assess incidence of AESIs defined as: AEs specified in the protocol related to cardiac function, abuse liability, and suicidality.
- Assess incidence of AEs by severity categorized as: leading to discontinuation of IMP, resulting in death or hospitalization, and continuing at Study Termination.
- Assess incidence of SAEs.
- Assess incidence of positive, elevated, or serious suicidal ideation and positive self-injurious or suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of each Experimental Session.
- Assess changes in QTcF from screening through study duration (in AN-R participants only).

Recruitment and Participant Population

Recruitment will occur in partnership with eating disorder support and treatment centers in the geographic areas where the study will take place. ED-Ps may be persons 21 to 65 years old who were assigned female at birth, meet DSM-5 criteria for AN-R or BED, and have completed at least one ED-specific episode of treatment (inpatient, residential, partial hospitalization, intensive
outpatient) to establish non-responsiveness to conventional treatment. ED-Ps must have an identified, consenting caregiver (i.e., parent or partner). CG-Ps must be providing formal or informal support to the ED-P for a minimum of 2 hours a week (e.g., companionship, meal support, emotional support, driving to appointments, etc.).

Prospective ED participants with medical or psychological conditions that are contraindications for MDMA use will be excluded. Additional inclusion and exclusion criteria are outlined in the Eligibility Criteria for ED Participants Section 3.0 of the protocol.

Statistical Analysis

A summary of the statistical analyses that will be performed is as follows:

- **Sample Size and Power Considerations:** MED1 is an exploratory one-arm safety and feasibility study. This is a pilot study intended to collect estimates of effect size for statistical power calculations for future adequately powered studies. Due to their exploratory nature, pilot studies are often not powered for detection of the desired effect. Thus, no power nor sample size calculations were conducted.

- **Analyses:** Effect size estimates will be generated for all effectiveness measures using Cohen’s D One Group Pretest Posttest methods. There may be an interim analysis before all participants have been enrolled for safety and effectiveness, in order to allocate subsequently enrolled participants between eating disorder subtypes.

- **Safety Analyses:** Safety data for ED-Ps will be summarized by exposure to IMP, unsolicited AEs, concomitant medications, AEs of Special Interest (AESIs), and vital signs overall. If an ED-P has more than one AE mapped to the same preferred term (PT), that AE will be reported once using the highest severity at the subject level. AEs that occur on Day 0 (Experimental Session), Day 1, and Day 2 after IMP administration will be presented separately. Incidence of AEs during Experimental Sessions such as clinical signs and symptoms, such as chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that may be indicative of a medical complication of the IMP will be tabulated. The effect of MDMA on cardiac repolarization will be analyzed using change in ECG parameters to derive QTcF.

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by analysis set and category. Concomitant medications taken on Day 0 (Experimental Session), Day 1, and Day 2 after IMP administration will be presented separately. Any psychiatric concomitant medications will be tabulated by period (Preparatory, Treatment Period, Follow-up Period). Vital signs (heart rate, blood pressure, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IMP administration, prior to the supplemental dose, and at the end of each Experimental Session. Additional details are available in the Statistical Analysis Plan.
Study Structure Overview

Summary of Events

Prestudy

Preparatory Sessions

Experimental Session 1

Integrative Sessions 1.1, 1.2, 1.3

V4* V5 V6 V7*

3 day Phase 1, Meet-up

V4 V5* V6 V7

V8 V9 V10 V11*

7 day Phase 2, Meet-up

Experimental Session 2

Integrative Sessions 2.1, 2.2, 2.3

Preparatory Period
Approximately 3 Weeks

Preparatory Period
Approximately 3 Weeks

Preparatory Period
Approximately 3 Weeks

Primary Outcome

Follow-up Period
Approximately 13 Weeks post Baseline

Medication Tapering

Recall

Screening V0

V1 V2* V3

Treatment 1
Approximately 3 Weeks

Treatment 2
Approximately 3 Weeks

Treatment 3
Approximately 3 Weeks

Treatment Period

Overall Exit

V14 V15

*EO3-P Visit Only
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<th>Description</th>
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<tr>
<td>ACE</td>
<td>Adverse Childhood Experience Questionnaire</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention deficit/hyperactivity disorder</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AESI</td>
<td>Adverse Event of Special Interest</td>
</tr>
<tr>
<td>AN</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>AN-R</td>
<td>Anorexia nervosa, restricting subtype</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ASQ-SF</td>
<td>Attachment Style Questionnaire-Short Form</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>BA/BE</td>
<td>Bioavailability and bioequivalence</td>
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<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory-II</td>
</tr>
<tr>
<td>BED</td>
<td>Binge eating disorder</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
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<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CG-P</td>
<td>Caregiver-participant</td>
</tr>
<tr>
<td>CIA</td>
<td>Clinical Impairment Assessment</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>CTL</td>
<td>Clinical Trial Leader</td>
</tr>
<tr>
<td>DERS-16</td>
<td>Difficulties with Emotion Regulation Scale</td>
</tr>
<tr>
<td>dlPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic Statistical Manual for Mental Disorders Edition 5</td>
</tr>
<tr>
<td>EBI</td>
<td>The Imperial Emotional Breakthrough Inventory</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ED</td>
<td>Eating disorder</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EDE</td>
<td>Eating Disorder Examination-Interview</td>
</tr>
<tr>
<td>EDI-3</td>
<td>Eating Disorder Inventory</td>
</tr>
<tr>
<td>ED-P</td>
<td>Eating disorder participant</td>
</tr>
<tr>
<td>ED-15</td>
<td>Eating Disorder-15</td>
</tr>
<tr>
<td>EDEQ</td>
<td>Eating Disorder Examination-Questionnaire</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EES</td>
<td>Experience of Embodiment scale</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FQ</td>
<td>Feedback Questionnaire</td>
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<tr>
<td>HC</td>
<td>Health Canada</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Code of Harmonisation</td>
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<tr>
<td>IIS</td>
<td>Investigator Initiated Sub-Study</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IR</td>
<td>Independent Rater</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>LEC-5</td>
<td>Life events checklist for DSM-5</td>
</tr>
<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MAPS</td>
<td>Multidisciplinary Association for Psychedelic Studies</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>MDMA</td>
<td>3,4-methylenedioxymethamphetamine</td>
</tr>
<tr>
<td>MFFS</td>
<td>McMaster Family Functioning Scale</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini-International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MAPS PBC</td>
<td>MAPS Public Benefit Corporation</td>
</tr>
<tr>
<td>NPP</td>
<td>Not Per Protocol</td>
</tr>
<tr>
<td>OT</td>
<td>Neurohormones oxytocin</td>
</tr>
<tr>
<td>PCL-5</td>
<td>PTSD Checklist for DSM-5</td>
</tr>
<tr>
<td>POTS</td>
<td>Postural Orthostatic Tachycardia Syndrome</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood count</td>
</tr>
<tr>
<td>RDW</td>
<td>Red cell distribution width</td>
</tr>
<tr>
<td>RMQ</td>
<td>Readiness and Motivation Questionnaire</td>
</tr>
<tr>
<td>RSES</td>
<td>Rosenberg Self-Esteem Scale</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SCS</td>
<td>The Self-Compassion Scale</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>STAI</td>
<td>State-Trait Anxiety Inventory</td>
</tr>
<tr>
<td>STV</td>
<td>Study Termination Visit</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment emergent adverse event</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States of America</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood count</td>
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<tr>
<td>WHOQOL-BREF</td>
<td>World Health Organization Quality of Life-Brief</td>
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</tbody>
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1.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor researching 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy for Anorexia Nervosa restricting subtype (AN-R) and Binge Eating Disorder (BED). MAPS-sponsored studies are implemented through MAPS’ wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (MAPS PBC).

1.1 Rationale

AN-R and BED will be the focus of this pilot study due to the great need for effective treatments. Anorexia nervosa (AN) among adults with more chronic symptomology is often resistant to recommended treatments and associated with poor outcomes [1]. Furthermore, completion rates for existing AN treatments are often low (e.g., 60% in 2). Among adults with BED, approximately 41 to 60% of individuals who receive treatment for BED continue to experience binge-eating symptoms after treatment [3]. While new and innovative treatments are also needed for Anorexia Nervosa binge-purge subtype and Bulimia Nervosa, medical complications related to serious patterns of purging may increase the risk of interaction with the drug and therefore this study will first explore the safety and feasibility of a MDMA-assisted psychotherapy protocol with AN-R and BED.

1.2 Background

1.2.1 Eating Disorders

In the 5th Edition of the Diagnostic Statistical Manual for Mental Disorders (DSM-5), AN is recognized as a mental disorder in the category of Feeding and Eating Disorders [4]. This disorder is most often characterized by problematic patterns of food intake, low self-esteem, and poor or distorted body image [4]. Anorexia Nervosa (AN) typically begins in adolescence and has a lifetime prevalence of 1 to 5% in Americans who are assigned female at birth [5]. AN is a debilitating illness that affects every system of the body [6]. Numerous psychological symptoms accompany AN, including comorbid mood and anxiety disorders, as well as substance misuse and post-traumatic stress disorder (PTSD) [7, 8]. These are associated with impaired quality of life [9], high morbidity, and premature mortality [10].

Binge Eating Disorder (BED) on the other hand is characterized in DSM-5 by recurrent binge eating episodes (at least one per week for 3 months) where there is loss of control. These episodes are not followed by inappropriate compensatory behaviors [4]. BED generally occurs later in adulthood and has a lifetime prevalence of 2 to 3% [11, 12]. BED is associated with high levels of obesity and psychological suffering [13]. As BED appears to affect a broader spectrum of the population than other eating disorders, it is considered a clinically significant disorder [14].

Both AN and BED are associated with a variety of physical and mental health conditions, including anxiety, depression, cardiovascular complications, etc. [15-19], as well as lower health-related quality of life and higher healthcare costs [14]. Significant shame and stigma underlie these disorders and often delay treatment. As such, only 23% of persons with an ED obtain treatment [20]. Among those who receive treatment for an ED, remission rates vary widely from 27 to 85% [21]. As few as 3% of adults meeting criteria for BED are formally diagnosed, indicating this disorder often goes unrecognized and untreated [11]. Of those who do receive treatment for BED, half do not fully respond to treatment [22]. While various interventions have been used to treat adults with AN, existing treatment approaches are relatively ineffective [23].
Furthermore, there is consensus in the field that risk for relapse in persons with AN is especially high within the first year following treatment [24].

Although various factors have been identified in the literature, it is widely accepted that deficits with emotion processing are central to the development and maintenance of ED symptoms [25]. Individuals with AN may present as highly over-regulated and it is postulated that core AN symptoms of rigid-thinking and obsessive control of food intake arise in an effort to modulate difficult emotions and support emotional avoidance [26-29].

Over the last several decades, advances in neuroimaging have contributed to our understanding of the neural mechanisms that may underlie the development and persistence of ED. Of particular relevance to this proposal, functional magnetic resonance imaging (fMRI) studies of EDs have revealed disruptions in the neural networks that support emotion processing (amygdala) and self-regulation (dorsolateral prefrontal cortex, dIPFC) [30, 31]. Specifically, increased amygdala and dIPFC activation in EDs are thought to generate heightened emotional responses in response to disorder-relevant stimuli and negative affective states [31]. Such hypervigilance in response to perceived threatening stimuli may lead to emotional over-control and/or dysregulation, which contributes to core ED symptoms. Unsurprisingly, greater capacity for emotional regulation in adults with ED predicts high treatment success rates [32]. To understand the neural circuitry that underlies the therapeutic effect of MDMA in AN-R in particular, a pilot functional magnetic resonance imaging (fMRI) Investigator Initiated Sub-Study (IIS) will be conducted using a select cohort of AN-R ED participants at pre-selected study sites in efforts to identify neuroimaging biomarkers of treatment response. This IIS will be conducted by the Hartford Hospital/Institute of Living in Hartford, Connecticut with Dr. Mirjana Domakonda as Clinical Investigator. Details regarding this IIS are listed separately in the fMRI IIS protocol.

1.2.2 Caregiver Involvement

EDs affect every member of the family. In the past, family dynamics were regarded as causal in the development of EDs and treatment frequently involved increasing ED patients’ separation and individuation from their families. Now, various lines of research have confirmed that EDs can develop in a wide range of family contexts, and that no specific family style is predictive in ED onset [33]. Furthermore, problematic patterns of behavior observed within families of individuals with EDs are now understood as amplified reactions to the presence of their chronic and potentially life-threatening illness [34].

In light of this evolved understanding of family factors, contemporary approaches to ED treatment now include caregivers as active supports in the recovery process [35-37]. Rather than a focus on family therapy per se, caregivers are provided with psychoeducation and specific skills to support their loved one’s physical and emotional illness recovery. Research suggests that caregiver involvement in the treatment of individuals with ED improves outcomes for all involved [33, 38, 39]. Specifically, those affected by the illness benefit from reduced ED psychopathology, improved quality of life, and reduced treatment duration. Caregivers experience reduced caregiver burden, fear, and self-blame, and report improvements in expressed emotion in the family [40-44].

In addition to the recruitment of individuals with AN-R and BED, this study will also enlist supportive caregivers as treatment allies to reflect this most recent development in science and practice. Caregivers will be provided with targeted support and skills to optimize their support of their loved one’s process both in Preparatory and Integrative Sessions, as well as in the home environment.
1.2.3 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [45, 46] and is currently off patent. MDMA is a monoamine releaser and re-uptake inhibitor with indirect effects on neurohormone release. MDMA concomitantly promotes release, inhibits reuptake, and extends the presence of serotonin, norepinephrine, and dopamine in the synaptic cleft. MDMA also increases levels of affiliative neurohormones oxytocin (OT), cortisol, arginine vasopressin (AVP), and prolactin.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the initial dose. Effects of the initial dose last 3 to 6 hours, which is extended to 5 to 8 hours with a supplemental half-dose administered 1.5 to 2 hours post initial dose. Orally administered doses of MDMA have a half-life of 7 to 9 hours in humans.

MDMA is capable of inducing unique psychopharmacological effects, including:

- Decreased feelings of fear
- Increased feelings of wellbeing
- Increased sociability and extroversion
- Reduced self-criticism
- Increased compassion for self and others
- Increased interpersonal trust
- Alert state of consciousness

MDMA produces anxiolytic and prosocial effects, which may counteract emotional avoidance and hyperarousal in the context of therapy [47]. MDMA also alters basic emotional processes by slowing identification of negative emotions and increasing responses to positive emotions in others [47]. Early observers noted increased acceptance of self and others, increased tolerance of emotionally upsetting topics and the ability to address these issues without extreme disorientation or ego loss [48-56]. As such, MDMA has theoretical promise as a treatment for ED-related emotional processing, including dysregulation and poor self-esteem. MDMA could also create a desirable psychological state that has the potential to enhance the therapeutic process by providing the opportunity to process feared emotional states and memories that fuel ED, as well as to offer corrective emotional experiences in a supportive framework.

1.2.4 Previous Clinical Experience with MDMA

MDMA-assisted psychotherapy is a novel treatment package that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct intended to enhance certain aspects of psychotherapy. Chemists Shulgin and Nichols were the first to report on the effects of MDMA in humans [57], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [57, 58]. MDMA was found to robustly influence human emotional status in a unique way [57] without adversely affecting physiological functions or perception, such as visual perception or cognition [59-62]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [63]. Legal therapeutic use continued until its placement on the United States (U.S.) list of Schedule I substances in 1985 [54, 56, 64]. An estimated 500,000 doses of MDMA were administered during psychotherapy and personal growth sessions in North America prior to its scheduling [56, 65]. A few uncontrolled human studies of MDMA assessing safety in a therapeutic setting occurred in the 1980s [53, 66].
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 [67, 68]. 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 psychotherapy without any safety concerns and with some PTSD symptom reduction [69]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS Investigational New Drug (IND).

Under IND #063384, MAPS initiated an international series of Phase 2 clinical trials to develop the medical use of MDMA-assisted psychotherapy for patients with chronic, at least moderate PTSD (CAPS-4 score: 50+), with at least 6 months of symptoms. Participants were not excluded for having more than one traumatic event, or for having tried, not tolerated, or refused a serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) prescribed for PTSD. Outcomes from six Phase 2 studies with evaluable data have been promising and have generated a range of methodological information for the design of future studies.

Results from two Phase 2 studies have been published: one study in the U.S. with a Long-Term Follow-Up conducted an average of 3.8 years after the final MDMA-assisted psychotherapy session (MP1) [70, 71] and one in Switzerland (MP2) [72, 73]. MP1 was followed by a small open-label extension study examining the treatment of relapse in three participants with a single MDMA-assisted psychotherapy treatment and a 12-month follow-up (MP1E2). Three additional studies have completed treatments (MP8, MP9, MP12) and two international studies were terminated early for logistical reasons with partial datasets (MP3, MP4). These studies tested a range of designs, such as a placebo control (MP1, MP4), low dose MDMA comparator control (MP2, MP9), and three-arm dose response studies (MP8, MP12). MP4 was terminated early due to delays in regulatory approval and enrollment timelines, with available efficacy data presented without a formal analysis. MP3 was terminated early by the sponsor due to inadequate data collection procedures at the site and insufficient therapy team training; efficacy data are not available for these reasons (MP3 is excluded from Phase 2 data).

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. In these studies, PTSD, independent of cause, appears treatable with a two to three-session treatment package of MDMA-assisted psychotherapy. As of April 30, 2020, with 279 individuals exposed to MDMA in the sponsor’s development program across various indications and at least 1,431 participants in MDMA research studies conducted without sponsor support, the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted psychotherapy. There have been no unexpected Serious Adverse Reactions (SARs) to date and Serious Adverse Events (SAEs) have been rare. A comprehensive review of MDMA research can be found in the IB supplied by the sponsor.

2.0 Protocol Objectives

The overall objective of this study is to use standard clinical measures to explore the safety and feasibility of open-label MDMA-assisted psychotherapy with a flexible dose of MDMA and adjunctive caregiver support in reducing eating disorder and associated symptoms for participants with AN-R or BED.
2.1 Primary Objective

The primary objective of the study is to evaluate the feasibility of MDMA-assisted psychotherapy for the subgroups of AN-R and BED based on a comparison of Eating Disorder Examination (EDE) results at Baseline to Visit 16 (Study Termination).

2.2 Secondary Objectives

The secondary objective of the study is to assess differences for readiness of change among individuals with eating disorders based on a comparison of Readiness and Motivation Questionnaire (RMQ) results at Baseline to Visit 16 (Study Termination).

2.3 Exploratory Objectives

Exploratory objectives of this study are as follows:

- To further review the treatment modality method and develop a manual specifically for the eating disorders patient population by collecting impressions on this from the study therapists after the study.
- To assess changes in eating disorder-related thoughts/symptoms and physiological markers for ED participants based on a comparison of the following standard clinical measure results:
  - From Baseline to Visit 11:
    - Eating Disorder Examination-Questionnaire (EDEQ)
  - From Baseline to Visit 15:
    - Eating Disorder-15 (ED-15)
  - From Baseline to Visit 16 (Study Termination):
    - Body mass index measures (BMI, calculated with height and weight)
    - Eating Disorder Inventory (EDI-3)
- To assess the numbers and types of adverse childhood experiences for ED participants based on the Adverse Childhood Experience Questionnaire (ACE) at Baseline.
- To assess ED participant perceptions about satisfaction of treatment received using a feedback questionnaire (FQ) at Visit 16 (Study Termination).
- To assess emotional breakthrough as a distinct component and possible therapeutic mechanism of psychedelic experiences based on The Imperial Emotional Breakthrough Inventory (EBI) at Visit 5, Visit 9, and Visit 13.
- To assess changes in psychological functioning, family functioning, and quality of life for both ED and CG participants based on a comparison of the following standard clinical measure results from Baseline to Visit 16 (Study Termination):
  - ED-P Exploratory Outcome Measures:
    - Attachment Style Questionnaire-Short Form (ASQ-SF)
    - Beck Depression Inventory-II (BDI-II)
    - Clinical Impairment Assessment (CIA)
    - Difficulties with Emotion Regulation Scale (DERS-16)
    - Experience of Embodiment scale (EES)
    - McMaster Family Functioning Scale (MFFS)
    - PTSD Checklist for DSM-5 (PCL-5) with Life Events Checklist (LEC-5)
    - Rosenberg Self-Esteem Scale (RSES)
    - The Self-Compassion Scale (SCS)
    - State-Trait Anxiety Inventory (STAI)
    - World Health Organization Quality of Life-Brief (WHOQOL-BREF)
  - CG-P Exploratory Outcome Measures:
2.4 Safety Objectives

The overall safety objective is to assess severity, incidence, and frequency of adverse events (AEs), Treatment Emergent AEs (TEAEs), AEs of special interest (AESIs), and serious adverse events (SAEs) in both ED-P subgroups: AN-R and BED. Concomitant medication uses and vital signs will also be assessed in ED-Ps. Changes in electrocardiogram (ECG) parameters will be assessed with QTcF in AN-R participants only. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy in a clinical practice setting:

- Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Medicinal Product (IMP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
- Assess incidence of AEs by severity.
- Assess incidence of TEAEs by severity reported during an Experimental Session, 1 day and 2 days after IMP administration.
- Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function, abuse liability, and suicidality.
- Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, resulting in death or hospitalization, and continuing at Study Termination.
- Assess incidence of SAEs.
- Assess incidence of positive, elevated, or serious suicidal ideation and positive self-injurious or suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of each Experimental Session.
- Assess changes in QTcF from screening through study duration (for AN-R participants only).

3.0 Eligibility Criteria for ED Participants

The investigators will recruit individuals aged 21 to 65 years old who were assigned female and birth and who have a diagnosis of AN-R or BED. At the completion of Screening, participants must agree to all lifestyle modifications, meet the study’s inclusion criteria, and not meet any exclusion criteria in order to be enrolled.

3.1 Inclusion Criteria for ED Participants

ED Participants are eligible to enroll in the protocol if they:

1. Are 21 to 65 years old.
2. Are assigned female at birth.
3. Are fluent in speaking and reading the English language and have the mental capacity to provide written informed consent.
4. Are able to swallow pills.
5. Agree to have study visits recorded to audio and video, including Preparatory Sessions, Experimental Sessions, and Integrative Sessions.
6. Are willing to include a consenting caregiver as a co-participant in elements of the study with whom the study team will have regular contact. This person must be willing and able to be reached by the investigators in the event of a participant becoming highly distressed, suicidal, or unreachable.
7. Have an identified Primary Care Physician (PCP) and provide consent for the investigator to communicate with PCP, as needed.
8. Are willing to sign a release for the investigators to communicate directly with their therapist, physician if relevant, as well treatment providers where they were currently or previously engaged in an ED-specific episode of treatment.
9. Live within reasonable driving distance of the study site (equal to or less than an estimated 2-hour drive from the study site).
10. If of childbearing potential, must have a negative pregnancy test at study entry and prior to each Experimental Session, and must agree to use adequate birth control through 10 days after the last Experimental Session (reference the Pregnancy for ED Participants Section 13.4 of this protocol). Not of childbearing potential is defined as permanent sterilization or postmenopausal.
11. Agree to inform the investigators within 48 hours of any medical conditions and procedures.
12. Agree to the following lifestyle modifications (described in more detail in Lifestyle Modifications Section 3.3): comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not participate in any other interventional clinical trials during the duration of the study, remain overnight at the study site (or at nearby accommodations such as a hotel approved by the research team) after each Experimental Session, not operate a vehicle within 24 hours after MDMA administration, and commit to medication dosing, therapy, and study procedures.

Medical History

13. Meet DSM-5 criteria for current Anorexia Nervosa, Restricting Type or Binge Eating Disorder as assessed by clinical interview and confirmed by medical records.
14. Current or past treatment were not successful to retain remission (i.e., continued to meet criteria for AN-R or BED) despite participating in at least one ED-specific episode of treatment (inpatient, residential, partial hospitalization, intensive outpatient), as confirmed by medical records, by a general practitioner, or by a specialist in ED.
15. Are medically stable according to screening 12-lead Electrocardiogram (ECG), blood pressure monitoring, and blood and urine laboratory screening results.

3.2 Exclusion Criteria for ED Participants

ED Participants will be ineligible to be enrolled in this study if they:

1. Are not able to give adequate informed consent.
2. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation.
3. Cannot identify a supportive caregiver to participate in the study (or the caregiver does not meet eligibility criteria).
Psychiatric History

4. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist.
5. Have a blood or needle phobia that interferes with obtaining necessary blood work.

Medical History

6. If AN-R diagnosis, have specific fMRI contraindications which include metal devices or clips or fragments in the body or a history of claustrophobia or significant anxiety during previous CT or MRI scans.
7. Have uncontrolled hypertension using the standard criteria of the American Heart Association (values of 140/90 milligrams of Mercury [mmHg] or higher assessed on three separate occasions).
8. Have a history of atrial flutter or any arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease. Participants with a history of paroxysmal supraventricular tachycardia, paroxysmal atrial tachycardia, or atrial fibrillation arrhythmia may be enrolled if successfully treated with ablation or cardioversion treatment at least 12 months prior and cleared by a cardiologist, the site physician, and Medical Monitor.
9. Have Wolff-Parkinson-White syndrome or any other accessory pathway.
10. Are pregnant or nursing, or are persons of childbearing potential who are not practicing (or not willing to practice) an effective means of birth control.
11. Are assessed to be medically unstable according to review of laboratory results at Screening for serum electrolytes, raised cardiac enzymes, hepatic or renal dysfunction, or other clinical indicators, as determined by the investigator or Medical Monitor.

3.3 Lifestyle Modifications for ED Participants

All ED Participants must agree to the following lifestyle modifications at enrollment and throughout the duration of the study. ED Participants are eligible to enroll in the study if they:

• Are willing to commit to MDMA dosing, psychotherapy sessions, completing evaluation instruments, and all necessary telephone contact.
• Are willing to receive meal-related and emotional support from the identified CG-P.
• Agree to not participate in any other interventional clinical trials during the duration of this study.

Leading up to Experimental Sessions

• Agree to appropriate nutritional intake (non-ketogenic diet) for a minimum of 3 days preceding the Experimental Sessions, including a meal the night before.
• Agree to take nothing by mouth except alcohol-free liquids and approved medications after 12:00 A.M. (midnight) the evening before each Experimental Session.
• If AN-R diagnosis, agree to blood draws for clinical laboratory testing (complete blood count, comprehensive metabolic panel, magnesium, and phosphorus) to ensure medical stability within 3 days of each Experimental Session at a designated laboratory approved by the study investigator.
• If AN-R diagnosis, agree to a urine sample the morning of the Experimental Session to test for ketones.
• If AN-R diagnosis, agree to an ECG test the morning of the Experimental Session to ensure cardiovascular safety.
• Agree not to use caffeine or nicotine for 2 hours before and at least 6 hours after the initial dose during each Experimental Session.
• Refrain from the use of any medication (including psychoactive medication) not approved by the research team from Enrollment through Study Termination.
• Are willing to comply with medication requirements per protocol (refer to Concomitant Medications for ED Participants Section 14.0). Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.
• Agree that, for 5 half-lives of the medication preceding each Experimental Session to refrain from:
  o Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) unless with prior approval of the research team.
  o Taking any prescription medications (with the exception of birth control, thyroid hormones, or medications approved by the research team).
• Agree that, for 1 week preceding each Experimental Session to refrain from:
  o Taking any specified herbal supplement (except with prior approval from the research team).

During and Post Experimental Session

• Are willing to have vitals monitored during the Experimental Session.
• If AN-R diagnosis, agree to an ECG test 1.5 to 2 hours after the initial dose (and prior to the administration of the supplemental dose) during the Experimental Session to ensure cardiovascular safety.
• Are willing to eat a snack in the afternoon of the Experimental Session and a dinner the evening of the Experimental Session. Meal replacements will be available if needed.
• Are willing to eat breakfast the morning after the Experimental Session.
• Are willing to remain overnight at the study site or nearby accommodations such as a hotel approved by the site research team with an attendant (or their own support person) after each Experimental Session until after the Integrative Session the next morning.
• Are willing to refrain from operating a vehicle for 24 hours following initial medication administration.

4.0 Eligibility Criteria for CG Participants

The investigators will recruit caregivers 18 years or older who are willing to provide their loved one with support during this study and attend non-drug psychotherapy sessions. At the completion of Screening, caregivers must meet the study’s inclusion criteria, and not meet any exclusion criteria in order to be enrolled.

4.1 Inclusion Criteria for CG Participants

CG Participants are eligible to enroll in the protocol if they:

1. Are fluent in speaking and reading the English language and have the mental capacity to provide written informed consent.
2. Are at least 18 years old.
3. Are the parent, partner, or other significant caregiver of the ED Participant.
4. Are involved in providing support at least 2 hours a week (i.e., companionship, meal support, emotional support, driving to appointments, etc.).
5. Are willing to provide their loved one with meal/symptom support and emotional support throughout the study.
6. Are willing to provide to their loved one with meal support (to ensure appropriate nutritional intake) and supervision (to resist the urge to purge) for a minimum of 3 days preceding the Experimental Sessions, including a meal the night before.
7. Live within reasonable driving distance of the study site (equal to or less than an estimated 2-hour drive from the study site).
8. If in ongoing psychotherapy at the time participants are recruited into the study, caregiver participants may continue to see their outside therapist during the course of the study. Caregiver participants must sign a release for the investigators to communicate directly with their therapist. CG Participants may not change therapists, increase the frequency of therapy, or commence any new type of therapy until after their Study Termination Visit.
9. Are willing to commit to Preparatory and Integrative Sessions, completion of evaluation instruments and other study procedures, and being contacted for all necessary telephone contacts.
10. Agree to have study visits recorded to audio and video, including Preparatory, Experimental (if in attendance), and Integrative Sessions.

4.2 Exclusion Criteria for CG Participants

CG Participants are ineligible to be enrolled in this study if they:

1. Present with current serious suicide risk, as determined by interview, responses to C-SSRS, and clinical judgement of the investigator.
2. Are unable to give adequate informed consent.
3. Report any current problem which in the opinion of the investigator or Medical Monitor might interfere with enrollment or ongoing participation.

5.0 Protocol Design

5.1 Study Design Overview

This Phase 2, open-label, multi-site study will explore the safety and feasibility of MDMA-assisted psychotherapy and adjunctive coaching and caregiver support for individuals with AN-R and BED. The study will enroll 12 participants who meet DSM-5 criteria for Anorexia Nervosa, Restricting-Type (AN-R) and 6 participants who meet DSM-5 criteria for Binge Eating Disorder (BED) for a total of 18 participants with an eating disorder.

This study will include a Safety Committee which will include members from the internal MAPS PBC Medical Monitors, the study’s Coordinating Investigator (a subject matter expert in the treatment of eating disorders), the site Qualified and Clinical Investigators, and an independent external physician not involved in the conduct of the clinical trial. The Safety Committee will meet to review safety data after the first two participants complete their first Experimental Session, then will continue to meet at enrollment milestones or more often as needed.

Severe AN participants will only be enrolled at a research site after two participants with mild or moderate AN have completed their first Experimental Session at the site and no clinically significant safety concerns have been identified during their safety data review by the study’s Safety Committee. study’s Safety Committee. The Safety Committee will perform safety review
of the study data based on enrollment and on an ongoing basis for the duration of the study. Reference protocol **Section 13.2 Safety Committee** for details.

Only persons assigned female at birth will be included in the study due to the biological sex bias in prevalence rate, the significant differences that exist between sexes with respect to treatment response, as well as the fact that some ED measures have not been validated among sufferers who are assigned male at birth. A supportive caregiver (i.e., parent or partner) to each participant will also be recruited to participate in the study and will receive non-drug psychotherapy support. Therefore, 36 participants (12 AN-R, 6 BED, and 18 caregivers) will be enrolled in the study. Any ED participant who drops out before the third Experimental Session may be replaced. Dropout rates will be recorded. Data will be collected on the psychological effects of MDMA-assisted psychotherapy to treat AN-R and BED. The study’s specific aims are to assess the safety and feasibility of MDMA-assisted psychotherapy and adjunctive caregiver involvement in the treatment of individuals with AN-R and BED.

After consenting, participants will enter the Screening period and will complete study measures and assessments. If the investigator determines that the participant is eligible, they will send an enrollment packet to the Medical Monitor to confirm eligibility prior to enrollment. Participants will be enrolled after meeting all inclusion criteria without meeting any exclusion criteria. Participants will be asked to complete study measures throughout their participation in the study.

Following study enrollment, the ED-P will attend three Preparatory Sessions (one dyadic with the CG-P and two individual). These sessions will be followed by three monthly Experimental Sessions. Three Integrative Sessions will follow each Experimental Session over ~11 weeks (individual and dyadic). Approximately 3 weeks following the third Experimental Session, the ED-P will complete the Study Termination session with the CG-P (i.e., parent or partner). The ED-P and/or CG-P will have the option to complete the Study Termination session individually, if desired.

The CG-P will participate in two Preparatory Sessions (one dyadic and one individual) during which they will be provided with psychoeducation, skills, and support to engage therapeutically with their loved one’s treatment process. They may also be provided with educational videos to view between sessions meant to solidify the material presented in the Preparatory Sessions. Any participant facing videos or materials will be reviewed by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) for approval prior to use with participants.

Following the first two ED-P Experimental Sessions, the CG-P will participate in one individual Integrative Session as well as a Dyadic Integrative Session. After the ED-P’s last Experimental Session, the CG-P will participate in one individual Integrative Session and two Dyadic Integrative Sessions. Approximately 3 weeks following the third Experimental Session, the CG-P will complete the Study Termination Session with the ED-P, and both will be given the option to complete the session individually.

Therefore, for each participant, the study will consist of:

- **Pre-Screening Period:** Pre-screening of potential participants according to a script approved by the IRB or EC in order to ascertain if basic eligibility criteria is met
- **Screening and Enrollment Period:** Informed consent, phone screen, Independent Rater assessment, eligibility assessment by investigator and the sponsor Medical Monitor, and enrollment of eligible participants
- **Preparatory Period:** Medication tapering (if applicable), Preparatory Sessions and Baseline assessments
• **Treatment Period:** 3 Experimental Sessions (for the Eating Disorder Participant [ED-P] only) and associated Integrative Sessions over ~9 weeks

• **Study Termination:** Approximately 1 week after the last Integrative Session visit both the ED-P and Caregiver Participant (CG-P) will complete their final study visit

The treatment for an ED-P weighing ≥ 48 kg consists of a standard initial dose of 80 mg MDMA at the first Experimental Session, and a flexible initial dose of MDMA (either 80 mg MDMA or 120 mg MDMA) at the second and third Experimental Sessions. In consideration of their low body weight, an alternate dosing regimen has been selected for AN-R participants weighing ≥ 45 kg and < 48 kg, which consists of a standard initial dose of 80 mg MDMA for all Experimental Sessions (see Rational of Dose Selection Section 5.5). The initial dose for all ED-Ps at all sessions will be followed by a supplemental half-dose unless contraindicated. Experimental Sessions are followed by an overnight stay either at the study site or at nearby accommodations such as a hotel approved by the research team.
Study Structure Overview

Summary of Events
### Table 1: Study Design Overview

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Eating Disorder Participant (ED-P)</th>
<th>Caregiver Participant (CG-P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>ED-P and CG-P Screening Period (~1-3 Weeks Prior to Visit 1) &amp; Enrollment</td>
<td></td>
</tr>
<tr>
<td><strong>Preparatory Period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>90-minute ED-P + CG-P Required Dyadic On-Site Preparatory Session</td>
<td></td>
</tr>
</tbody>
</table>
| 2     | 2    | 90-minute ED-P Individual Preparatory Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V3 is conducted on-site.* | (No CG-P Session) |
| 3     | 3    | 90-minute ED-P Individual Preparatory Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V2 was conducted on-site.* | 60-minute CG-P Individual Preparatory Session  
*May be conducted remotely via telemedicine.* |
| **Treatment Period** | | | |
| 4     | 4    | 8-hour On-Site ED-P Experimental Session 1 | (No CG-P Session) |
| 5     | 5    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 6     | 6    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
| 7     | 6    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 8     | 7    | 8-hour On-Site ED-P Experimental Session 2 | (No CG-P Session) |
| 9     | 8    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 10    | 9    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
| 11    | 9    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 12    | 10   | 8-hour On-Site ED-P Experimental Session 3 | (No CG-P Session) |
| 13    | 10   | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 14    | 11   | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for CG-P individual sessions.* | |
### Visit Week Eating Disorder Participant (ED-P) Caregiver Participant (CG-P)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Session Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>12</td>
<td>90-minute ED-P + CG-P Required Dyadic Integrative Session</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P.</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>ED-P + CG-P Required Dyadic On-Site Study Termination Visit</td>
</tr>
</tbody>
</table>

All ED-P sessions (individual and dyadic) will be facilitated by a two-person therapist team. CG-P individual sessions may be led by one of the study therapists. The therapists and ED-Ps will have discretion regarding the appropriateness of the Visit 6, 10, and 14 Dyadic Integrative Sessions. These visits may be conducted as individual sessions for both the ED-P and the CG-P. Visit 15 is a required Dyadic Integrative Session since it is the last session before the Study Termination Visit.

### 5.2 Planned Duration of Study

After completion of the consenting visit, full Screening activities may take 1 to 3 weeks, depending on participant needs. Enrollment takes place at the completion of Screening. The duration of active participation in the protocol will be approximately 13 weeks, with the Study Termination Visit occurring approximately 1 week after the last Integrative Session. The average time that a participant who completes all study visits from Screening to Study Termination is approximately 16 weeks. Any delays between visits outside of the protocol-defined windows may result in a corresponding extension of study duration and should be documented as a deviation as appropriate. Safety information and measures will be collected throughout the study. The protocol may remain active up to enrollment of all participants.

### 5.3 Discontinuation and Completion Criteria

#### 5.3.1 Complete or Evaluable Participants

An ED Participant is considered ‘Evaluable’ and eligible for the analysis population if they receive IMP in at least one Experimental Session and have at least one follow-up EDE assessment post-treatment.

An ED Participant is considered ‘Completed Per Protocol (PP)’ if they meet eligibility criteria, receive IMP in all planned Experimental Sessions, and complete all follow-up EDE assessments post-treatment. These participants will be included in the analysis population set and the PP analysis set.

An ED Participant is considered ‘Early Study Termination’ if they receive IMP in at least one Experimental Session and have at least one follow-up EDE assessment post-treatment, but terminated early. These participants will be included in the analysis population.

A CG Participant is considered ‘Evaluable’ and eligible for the analysis population if they complete Visit 1.

A CG Participant is considered ‘Completed PP’ if they meet eligibility criteria and complete all follow-up assessments from Visit 16. These participants will be included in the analysis population set and the PP analysis set.

A CG Participant is considered ‘Early Study Termination’ if they have completed Visit 1 but terminated early. These participants will be included in the analysis population.
Any participant is considered to be in good standing with the clinical site if, in the opinion of the investigator and/or therapy team, the participant was compliant with protocol requirements, even if they were unable to complete all study visits.

5.3.2 Screen Failures

‘Screen Failures’ are defined as participants who pass screening but are deemed ineligible before successfully enrolling in the study at Visit 0. Screen failures may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to Enrollment. All potential participants who begin Screening will be tracked on a Screening Log, and reasons for Screen Failure will be recorded. Screen Failures are not considered evaluable.

At any time during Screening, if a potential participant is deemed to be ineligible, they will be classified as a Screen Failure. These participants will be notified that they are unfortunately not eligible for the study, and will not have additional Screening assessments scheduled. Participants who fail Screening may rescreened at a later date if deemed appropriate by the investigator but should sign a new Informed Consent Form (ICF). ED-Ps who screen fail may request a referral to an outside therapist if needed. If a CG-P screen fails prior to an ED-Ps first Experimental Session, they may be replaced with another eligible CG-P. If one cannot be located, the ED-P must also be screen failed. If an ED-P screen fails from the study the CG-P will also be screen failed.

5.3.3 Withdrawal Criteria for Enrolled Participants

Participants who have been enrolled into the study and assigned a Participant ID may still withdraw from the study at any time, or may meet criteria for early withdraw by the investigator. Criteria for early withdraw by the investigator includes failing to continue to meet all Inclusion Criteria or meeting at least one Exclusion Criteria, after Clinical Investigator (CI) (or Qualified Investigator [QI]) review with the Medical Monitor. Criteria for early withdraw by the investigator also includes meeting at least one early withdraw criteria listed here:

1. ED Participants Additional Early Withdraw Criteria:
   a. Rapid weight loss deemed unsafe for continuation by the study investigator
   b. Development of concurrent physical illness that necessitates the participant’s removal from the trial
   c. Deterioration of mental or physical health warranting additional input and support
   d. Development of dependency or problematic alcohol or illicit substance use
   e. Any current problem which, in the opinion of the CI, QI, or Medical Monitor might interfere with ongoing participation

2. CG Participants Additional Early Withdraw Criteria:
   a. Withdrawal of their loved one (ED-P) from the study
   b. Development of concurrent mental or physical illness that necessitates the caregiver’s removal from the trial
   c. Deterioration of mental or physical health warranting additional input and support
   d. Develop any current problem which in the opinion of the investigator or Medical Monitor might interfere with ongoing participation

Participants who meet criteria for early withdraw by the investigator will not be eligible for re-enrollment into this study at a later date. All enrolled participants, even those who are withdrawn, will be maintained in the Electronic Data Capture (EDC) system.
5.3.4 Pre-Study Treatment Early Study Termination

‘Pre-Study Treatment Early Terminations’ are defined as ED or CG participants who were deemed eligible and enrolled in the study at Visit 0, but are deemed ineligible prior to the ED-Ps first Experimental Session. These participants may fail to meet all Inclusion Criteria, may meet at least one Exclusion Criteria or early withdraw criteria, or withdraw consent prior to the ED-Ps first treatment with MDMA-assisted psychotherapy. ED or CG participants who meet this criteria may not be re-enrolled into this study at a later date. If a CG-P is withdrawn prior to an ED-Ps first Experimental Session, they may be replaced with another eligible CG-P. All enrolled participants, even those meeting ‘Pre-Study Treatment Early Study Termination’ criteria, will be maintained in the EDC system. Pre-Study Treatment Early Terminations are not considered evaluable.

Pre-Study Treatment Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the ED or CG participant. At any time during the Preparatory Period, if a potential ED or CG participant is deemed to be ineligible, classify as a Pre-Study Treatment Early Study Termination. Then, notify the individual that they are unfortunately not eligible for the study and will not have any additional assessments scheduled. Pre-Study Treatment Early Terminations for ED-Ps may be provided with a Plan for Moving Forward as described in the Plan for Moving Forward Section 8.6.1 of this protocol.

5.3.5 Early Termination from the Study

ED or CG participants who withdraw or are removed from the study after the ED-Ps first Experimental Session and their receiving of IMP may fall into one of these categories: Post-Study Treatment Early Study Termination or Dropout. If the ED-P has received IMP in at least one Experimental Session, the ED-P and/or CG-P will be considered evaluable and will be included in all safety analyses.

Participants can withdraw consent and their participation in the study at any time for any reason without judgment. The site team can withdraw an ED-P or CG-P if in their clinical judgment it is in the best interest of the participant, if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study, if the participant fails continuing to meet all Inclusion Criteria, if the participant meets at least one Exclusion Criteria, or if the participant meets at least one early withdraw criteria listed in the Withdrawal Criteria for Enrolled Participants Section 5.3.3 of this protocol. If a CG-P is withdrawn from the study after the ED-Ps first Experimental Session, the ED-P may continue in the study without an enrolled CG-P. CG-Ps will not be replaced after the ED-Ps first Experimental Session. If an ED-P is withdrawn from the study at any time, the CG-P will also be withdrawn.

If the site team makes the decision to terminate a participant from the study, they will explain the reason for withdrawal and document in the participant’s source records and Electronic Case Report Form (eCRF). If an ED-P meets any Exclusion or Withdraw Criteria that, in the opinion of the Medical Monitor or Site, affects their safety, including psychiatric diagnosis, medical diagnosis, elevated QTcF interval results during the study, pregnancy, or requiring use of prohibited medications, the ED-P will discontinue treatment in last Experimental Sessions but remain in the study for the associated Integrative Sessions along with their CG-P. Any time an ED-P terminates from the study early, the site team will attempt to obtain information about AE outcomes if appropriate, as determined by the site physician and Medical Monitor. The site team will provide the participant with a Plan for Moving Forward as described in the Plan For Moving Forward Section 8.6.1 of this protocol.
If an ED-P decides to withdraw consent completely, they will terminate without further follow-up. If the participant agrees, they will complete a Study Termination Visit. These ED-Ps are defined as dropouts who withdraw consent due to any reason after receiving at least one dose of IMP and no longer participate in the study (i.e., no further contact with investigators or site staff). Data collected on any study participant up to the time of withdrawal of consent will remain in the trial database in order to maintain scientific validity. Removal of data from the database would undermine the scientific and ethical integrity of the research.

5.3.6 Lost to Follow-up

Any participant will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the site staff. If a participant does not attend a scheduled visit, the site must attempt to contact the participant to reschedule the visit as soon as possible and emphasize the importance of complying with future visits. If a participant does not respond to this initial contact, the site staff must make multiple efforts to contact the study participant and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 7 days, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. The emergency contact the participant provided should be contacted and asked to attempt contact with the participant. Lastly, a certified letter (or equivalent) should be sent to their last known mailing address. If the participant fails to respond to all of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up. In these instances, the Discontinuation and Completion Criteria Section 5.3 should be referenced applicable to the participant’s last visit in the study. The same definitions, rules, and standards will apply such as participant replacement and evaluable data determinations.

5.4 End of Study Definition and Premature Discontinuation

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure at the Study Termination Visit for the last participant in the trial globally.

The sponsor has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform participants and will ensure they receive appropriate therapy, follow-up, and a Plan for Moving Forward. 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 federal and state regulations.

5.5 Rationale of Dose Selection

Similar MDMA doses to those proposed in this study have been safely used in previous PTSD studies sponsored by MAPS. A flexible dosing regimen has been explored previously in Phase 2 PTSD studies, where participants who received doses of 0 mg to 75 mg MDMA in the blinded portion of the study crossed over to receive open-label 100 mg MDMA in the first Experimental Session with an option to increase to 125 mg MDMA in the second and third Experimental Sessions. In the opinion of the participants and therapy teams administering this treatment in Phase 2 studies, this flexible dosing regimen and three Experimental Sessions produced an optimal treatment response. Larger doses have been administered safely in MP2 (150 mg and 75 mg supplemental) and in Phase 1 studies (150 mg and 160 mg). The results of these Phase 2
studies led to the selection of 80 mg and 120 mg MDMA as the initial active doses to be compared to inactive placebo in Phase 3 PTSD trials.

This open-label pilot study will explore the use of MDMA-assisted psychotherapy as treatment for specified eating disorders, often populations with significant weight loss or gain. For participants weighing 48 kg or higher, it will keep the standard dosing regimen of 80 mg and 120 mg MDMA as initial active doses and the regimen will not be dose ranges based on body weight. This is due to a wide range of responses seen in identical milligram per kilogram (mg/kg) dosing, to epidemiological information, and lack of linear dose response with behavior effects in Phase 1 and sponsor-supported studies [46, 74]. However, in consideration of their low body weight, an alternate dosing regimen has been selected for AN-R participants weighing ≥45 kg and < 48 kg. Further supporting information can be found in the IB supplied by the sponsor.

The initial dose for the first Experimental Session for participants weighing 48 kg or higher will be 80 mg, followed 1.5 to 2 hours later by a supplemental half-dose of 40 mg. Then, for these participants the initial doses for the second and third Experimental Sessions will be either 80 mg or 120 mg of MDMA, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg). The choice of whether to keep the initial dose the same in the second and third sessions (at 80 mg) or increase it to 120 mg will be made by the site team based on observed response, safety and tolerability of the previously administered dose, and discussion with the participant.

The initial dose for all Experimental Sessions for participants weighing ≥45 kg and < 48 kg will be 80 mg, followed 1.5 to 2 hours later by a supplemental half-dose of 40 mg.

In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental half-dose unless contraindicated (which also includes observed response, safety and tolerability of the previously administered dose, and discussion with the participant).

The dosing regimens were chosen to mimic proposed clinical practice and better adapt to risk-benefit considerations. The initial active doses of 80 mg and 120 mg are expected to produce all commonly reported effects of MDMA. The supplemental half-dose will prolong subjective effects of MDMA without producing physiological effects much greater than peak effects occurring after the initial dose, and will be administered unless contraindicated. Total amounts of MDMA to be administered per Experimental Session are listed in the following tables.

**Table 2: Dose Regimen of MDMA for ED-Ps Weighing 48 kg or Higher**

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Initial Dose</th>
<th>Supplemental Dose*</th>
<th>Min-Max Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
<tr>
<td>2</td>
<td>80 mg or 120 mg</td>
<td>40 mg or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
<tr>
<td>3</td>
<td>80 mg or 120 mg</td>
<td>40 mg or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
<tr>
<td><strong>Total Cumulative Dose</strong></td>
<td></td>
<td></td>
<td>240 mg to 480 mg</td>
</tr>
</tbody>
</table>

*A supplemental dose will be administered unless contraindicated or refused by the ED-P. Observed response, safety and tolerability of the previously administered dose, and discussion with the participant will all be taken into consideration as potential contraindications for the supplemental dose, and when considering escalating the initial dose in the second and third Experimental Sessions.

**Table 3: Dose Regimen of MDMA for ED-Ps Weighing ≥45 kg and < 48 kg**

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Initial Dose</th>
<th>Supplemental Dose*</th>
<th>Min-Max Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
<tr>
<td>2</td>
<td>80 mg</td>
<td>40 mg</td>
<td>80 mg to 120 mg</td>
</tr>
</tbody>
</table>
6.0 Psychotherapy

6.1 Description of Therapeutic Method

The therapeutic method of MDMA-assisted psychotherapy is described in detail in the MAPS Treatment Manual, which was created for treatment of PTSD. The non-directive approach in the manual pertains to inviting inquiry and providing suggestion rather than directing the participant in the therapeutic approach. This requires active or engaged listening and responding, as well as facilitation of therapeutic action by providing support for approaching difficult material in a manner that does not interfere with the participant’s spontaneous experience. This study will follow the same approach and guiding principles for the treatment of the AN-R and BED eating disorders, and may also include other therapeutic approaches that more adequately facilitate emotional regulation for this patient population such as Emotion-Focused Family Therapy, Internal Family Systems, and/or Emotion-Focused Therapy.

An exploratory objective of this study is to further review the treatment modality method and develop a manual specifically for the eating disorders patient population by collecting impressions on this from the study therapists after the study. For the eating disorder population, there is more of a focus on body-image, internal family systems, and/or emotional regulation rather than trauma. Therefore, each therapist will be collecting qualitative data during their treatment sessions to further research and understanding of MDMA-assisted psychotherapy for the treatment of eating disorders. Based on the information obtained, the therapeutic method will be continually evaluated and possibly adjusted to better suite this patient population. Caregivers will be supported using principles and techniques of Emotion-Focused Family Therapy [28].

6.2 Therapy Team Qualifications

Therapy teams will be trained by the sponsor. Sites must ensure that the minimum requirements below are met:

- One or more two-person therapy pairs will be on the study team, who have been reviewed and approved by the MDMA Therapy Training Program.
- One person per therapy pair is required to be licensed to provide psychotherapy according to state or province and local requirements.
- If one person on the therapy team is unlicensed, they will be required to have, at a minimum, a bachelor’s degree and either be trained in mental health (including students in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments) or have completed 1000 hours of behavioral health experience prior to co-facilitating sessions as a part of a co-therapy pair.

A physician will be required to be on the study team, and to be on-site for the duration of Experimental Sessions, to assess participant safety. Each site will also be required to have one person licensed to manage and administer controlled substances.
6.3 Training

The MDMA Therapy Training Program is designed to teach competency in applying the essential elements of MDMA-assisted psychotherapy. In addition to having the proper background, education, and experience, therapy team members will receive specific training in the MDMA-assisted psychotherapy method, protocol, and latest version of the MDMA Investigator’s Brochure. Training in the psychotherapy method consists of reading the MAPS Treatment Manual, completing an online training module, and participating in an in-person training program that includes watching and discussing videos of Experimental Sessions and non-drug therapy sessions. The final part of training includes supervision from the training team.

Each therapy team member will complete training in Emotion-Focused Family Therapy. In addition, they will also complete Internal Family Systems and/or Emotion-Focused Therapy to more adequately facilitate emotional regulation in this patient population.

6.4 Supervision in the Therapeutic Method

Psychotherapy sessions, including Experimental Sessions, will be recorded to audio and video for research and training purposes. Supervision of a therapist pair’s ED-P study sessions may be conducted by qualified and trained Supervisors in the MDMA Therapy Training Program. These Supervisors may review video recordings and provide feedback to new therapy teams.

7.0 Measures and Reliability for ED and CG Participants

The following primary outcome, eligibility, safety, and exploratory outcome measures will be used in the study for ED and CG participants, in accordance with the ED Participant Time and Events-Study Measures Tables 4 and 5, and the CG Participant Time and Events-Study Procedures and Measures Table 6.

Table 4: Protocol Objectives and Assessment Tools for Participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>Objectives</th>
<th>Measure</th>
<th>Measure Type</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED-P</td>
<td>Examine changes in body mass index (BMI), calculated by height and weight</td>
<td>BMI</td>
<td>Exploratory Outcome and Eligibility</td>
<td>Site</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess physical health status</td>
<td>Physical Exam</td>
<td>Eligibility</td>
<td>Site</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess physical health status at screening. For AN-R participants only, assess health status for continued eligibility and safety up to 3 days prior to the Experimental Session</td>
<td>Lab Tests</td>
<td>Eligibility and Safety</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Participant</td>
<td>Objectives</td>
<td>Measure</td>
<td>Measure Type</td>
<td>Administration</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>ED-P</td>
<td>Assess physical health status at screening. For AN-R participants only, assess health status for continued eligibility and safety prior to initial dose and 1.5-2 hours after (and prior to supplemental dose) at each Experimental Session</td>
<td>12-lead ECG</td>
<td>Eligibility and Safety</td>
<td>Site</td>
</tr>
<tr>
<td>ED-P</td>
<td>For AN-R participants only, determine potential health dangers by measuring the presence of ketones prior to an Experimental Session</td>
<td>Urine Ketone Test</td>
<td>Safety</td>
<td>Site</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess physical health status for eligibility. Assess health status for continued eligibility and safety during Experimental Sessions; blood pressure, heart rate, and body temperature will be collected</td>
<td>Vital Signs</td>
<td>Eligibility and Safety</td>
<td>Site</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess the number and types of adverse childhood experiences</td>
<td>ACE</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess adult attachment behaviors</td>
<td>ASQ-SF</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess changes in depression symptoms</td>
<td>BDI-II</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Measure of severity of psychosocial impairment due to ED features</td>
<td>CIA</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>CG-P</td>
<td>Assess CG skills that may be helpful in support of ED-P</td>
<td>CASK</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>ED-P and CG-P</td>
<td>Measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors</td>
<td>C-SSRS</td>
<td>Eligibility for both ED-P and CG-P; Safety for ED-P</td>
<td>Site/Clinician Administered</td>
</tr>
<tr>
<td>CG-P</td>
<td>Examines the extent to which caregivers feel vulnerable to fears that affect ability to support ED-P in recovery</td>
<td>CTS</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>ED-P and CG-P</td>
<td>Measure of emotion regulation difficulties</td>
<td>DERS-16</td>
<td>Exploratory Outcome</td>
<td>Participant Self-Report</td>
</tr>
<tr>
<td>Participant</td>
<td>Objectives</td>
<td>Measure</td>
<td>Measure Type</td>
<td>Administration</td>
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</tr>
<tr>
<td>ED-P</td>
<td>Assess emotional breakthrough as a distinct component and possible therapeutic mechanism of psychedelic experiences</td>
<td>EBI</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Measure of eating attitudes and behaviors over the previous week</td>
<td>ED-15</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess the key behavioral features of eating disorders</td>
<td>EDE</td>
<td>Primary Outcome</td>
<td>Site/Clinician Administered</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess the frequency of ED-related behaviors over the past 28 days, as well as shape and weight concerns</td>
<td>EDEQ</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>CG-P</td>
<td>Measures caregiving burden related to symptoms specific to the ED</td>
<td>EDSIS</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Measure of positive and negative aspects of the quality of engagement of one’s body with the world</td>
<td>EES</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess ED symptomology</td>
<td>EDI-3</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess psychiatric disorders and record PTSD as applicable for comorbidity</td>
<td>MINI</td>
<td>Eligibility</td>
<td>Independent Rater (IR) Administered</td>
</tr>
<tr>
<td>ED-P and CG-P</td>
<td>Measure of structural, organizational, and transactional characteristics of families</td>
<td>MFFS</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Confirm PTSD diagnosis and severity</td>
<td>PCL-5 with LEC-5</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Examine readiness to change in various ED symptom domains</td>
<td>RMQ</td>
<td>Secondary Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Measure of global self-esteem</td>
<td>RSES</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess personality disorders</td>
<td>SCID-5-PD</td>
<td>Eligibility</td>
<td>Independent Rater (IR) Administered</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess personality disorders</td>
<td>SCID-5-SPQ</td>
<td>Eligibility</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Measure of self-compassion</td>
<td>SCS</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
</tbody>
</table>
7.1 Description of Measures

Listed below are the descriptions of the study measures.

### 7.1.1 Adverse Childhood Assessment Questionnaire (ACE)

The ACE is a 10-item checklist measure assessing number and types of adverse childhood experiences, including neglect and emotional, physical, and sexual abuse. Respondents are asked if an experience happened “often” and if so, to write “1”. The total score reflects the number of adverse childhood experiences. The measure was first used in the context of a study investigating the relationship between childhood adverse experiences and health outcomes in adulthood [75]. Number of frequent adverse childhood experiences is associated with adverse health outcomes in adulthood, including greater likelihood of heart disease, chronic pain, and poor work performance [76-79]. The scoring method has been used in archival research, finding an association between increased scores and health problems in several generations [78]. The ACE takes approximately 1 to 3 minutes to complete.

### 7.1.2 Attachment Style Questionnaire-Short Form (ASQ-SF)

The ASQ-SF is a 29-item sub-set self-report measure of the full ASQ, assessing adult attachment behaviors specifically for two primary factors: attachment anxiety (containing 13 items) and avoidance (containing 16 items). The ASQ-SF can be used to tap into the five faucet factors originally identified in the ASQ: one representing secure attachment (“Confidence”) and the other four representing aspects of insecure attachment (“Discomfort with Closeness”, “Relationships as Secondary”, “Need for Approval”, and “Preoccupation with Relationships”. The ASQ combines theory driven prototypes of attachment with a dimensional approach, allowing the assessment of non-relationship-specific attachment [80-82]. The ASQ-SF takes approximately 5 to 10 minutes to complete.

### 7.1.3 BDI-II (Beck Depression Inventory II)

The BDI-II is a revision of the BDI, a 21-item self-report measure [83, 84] that will serve as a measure of depression symptom severity [85]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability, and is not overly sensitive to daily variations in mood. It takes 5 to 10 minutes to complete [85]. Score cutoffs indicate: 0 to 13 minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. Initial and subsequent studies report that the BDI-II total score has a reliability coefficient of 0.90 to 0.91 which is related to other measures of depression symptoms [85, 86]. Higher scores indicate more severe depressive symptoms.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Objectives</th>
<th>Measure</th>
<th>Measure Type</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED-P</td>
<td>Measure of transient and enduring levels of anxiety</td>
<td>STAI</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P</td>
<td>Assess participant perception of satisfaction with treatment received</td>
<td>FQ</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
<tr>
<td>ED-P and CG-P</td>
<td>Measure of quality of life</td>
<td>WHOQOL-BREF</td>
<td>Exploratory Outcome</td>
<td>Participant Self- Report</td>
</tr>
</tbody>
</table>
7.1.4 Clinical Impairment Assessment (CIA)

The CIA is a 16-item self-report measure of the severity of psychosocial impairment due to eating disorder features. It focuses on the past 28 days. The 16 items cover impairment in domains of life that are typically affected by eating disorder psychopathology: mood and self-perception, cognitive functioning, interpersonal functioning and work performance (Bohn & Fairburn, 2008). It has been validated among a sample of caregivers of a loved one with an eating disorder [87]. The CIA takes approximately 3 minutes to complete.

7.1.5 Caregiver Skills Scale (CASK)

The CASK is a 27-item self-report measure assessing caregiver skills that may be helpful in the support of people with EDs. The scale contains six factors: Bigger Picture, Self-Care, Biting-Your-Tongue, Insight and Acceptance, Emotional Intelligence, and Frustration Tolerance [41]. Caregivers rate on an 11-point Likert scale from 0 to 100 how confident they are that they can engage in adaptive caregiver skills (e.g., “Accept that the eating disorder is not your fault?”, “Find time to spend with other members of the family?”). Higher scores indicate a caregiver is more confident they can engage in these skills. Reliability coefficients for the scale factors range from 0.71 to 0.84. The total score (achieved by summing all factors) has a reliability coefficient of 0.92. Caregivers who participated in a skills training intervention showed improvement on all factors and the total score of the CASK, while caregivers who did not participate in the intervention saw no improvement. Caregiver’s expressed emotion, accommodating and enabling behaviors, general health, and distress correlated negatively with various CASK subfactors. The CASK takes approximately 3 to 6 minutes to complete.

7.1.6 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 trial. It consists of a Lifetime version and a Since Last Visit version that assess suicidal ideation, ideation intensity, and behavior [88, 89]. The C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The Lifetime version will only be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. The C-SSRS Intensity scale for Lifetime obtained a Cronbach’s alpha of 0.93 and 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI “suicide thoughts” item [90]. The C-SSRS takes approximately 3 to 20 minutes to complete.

7.1.7 Caregiver Traps Scale (CTS)

The CTS is a 14-item measure that examines the extent to which caregivers feel vulnerable to fears that interfere with their ability to support their loved ones through recovery. Caregivers rate on a seven-point Likert scale (ranging from 1 = not at all likely to 7 = extremely likely) the extent to which they feel vulnerable to 14 different fears when supporting their loved one's recovery. Example items include “I worry about being rejected by my loved one.” And “I worry that my loved one will miss out on normal activities or special occasions.” Reliability coefficients ranging from 0.71 to 0.90 have been reported [91, 92]. Higher scores indicate a higher level of caregiver fear related to engagement in treatment [92, 93]. The CTS takes approximately 1 to 3 minutes to complete.
7.1.8 Difficulties with Emotion Regulation Scale (DERS-16)

The DERS-16 is a 16-item self-report measure of emotion regulation difficulties. The scale includes five dimensions: 1) nonacceptance of negative emotions, 2) inability to engage in goal-directed behaviors when distressed, 3) difficulties controlling impulsive behaviors when distressed, 4) limited access to emotion regulation strategies perceived as effective, and 5) lack of emotional clarity. Respondents endorse items on a 5-point Likert-type scale from 1 (almost never) to 5 (almost always). Higher scores reflect greater levels of emotion dysregulation. The DERS-16 has excellent internal consistency (Cronbach’s alpha = 0.92). The scale correlates strongly with the original 36-item DERS (r = .80). The validity of the DERS-16 is supported by positive associations with psychiatric symptoms (r = .43 to .56), self-harm (r = .22 to .30), and self-destructive behaviors (r = .36 [94]. The DERS-16 takes approximately 1.5 to 3 minutes to complete.

7.1.9 The Imperial Emotional Breakthrough Inventory (EBI)

The EBI is a 6-item self-report measure that assesses emotional breakthrough as a distinct component and possible therapeutic mechanism of psychedelic experiences. Higher scores indicate greater emotional release or breakthrough in following a psychedelic experience. The EBI’s validity is supported by positive correlations between EBI scores and drug dose, therapeutic intent of psychedelic use, willingness to confront difficult emotions, therapeutic nature of setting where psychedelic was taken, and increased wellbeing 2 weeks after the psychedelic experience. The scale has a Cronbach’s alpha of 0.93. Factor analysis demonstrated that EBI was related to, but also distinct from mystical and challenging experiences associated with taking psychedelics [95]. The EBI takes approximately 1 to 2 minutes to complete.

7.1.10 Eating Disorder-15 (ED-15)

The ED-15 is a brief self-report measure of eating attitudes and behaviors over the past week, developed for use at weekly sessions in clinical settings. Respondents select a response on a 7-point Likert scale ranging from 0 (“not at all”) to 6 (“all the time”) for items such as, “worried about losing control over my eating” and “felt distressed about my weight.” The scale’s ten attitudinal items form two factors: 1) weight and shape concerns and 2) eating concerns. Five behavioral items assess the frequency of objective binges, vomiting, laxative use, exercise, and restriction. Reliability coefficients for the scale’s two factors range from 0.80 to 0.94. Among women with eating disorders who were not in therapy, test-retest reliability over 2 to 3 weeks was 0.79. This temporal stability in a non-treatment sample suggests that changes observed week to week would not be due to random fluctuations, but instead reflect therapeutic change. ED-15 scores correlated positively and strongly with scores from EDE-Q, a standard measure of eating behaviors and attitudes [96]. The ED-15 will be completed by the ED participant on a weekly basis during study participation (unless the EDEQ or EDE is already being administered). The ED-15 takes approximately 1 to 3 minutes to complete.

7.1.11 Eating Disorder Examination-Interview (EDE)

The EDE is a semi-structured interview that assesses the frequency of key behavioral features of eating disorders, as well as the severity of specific ED psychopathology with subscale scores for Restraint, Eating Concern, Shape Concern, and Weight Concern. Behavioral symptoms such as binge eating, self-induced vomiting, and excessive exercise are assessed. The EDE is widely considered to be the gold standard for assessing eating disorder pathology. The EDE has been shown to detect differences between individuals with eating disorders and those without, including individuals with AN and BED. The EDE also correlates positively with other measures.
of eating pathology. Frequency of binge eating and compensatory behaviors as measured by the EDE also correlate positively with daily food records tracking these behaviors. Internal consistency coefficients of the subscales ranged from 0.58 to 0.78 for the Restraint subscale, 0.44 to 0.78 for the Eating Concern subscale, 0.68 to 0.85 for the Shape Concern subscale, and 0.51 to 0.76 for the Weight Concern subscale, while interrater reliability coefficients have ranged from 0.65 to 0.99 for the different subscales [97]. The EDE takes 45 minutes to one hour and 15 minutes to administer and participants are mainly asked to answer questions with respect to the previous 4 weeks. The four subscale scores may be averaged to generate a global EDE score [98, 99].

7.1.12 Eating Disorder Examination-Questionnaire (EDEQ)

The EDEQ is a 32-item self-report questionnaire based on the EDE-Interview, the gold standard for measurements of disordered eating [97]. Participants report on the frequency of eating disorder related behaviors over the past 28 days (e.g., bingeing, self-induced vomiting, etc.), as well as shape and weight concerns. Like the EDE-Interview, the EDEQ provides subscores for Restraint, Eating Concern, Shape Concern, and Weight Concern, as well as a Global EDE score [99]. A systematic review found that reliability coefficients for the EDE-Q subscales ranged from 0.70 to 0.93. Test-retest reliability for the subscales has ranged from 0.66 to 0.94 over intervals ranging from 1 to 14 days. Individuals with eating disorders (including AN and BED) have demonstrated higher EDEQ scores relative to control groups. Positive correlations have also been found for behavioral items on EDEQ and daily food records [97]. The EDEQ takes approximately 5 to 10 minutes to complete.

7.1.13 Eating Disorder Symptom Impact Scale (EDSIS)

The EDSIS is a 24-item scale that measures caregiving burden related to symptoms specific to the eating disorder using a 5-point Likert scale (α = 0.9). The scale contains four factors: Nutrition, Dysregulated Behavior, Guilt, and Social Isolation [38, 100]. Reliability has been acceptable showing a Cronbach’s alpha range from 0.84 to 0.90. The EDSIS scales convergent validity has been moderately supported with associations with the following: psychological distress (General Health Questionnaire-12, r = 0.33), perceived functioning of relatives (Children Global Assessment Scale, r = -0.30), general caregiving (Experience of Caregiving Inventory, r = 0.42 to 0.60). The EDSIS takes approximately 2 to 4 minutes to complete.

7.1.14 Eating Disorder Inventory (EDI-3)

The EDI-3 is a 91-item self-report measure of ED symptomology. The inventory consists of 12 scales: Drive for Thinness, Bulimia, Body Dissatisfaction, Low Self-Esteem, Personal Alienation, Interpersonal Insecurity, Interpersonal Alienation, Interceptive Deficits, Emotional Dysregulation, Perfectionism, Asceticism, and Maturity Fears. Six composite scores may be generated: Eating Disorder Risk, Ineffectiveness, Interpersonal Problems, Affective Problems, Overcontrol, and General Psychological Maladjustment. Internal reliability coefficients exceed 0.80 for most subscales. Short term test-retest reliability coefficients ranged from 0.93 to 0.98 among women with eating disorders. Correlations with other established measures of disordered eating support convergent validity and correlations with measures of general psychopathology demonstrate adequate discriminant validity [101]. The EDI-3 takes approximately 20 minutes to complete.
7.1.15 Experience of Embodiment scale (EES)

The EES is a self-report measure that captures both positive and negative aspects of the quality of engagement of one’s body with the world. The scale taps into the following themes: body connection and comfort; body disrupted adjustment; agency and expression; experience and expression of desire; attuned self-care; and inhabiting the body as a subjective site [102]. Total and subscale EES scores can describe experience of embodiment changes that occur across a person’s lifetime. The EES takes approximately 3 to 5 minutes to complete.

7.1.16 Feedback Questionnaire (FQ)

The feedback questionnaire is a MAPS PBC developed, non-validated self-report measure specifically for the MED1 study. This FQ will assess the ED participant’s perception of satisfaction with treatment received at the ED-Ps final visit. The FQ contains 10 questions and contains space for an optional narrative to collect qualitative data from the ED-P about their experience. The FQ takes approximately 5 to 10 minutes to complete.

7.1.17 McMaster Family Functioning Scale (MFFS)

The MFFS is a 12-item subscale assessing general family functioning that is part of the larger McMaster Family Assessment Device (MFAD). Respondents endorse how much they agree or disagree with statements regarding their partner or family (e.g., “Planning family activities is difficult because we misunderstand each other”) on a 4-point Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree). Negative items are reverse scored and all items are summed and averaged to provide a total score, with higher scores indicating greater dysfunction within the family. A cutoff score of greater than 2.0 is used to indicate unhealthy family functioning [103]. MFFS scores have been shown to be elevated (indicating poorer functioning) in clinical samples relative to community samples. The MFFS has demonstrated moderate to strong correlations with other dimensions of family functioning as measured by the MFAD, including problem solving, communication, roles, affective responsiveness, affective involvement, and behavior control [104]. The MFFS takes approximately 2 to 4 minutes to complete.

7.1.18 MINI (Mini-International Neuropsychiatric Interview)

This version of the MINI (7.0.2), a structured interview that was first developed in 1998 to be compatible with DSM and International Classification of Disease (ICD) criteria for psychiatric illnesses [105], is now compatible with DSM-5 and will be administered to screen for psychiatric conditions per DSM-5, and to record PTSD as a comorbidity with the additional PTSD module. Each module of the MINI consists of two or three questions where the answer is either “Yes” or “No,” and decision-tree logic is used to determine whether to ask additional questions [106]. The MINI takes between 15 and 20 minutes to perform and addresses major psychiatric disorders. MINI items were highly reliable (intrarater reliability between kappa of 0.8 and 0.99; test-retest reliability between 0.6 and 0.9 for all scales save “current mania”), and diagnosis via MINI was comparable to that made with the Composite Diagnostic Interview and the SCID [106, 107]. Testing on nonpsychiatric samples did not create false positives [105].

7.1.19 PTSD Checklist (PCL-5)

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the symptoms of PTSD per DSM-5 [108]. Participants indicate how much distress they have experienced due to symptoms such as "Repeated, disturbing
memories, thoughts, or images of a stressful experience from the past," "Trouble remembering important parts of a stressful experience from the past," and "Feeling irritable or having angry outbursts" on a five-point Likert-type scale (1=Not at all to 5=Extremely). The PCL-5 takes about 5 to 10 minutes to complete.

7.1.20 Life Events Checklist for DSM-5 (LEC-5)

The LEC-5 is a 17-item self-report instrument designed to determine the presence of traumatic life events in the assessment and diagnosis of PTSD. It is a companion measure to the PCL-5 and will be used to assess PTSD. The participant indicates whether each event listed has occurred during their lifetime, permitting the possibility of marking multiple events [109]. The LEC-5 takes about 5 to 10 minutes to complete.

7.1.21 Readiness and Motivation Questionnaire (RMQ)

The RMQ is a self-report measure intended to assess readiness for change among individuals with eating disorders as conceptualized according to the Transtheoretical Model of Change. For each eating disorder symptom of the EDE, the RMQ asks individuals to provide ratings for precontemplation, action/maintenance, and internality. The RMQ does not provide a contemplation rating, but does include a confidence rating to assess perceived self-efficacy for change. Symptoms are grouped into restriction, cognitive, compensatory, and bingeing domains. Average precontemplation, action/maintenance, internality, and confidence scores may be calculated for symptom domains or for a total score reflecting overall readiness to change. Internal reliability coefficients for different stages of change across symptom domains are low to moderate (precontemplation \( \alpha = 0.55 \), action \( \alpha = 0.66 \), confidence \( \alpha = 0.77 \), and internality \( \alpha = 0.80 \)). These low to moderate alphas reflect that individuals motivation to change may vary by symptoms (e.g., an individual may be more motivated to change disordered eating symptoms they find distressing compared to symptoms they do not view as problematic). Test-retest coefficients varied from 0.62 to 0.81. Validity of the RMQ is supported by positive correlations between the action subscale and completion of recovery activities. In addition, expected difficulty of recovery correlated positively with precontemplation and negatively with action, internality, and confidence, consistent with the Transtheoretical Model of Change [110]. The RMQ takes approximately 5 to 15 minutes to complete.

7.1.22 Rosenberg Self-Esteem Scale (RSES)

The RSES is a 10-item self-report measure of global self-esteem. Respondents endorse items related to self-worth and self-acceptance on a 4-point scale, ranging from strongly disagree to strongly agree. The scale’s total score is often used as an overall measure of self-esteem, however, subscores for positive and negative self-esteem are sometimes calculated [111, 112]. The RSES takes approximately 2 minutes to complete.

7.1.23 SCID-5-PD (Structured Clinical Interview for DSM-5 for Personality Disorders) with SCID-5-SPQ (SCID-5 Self-report Personality Questionnaire)

The SCID-5-PD will be administered by an Independent Rater (IR) via telemedicine [113]. Prior to the SCID-5-PD clinical interview, participants will complete a brief self-report questionnaire called the SCID-5 Self-report Personality Questionnaire (SCID-5-SPQ) as a self-report screening tool used to assess for personality disorders. Potential personality disorders that satisfy diagnostic thresholds will be further assessed via clinical interview during the SCID-5-PD. IRs will receive training on administering these measures from a research reliable trainer. The SCID-5-SPQ takes
approximately 20 minutes to complete, while the SCID-5-PD takes approximately 30 to 120 minutes to complete.

7.1.24 The Self-Compassion Scale (SCS)

The SCS is a 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience [114]. Respondents complete the SCS by indicating how typical they feel on each item on a five-point Likert scale (1=Almost never and 5=Almost always). The scale has six sub-scales: Self-Kindness, Self-Judgment, Common Humanity, Isolation, Mindfulness, and Over-Identified. The mean of subscale scores serves as a total score. Analysis of SCS response indicated that subscales are all related to a higher order factor of self-compassion, and the measure has high test-retest reliability at a level of 0.93. Neff et al. reported an inverse relationship between SCS total scores and scores on measures of depression and anxiety. Self-compassion and global self-esteem are both related to positive mood and optimism, but self-compassion may be more strongly associated with stable mood and less associated with self-rumination and anger [115]. The SCS takes approximately 4 to 8 minutes to complete.

7.1.25 State-Trait Anxiety Inventory (STAI)

The STAI is a 40-item instrument, measuring both transient and enduring levels of anxiety. The state anxiety scale captures one’s current state of anxiety, using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The Trait Anxiety Scale evaluates relatively stable aspects of “anxiety proneness,” including general states of calmness, confidence, and security [116]. Internal reliability coefficients for the state and trait subscales range from 0.90 to .94 and 0.89 to 0.96 respectively. As would be expected, the trait subscale shows higher test-retest reliability coefficients compared to the state subscale. Norms for state anxiety scores also demonstrate higher state scores under stressful situations (e.g., taking an exam) compared to nonstressful situations. The trait subscale also demonstrated positive correlations with other established measures of trait anxiety [117]. The STAI takes approximately 10 minutes to complete.

7.1.26 World Health Organization Quality of Life-Brief (WHOQOL-BREF)

The WHOQOL-BREF is a 26-item measure of quality of life adapted from the longer WHOQOL-100. This scale assesses the quality of life in four domains: physical health, psychological, social relationships, and environment [118]. Items inquire about “how much”, “how completely”, “how often”, “how good”, or “how satisfied” respondents felt in the last 2 weeks with respect to the different domains. Respondents indicate their answers using a 5-point Likert scale. In an international field trial across 23 countries, the reliability coefficients for each subscale were 0.82 for physical health, 0.81 for psychological, 0.68 for social relationships, and 0.80 for environment. Comparing samples of individuals with and without illnesses, the greatest difference in scores was observed within the physical domain followed by the psychological domain [119]. The WHOQOL-BREF takes approximately 2 to 4 minutes to complete.

8.0 Study Procedures and Visits

All assessments must be performed by qualified study staff delegated these duties on the Site Responsibilities Log. The Clinical Trial Leader (CTL) and/or the Clinical Research Associate (CRA) should be notified of any delays or deviations to study procedures and the Medical Monitor consulted if necessary. If there are delays of more than 7 days between visits or contact,
the site should assess the need for additional telephone contact with the participant to ensure safety.
## Table 5: ED Participant Time and Events-Study Procedures

<table>
<thead>
<tr>
<th>Visit Type/Number</th>
<th>Pre-Screening Period</th>
<th>Screening &amp; Enrollment Period</th>
<th>Preparatory Period</th>
<th>Experimental Sessions</th>
<th>Next-Day Integrative Sessions</th>
<th>Treatment Period</th>
<th>Phone Contacts After MDMA Administration</th>
<th>Weekly Integrative Sessions</th>
<th>Study Termination Visit (STV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Timing and Windows</td>
<td>Prior to Screening</td>
<td>1-3 Weeks Prior to V1</td>
<td>V1 0-12 days after V0; V2 &amp; V3 are 7-12 days after V1 and V2A</td>
<td>V4, V8, &amp; V12</td>
<td>V5, V9, &amp; V13</td>
<td>(No Visit)</td>
<td>Perform 4 calls over the next 7 days after the Experimental Session Visit</td>
<td>Each are 7-12 days after V5, V6, V9, V10, V13, &amp; V14A</td>
<td>7-12 days V15</td>
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<tr>
<td>Pre-Screening Script</td>
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<td>Collect AE/SAEs</td>
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</tbody>
</table>

*Respectively.  ‡ May be done remotely.  § If Applicable.  ¶ Perform procedure and review results prior to drug administration.  ✡ Perform at beginning of session.  ✓ Perform approximately 6 hours after drug administration.  ✹ Perform as needed.  † Perform approximately 1.5 to 2 hours after drug administration, and before supplemental dose administration.  $ Perform within 3 days prior to this visit.  ‡ May be performed as either a dyad visit with both the ED-P and the CG-P, or separate visits for each participant if deemed necessary.  ¶ For AN-R participants only.  ‡ With 1-minute rhythm strip.  ‡ Required dyad visit.
<table>
<thead>
<tr>
<th>Visit Type/Number</th>
<th>Pre-Screening Period</th>
<th>Screening &amp; Enrollment Period</th>
<th>Preparatory Period</th>
<th>Experimental Sessions</th>
<th>Next-Day Integrative Sessions</th>
<th>Treatment Period</th>
<th>Phone Contacts After MDMA Administration</th>
<th>Weekly Integrative Sessions</th>
<th>Study Termination Visit (STV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Timing and Windows</td>
<td>Prior to Screening</td>
<td>1-3 Weeks Prior to V1</td>
<td>V0</td>
<td>V1, V2, &amp; V3</td>
<td>V4, V8, &amp; V12</td>
<td>V5, V9, &amp; V13</td>
<td>(No Visit) Perform 4 calls over the next 7 days after the Experimental Session Visit</td>
<td>V6, V7, V10, V11, V14, V15</td>
<td>V16</td>
</tr>
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</table>

**Screening Only Measures:** MINI, and SCID-5-PD with SCID-5-SPQ

**Baseline & STV Only Measures:** ASQ-SF, LEC-5, MFFS, and WHOLQOL-BREF

**Primary Outcome Measure:** EDE

**Safety Measure:** C-SSRS

**ACE & PCL-5**

**SCS**

**EBI**

**FQ**

**CIA, BDI-II, DERS-16, EDI-3, EES, RMQ, STAI, & RSES**

**EDEQ**

**ED-15**

---

\(^A\) Respectively. \(^B\) Perform at beginning of session. \(^D\) May be performed as either a dyad visit with both the ED-P and the CG-P, or separate visits for each participant if deemed necessary. \(^D\) Perform approximately 6 hours after drug administration. \(^D\) May be done remotely. \(^D\) Required dyad visit.
### Table 7: CG Participant Time and Events-Study Procedures and Measures

<table>
<thead>
<tr>
<th>Visit Type/Number</th>
<th>Pre-Screening Period</th>
<th>Screening &amp; Enrollment Period</th>
<th>Preparatory Period</th>
<th>Preparatory Sessions</th>
<th>Experimental Sessions</th>
<th>Next-Day Integrative Sessions</th>
<th>Phone Contacts After MDMA Administration</th>
<th>Weekly Integrative Sessions</th>
<th>Study Termination Visit (STV)</th>
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<tr>
<td>0</td>
<td>V0</td>
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<td></td>
<td></td>
<td>V6(^6), V10(^B), V11(^B), V14(^D), V15(^D)</td>
</tr>
<tr>
<td>1</td>
<td>V1(^a), V2(^a), &amp; V3(^a)</td>
<td>Each are 7-12 days after V1 and V2(^A)</td>
<td>V4(^B), V5(^B), &amp; V12(^B)</td>
<td>V5(^B), V9(^B), &amp; V13(^B)</td>
<td>Each are the morning after V4, V8, and V12(^A)</td>
<td>(No Visit) Perform 4 calls over the next 7 days after the Experimental Session Visit</td>
<td>Each are 7-12 days after V5, V6, V9, V10, V13, &amp; V14(^A)</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>V1(^a)</td>
<td>V0 (Visits 1 Only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V1(^6)</td>
</tr>
<tr>
<td>3</td>
<td>V1(^a)</td>
<td>V0 (Visits 1 Only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V16(^f)</td>
</tr>
</tbody>
</table>

- \(^a\) Respectively.
- \(^B\) May be done remotely.
- \(^C\) Visits 1 and 3 only. CG-P does not attend Visit 2.
- \(^D\) May be performed as a dyad visit with both the ED-P and the CG-P.
- \(^E\) No C-G Visit on this day.
- \(^F\) Required dyad visit.
8.1 Pre-Screening

Prospective ED and CG participants may be pre-screened according to an IRB or EC approved script to ascertain if they meet basic eligibility criteria. This may be done remotely (such as by telephone or video call). If deemed potentially eligible, the prospective participant will receive a copy of the ICF for review prior to their invitation for a consenting visit and should be assigned a Screening Number which will be recorded on the Screening Log.

8.2 Screening

Qualified site staff (preferably the therapy team who would be treating the potential participant) will explain and obtain written informed consent using the current IRB or EC approved ICF. Written consent must be obtained prior to performing any tests or evaluations for the study. The ICF discussion may be done remotely via video call, or at an in-person visit.

Prospective ED and CG participants should be allowed sufficient time to decide their interest in the study. If they are still interested in participation after reviewing the ICF, then they will be instructed to countersign the ICF at the same time. The participant will be given a copy of the signed ICF.

After consenting to take part in the protocol, ED and CG participants will be screened by the treating therapist and site physician. The site physician may delegate medical screening activities to qualified site personnel such as a second site physician, nurse practitioner, or physician’s assistant. Screening will take place over multiple visits and up to 3 weeks prior to Visit 1. If a potential participant is deemed ineligible during screening, they will be classified as a Screen Failure and notified that they are not eligible for the study. If a CG-P is deemed ineligible during screening, another caregiver who potentially meets eligibility criteria may be pre-screened, consented, and undergo screening procedures.

Data from potential participants who do not pass screening will not be entered in the eCRF but the reason of ineligibility will be documented on the Screening Log. If a participant fails screening and is rescreened at a later date, a new copy of the ICF should be signed and a new Screening Number should be assigned.

Screening procedures will be completed in-person or remotely (e.g., via telemedicine or over the telephone). All procedures must be completed but there can be some flexibility in timing and order of individual assessments within the Initial Eligibility and Medical Assessments categories below:

- Initial Eligibility: including measures, in-person discussions, and review of medical records (for ED-Ps only)
- Medical Assessments for ED-Ps: including labs, 12-lead ECG, and physical exam
- The site staff will schedule the IR assessment and send IR the results of initial measures

The sponsor recommends that the ED-P be screened prior to the CG-P, to ensure initial ED-P eligibility requirements are met.
8.2.1 ED Participant Screening Assessments

The sponsor recommends the following order of assessments:

*Initial Eligibility*

- Procure demographics and review medical/psychiatric history with the ED-P via interview and review of provided records. If no records were provided or those provided are not sufficient, request additional records. The interviewer may require consent to obtain any medical records deemed necessary to clarify or provide more information about medical history if needed. Relevant medical and psychiatric records are required for the site physician to obtain a well-characterized medical history and assess eligibility.
- Administer the Lifetime C-SSRS to assess history of suicidal behavior and ideation.
- Administer the EDE to assess eating disorder and Baseline primary outcome.
- Pre-study medications will be reviewed and recorded.
- Assess childbearing potential and discuss requirement for commitment to adequate birth control for the duration of the study. Perform urine pregnancy test for ED-Ps who are of childbearing potential.
- Perform a urine drug test.
- Direct the ED-P to complete the SCID-5-SPQ self-reported screening measure.
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, the ED-P will be provided with instructions (and appointments, if applicable) for a physical exam, laboratory assessments, and a 12-lead ECG with 1-minute rhythm strip. Some or all of these assessments may be performed at outside facilities.

*Medical Assessments*

- A physical examination must be conducted by a qualified physician and must include:
  - Blood pressure and pulse rate will be measured lying, sitting, and standing in succession. Body temperature will also be measured.
    - For AN-R participants, record these vitals once at resting state, then again after the participant walks for 20 seconds to assess for significant increases in heart rate which may indicate cardiac de-conditioning.
    - If the blood pressure measurement is at or above 140/90, the site physician should assess further to determine if there is a diagnosis of essential hypertension. If essential hypertension is not diagnosed, the site physician should document the reason for the elevated blood pressure and their assessment with supporting rationale if they determine the participant does not face risk for study participation.
  - Height and weight, which will be used to calculate Body Mass Index (BMI).
  - Examination of head, eyes, ears, nose, and throat, skin, heart, lungs, abdomen, and extremities.
  - Brief neurological exam (cranial nerves 2 to 12, sensory, motor, reflexes, and cerebellar function).
- 12-lead ECG with 1-minute rhythm strip, which should be performed and evaluated by a qualified site physician. A central physician will read the ECG and evaluate results.
- Clinical laboratory assessments, per the Clinical Laboratory Assessments for ED Participants Section 15.0 of this protocol. The clinical laboratory values will not be captured in the eCRF but will be used to establish eligibility and will be kept with the participant’s source record. Clinically significant abnormal values will be captured as
medical history. The site physician will use a list of normal ranges to decide whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values.

- If there is evidence of possible liver disease by history, physical examination or laboratory testing, HCV serology will be performed.
  - If there is evidence of significant hepatic disease other than HCV, the potential participant will not be eligible for enrollment and will be advised to see their personal physician for further evaluation.
  - If HCV serology is positive and the potential participant has not already been evaluated for possible treatment of HCV, they will be referred to a physician with expertise in evaluating and treating liver disease. After this evaluation and after completion of any recommended treatment, if the HCV is judged by this physician to be relatively stable and of mild severity, the participant may be enrolled, if there are no other contraindications.

- If the ED-P has a condition such as controlled hypertension or Diabetes Mellitus (Type 2) that warrants additional testing to ensure they do not have evidence of significant vascular or other cardiac disease, and they have no other evidence of cardiovascular or cerebrovascular disease (by history, physical exam or ECG), and if the investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for nuclear exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the ED-P may be enrolled if there are no other contraindications. ED-Ps taking one more antihypertensives may be enrolled in the study. The investigators will record and review medications used to control hypertension prior to enrollment.

### 8.2.2 CG Participant Screening Assessments

If the ED-P is deemed initially eligible at this point, the CG-P screening procedures may commence as follows:

**Initial Eligibility**

- Procure demographics and review medical/psychiatric history with the CG-P via clinical interview.
- Administer the Lifetime C-SSRS to assess history of suicidal behavior and ideation.
- Direct the CG-P to complete the SCID-5-SPQ self-reported screening measure.
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility.

### 8.2.3 ED and CG Participant Initial Screening Assessments Review

Additional visits (in person, by telephone, or via telemedicine) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the ED-P. Once all results are obtained, the site team will review all medical assessments, notes from interviews and discussions, medical records, and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the site physician will request additional tests, assessments, or measures as indicated. The site physician may also contact outside providers with participant permission as needed.
8.2.4 Independent Rater Assessment

If both the ED-P and the CG-P are deemed initially eligible, the site staff will schedule separate IR screenings for both participants and send the results of the SCID-5-SPQ to the IR. Although the IR visit is by telemedicine, the participants will be provided a location to complete the telemedicine visits at the study site if needed. For the IR visit, discuss with the participants that they should have adequate internet access and be in a private and quiet space where they are comfortable talking about personal matters. An IR will continue the eligibility assessment via telemedicine after reviewing the results of the SCID-5-SPQs. The IR interview may be recorded to assess reliability of ratings.

For both the ED-P and the CG-P IR call:

- The IR will administer the since last visit C-SSRS to assess suicidal behavior and ideation.
- Using the results of the SCID-5-SPQ to guide the interview, the IR will perform the SCID-5-PD.
- The IR will complete the MINI interview (with the PTSD module).

The results from the MINI and the SCID-5-PD will be provided to the therapy team at the site to review along with all other Screening information to determine eligibility.

8.3 Enrollment

In advance of Visit 0, the site team will review all notes from Screening visits, medical assessments, notes, discussions, medical records, IR results, and measures against eligibility criteria. If the ED participant is eligible, medication tapering and concomitant medications dose adjustments will be discussed, if applicable. The site physician will consult the prescribing physician to develop a plan for medication tapering for participants. For all details on concomitant medications, tapering, allowed, and prohibited medications refer to the Concomitant Medications for ED Participants Section 14.0 in this protocol.

If a potential ED and CG participant are deemed eligible, the study team will contact the sponsor’s Medical Monitor and send all preliminary screening assessment information for their review and approval prior to enrolling the potential participants. If the ED and CG participant are approved by the Medical Monitor, the participants will be notified of enrollment at Visit 0 in-person, via telemedicine, or by telephone. Medical history and medication information will be reviewed for completeness. The medication tapering plan will be discussed with the ED participant, if applicable. If agreeable, the participants will be enrolled in the study. Once enrolled, AE collection requirements begin for ED-Ps (refer to the Safety Section 13.3 of this protocol). Visit 0 and Visit 1 may take place on the same day.

For pre-selected study sites participating in the fMRI sub-study: ED participants with an AN-R diagnosis who are enrolled in the main study may be approached to participate in the fMRI sub-study at this time. fMRI sub-study participants will be recruited consecutively until enrollment is complete according to the fMRI IIS protocol.

8.4 Preparatory Period

ED participants will undergo three Preparatory Sessions (Visits 1, 2, and 3) lasting approximately 90 minutes with the therapy team prior to the first Experimental Session. The Preparatory Period will be initiated within 12 days of Visit 0 and last approximately 3 weeks. Visit 1 will be a
required dyadic preparatory visit with both the ED and the CG participant, and must be conducted at the study site. Visit 2 will be an individual preparatory visit for the ED-P only, and may be conducted remotely via telemedicine if prior notification is given to the Medical Monitor and Visit 3 is conducted in person. Visit 3 will be final individual Preparatory Sessions for both the ED-P and the CG-P. Visit 3 may be conducted remotely via telemedicine for the ED-P if prior notification is given to the Medical Monitor and Visit 2 was conducted in person.

The CG-P Individual Preparatory Session may be conducted remotely via telemedicine.

**Table 8: Preparatory Period Visit Reference**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Eating Disorder Participant (ED-P)</th>
<th>Caregiver Participant (CG-P)</th>
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<td></td>
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<td>Preparatory Period</td>
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</tr>
<tr>
<td>1</td>
<td>1</td>
<td>90-minute ED-P + CG-P Required On-Site Dyadic Preparatory Session</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>90-minute ED-P Individual Preparatory Session</td>
<td>(No CG-P Session)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V3 is conducted on-site.</em></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>90-minute ED-P Individual Preparatory Session</td>
<td>60-minute CG-P Individual Preparatory Session</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>May be conducted remotely via telemedicine with prior notification to the Medical Monitor and if V2 was conducted on-site.</em></td>
<td><em>May be conducted remotely via telemedicine.</em></td>
</tr>
</tbody>
</table>

During the Preparatory Period the therapy team will work with the participants to prepare for MDMA-assisted psychotherapy, build safety for the therapeutic relationship, develop the therapeutic alliance, obtain background for the eating disorder, and promote a safe setting for confronting trauma-related memories, emotions, and thoughts. Telephone calls may be scheduled between visits if indicated for tapering, safety, or any further questions about medical history.

**8.4.1 Preparatory Sessions (Visits 1, 2, and 3)**

Preparatory Session 1 (Visit 1) will occur 0 to 12 days after Visit 0. The proceeding Preparatory Session visits (2 and 3) will occur approximately weekly thereafter. The visit timing should take into account appropriate times for monitoring medication tapering.

Prior to the start of Visit 1, the ED-P and CG-P will complete Baseline study measures as follows:

- **ED-P**: ACE, ASQ-SF, CIA, BDI-II, DERS-16, EDI-3, EDEQ, EES, PCL-5 with LEC-5, MFFS, RMQ, RSES, SCS, STAI, and WHOLQOL-BREF
- **CG-P**: CASK, CTS, DERS-16, EDSIS, MFFS, and WHOLQOL-BREF

Prior to the start of Visit 2 and Visit 3 for the ED-P, they will complete the following study measures:

- **ED-P**: ED-15

Each Preparatory Visit with the ED-P will consist of 90 minutes of psychoeducation and psychotherapy, while the individual session with the CG-P may be 60 minutes consisting of
therapy and support. The therapy team will perform the following at each ED-P Preparatory Sessions:

- Administer the Since Last Visit C-SSRS for the ED-P.
- Record the therapy session to audio and video.
- Inquire about any possible changes in health for ED-Ps to ensure the participant continues to meet all eligibility requirements. Record AEs for ED-Ps as described in the Safety Section 13.3 of this protocol.
- Inquire about concomitant medication use and adherence for ED-Ps, and confirm that medication tapering is ongoing or complete, as appropriate.
- Discuss goals and expectations for the Experimental Session, following standard procedures and techniques described in the Treatment Manual [120].

At any time during the Preparatory Period, if an ED-P or CG-P is deemed to be ineligible, the site team will classify them as a Pre-Study Treatment Early Study Termination, following procedures listed in the Discontinuation and Completion Criteria Section 5.3 of this protocol.

If the ED-P would like a support-person, or their caregiver, present during the Experimental Session and/or overnight after the Experimental Session, a meeting between the therapy team and that individual will be scheduled prior to the first Experimental Session. There must be mutual agreement between the participant and therapy team concerning the presence of the support-person during the Experimental Sessions. If a support-person cannot be identified for the overnight stay, an attendant on the site study team will stay with the ED-P during the evening and overnight (at the study site or at nearby accommodations such as a hotel approved by the site team) after each Experimental Session. The therapy team should introduce the ED-P to this person during one of the Preparatory Sessions, if possible. The attendant will be an individual with previous training in managing psychological distress. The site will make all attempts to have the same attendant for each Experimental Session for a given ED-P, but it is not guaranteed.

8.5 Treatment Period

During the Treatment Period, which occurs over a duration of approximately 9 weeks (Visits 4 to 15), ED participants will complete three treatments. Each treatment consists of:

- An On-Site Experimental Session.
- An On-Site Integrative Session the following morning after the Experimental Session.
- Four phone follow-ups over the next week after the Experimental Session.
- A second dyadic Integrative Session with the CG-P approximately 1 week after the Experimental Session. The therapists and the ED-P may determine not to have this visit as dyadic with the CG-P. In this case, the visit may be done as individual sessions for both the ED-P and CG-P. This session for the ED-P (dyadic or individual) may be conducted remotely via telemedicine, and if prior notification is given to the Medical Monitor.
- A third Integrative Session (individual for ED-P for visits 7 and 11; required dyadic for Visit 15) approximately 1 week thereafter, which may be conducted remotely via telemedicine for the ED-P if prior notification is given to the Medical Monitor.

The CG participant will have an individual Integrative support session the day after each of the ED-P’s Experimental Session. Individual CG-P integrative visits may be done remotely via telemedicine.
### Table 9: Treatment Period Visit Reference

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>Eating Disorder Participant (ED-P)</th>
<th>Caregiver Participant (CG-P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Treatment Period</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8-hour On-Site ED-P Experimental Session 1</td>
<td>(No CG-P Session)</td>
</tr>
</tbody>
</table>
| 5     | 5    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 6     | 5    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for the CG-P individual sessions.* |                             |
| 7     | 6    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 8     | 7    | 8-hour On-Site ED-P Experimental Session 2 | (No CG-P Session) |
| 9     | 7    | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 10    | 8    | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for the CG-P individual sessions.* |                             |
| 11    | 9    | 90-minute ED-P Individual Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor.* | (No CG-P Session) |
| 12    | 10   | 8-hour On-Site ED-P Experimental Session 3 | (No CG-P Session) |
| 13    | 10   | Next-Day On-Site Individual Integrative Session followed by four phone check-ins over the following 7 days. | 60-minute Individual Integrative Support Session  
*May be conducted remotely via telemedicine.* |
| 14    | 11   | 90-minute ED-P + CG-P Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P. Prior notification to the Medical Monitor is not required for the CG-P individual sessions.* |                             |
| 15    | 12   | 90-minute ED-P + CG-P Required Dyadic Integrative Session  
*May be conducted remotely via telemedicine with prior notification to the Medical Monitor for the ED-P.* |                             |

**8.5.1 Experimental Sessions for the ED Participant**

There will be three open-label Experimental Sessions (Visits 4, 8, and 12) with the ED participant. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions and all procedures regardless of dose received. Experimental Sessions must be at least 8 hours long, measured from 30 minutes prior to IMP administration. A study team physician must
be on-site for the duration of the Experimental Session in order to assess participant safety. The three Experimental Sessions are summarized as follows:

- **Experimental Session 1 (Visit 4)** will occur 7 to 12 days after Visit 3. For all ED-Ps, this session will include 80 mg of MDMA followed by a supplemental half-dose (40 mg) 1.5 to 2 hours after the initial dose, unless contraindicated or refused by the ED-P.
- **Experimental Session 2 (Visit 8)** will occur approximately 7 to 12 days after Visit 7. A dose of 80 or 120 mg MDMA will be administered for ED-Ps weighing 48 kg or higher. A dose of 80 mg MDMA will be administered for ED-Ps weighing ≥45 kg and < 48 kg. A supplemental half-dose will be administered 1.5 to 2 hours after the initial dose unless contraindicated or refused by the ED-P.
- **Experimental Session 3 (Visit 12)** will occur approximately 7 to 12 days after Visit 11. A dose of 80 or 120 mg MDMA will be administered for ED-Ps weighing 48 kg or higher. A dose of 80 mg MDMA will be administered for ED-Ps weighing ≥45 kg and < 48 kg. A supplemental half-dose will be administered 1.5 to 2 hours after the initial dose unless contraindicated or refused by the ED-P.

Observed response, safety and tolerability to the previously administered dose, and discussion with the ED-P will all be taken into consideration as potential contraindications for the supplemental half-dose administration, and when considering escalating the initial dose in the 2nd and 3rd Experimental Sessions for ED-Ps weighing 48kg or higher.

### Table 10: Schedule of Procedures for Experimental Sessions

<table>
<thead>
<tr>
<th>Approximate Time</th>
<th>Procedure or Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 3 days prior to the Experimental Session Visit (AN-R participants only)</td>
<td>Clinical laboratory testing (complete blood count, comprehensive metabolic panel, magnesium, and phosphorus)</td>
</tr>
<tr>
<td>9:30</td>
<td>Urine drug screen, pregnancy test (if applicable), urine ketone testing (AN-R only), 12-lead ECG (AN-R only), weight measurement, concomitant medication information collected, ED-P acclimated to environment, C-SSRS</td>
</tr>
<tr>
<td>9:55</td>
<td>Baseline blood pressure (BP), body temperature, pulse rate</td>
</tr>
<tr>
<td>10:00</td>
<td><strong>IMP Administration</strong>, Begin video recording</td>
</tr>
<tr>
<td>11:30</td>
<td>BP, body temperature, pulse rate, <strong>Supplemental Dose Administration</strong>, unless contraindicated</td>
</tr>
<tr>
<td>17:30</td>
<td>C-SSRS, BP, body temperature, pulse rate</td>
</tr>
</tbody>
</table>

The following procedures will occur at the Experimental Session:

**Pre-IMP Administration**

- Within 3 days prior to each Experimental Session, the AN-R participants will undergo clinical laboratory testing to ensure medical stability (complete blood count, comprehensive metabolic panel, magnesium, and phosphorus). The results will be provided to the site physician who will determine and document if there are any clinically significant issues that may prohibit the ED-P from undergoing the Experimental Session. If the site physician determines there is a clinically significant issue, the Medical Monitor should be contacted and there may be cause for delaying IMP administration to a later time, rescheduling the session to a later date, or withdrawing the ED-P from the study based on site physician and Medical Monitor review.
On the day of the Experimental Session, the ED-P will arrive approximately 60 minutes prior to IMP administration.

The site team will ensure the ED-P has not used caffeine or nicotine 2 hours prior, and has fasted for at least 10 hours prior to IMP administration, and has complied with all other requirements per the Lifestyle Modifications for ED Participants Section 3.3 of this protocol.

The site team will inquire about any possible changes in health to ensure the ED-P continues to meet all eligibility requirements and record AEs as described in the Safety Section 13.3 of this protocol.

The site team will instruct the ED-P that they will not be able to use caffeine or nicotine at least 6 hours after the initial IMP administration.

The site team will complete the urine drug screen, urine ketone test, pregnancy test (if applicable), weight measurement, and concomitant medication review. ED-Ps will not be eligible to proceed with the Experimental session and receive Investigational Product if their weight has fallen below 45 kg. The site physician will conduct the 12-lead ECG for AN-R participants only.
  - A positive drug screen will be reviewed by the site physician and may be cause for delaying IMP administration to a later time, rescheduling the session to a later date, or withdrawing the ED-P from the study, based on site physician and Medical Monitor review.
  - A positive ketone screen for AN-R participants will be reviewed by the site physician.
  - A positive pregnancy screen is cause for withdrawal from the protocol.
  - Development of any abnormalities on the ECG which the investigator deems as clinically significant will be cause for delaying IMP administration to a later time, rescheduling the session to a later date, or withdrawing the ED-P from the study, based on site physician and Medical Monitor review.

The therapy team will administer Since Last Visit C-SSRS.

The therapy team will review procedures for the Experimental Session with the ED-P and discuss the participant’s goals, intentions, and concerns and some of the commonly experienced effects of MDMA.

If the ED-P continues to be eligible, the session will proceed.

Baseline blood pressure, body temperature, and pulse will be measured just prior to administration of the initial dose.
  - Transient increases in blood pressure may occur in some participants. If the blood pressure measurement is at or above 140/90 mmHg, the ED-P should be given time to relax before the site physician repeats the blood pressure measurement up to two additional times to assess further and document the reason for the elevated blood pressure. If the appropriately taken repeat blood pressure measurements are consistently out of range, the site physician will assess if the participant presents symptoms and clinical features that would determine the Experimental Session dosing to be contraindicated, if the session should be rescheduled, or if the participant should be withdrawn from the study. If the site physician assesses that the participant may continue in the study, the Safety Committee will review and make a determination if the ED-P can continue in the study. If the Safety Committee agrees that the participant may continue, they may propose an evaluation by a cardiologist before continuing in the study where indicated. Details of the blood pressure measurement instructions are provided in the Study Operations Manual.
During the Experimental Session

- After video recording has begun, at approximately 10:00 a.m. in the morning, a qualified staff member will administer the initial dose of IMP with an electrolyte-containing fluid. The ED participant will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided for the ED-P if they wish to use them. Whenever they wish, ED-Ps may speak to the therapy team, who will provide guidance and support, as needed.
- After the first hour, if the ED-P has not spoken spontaneously, the therapy team will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the therapy team will support and encourage the ED-P in emotional processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.
- Electrolyte-containing fluids will be provided throughout the session but not to exceed three liters overall.
- Vitals (blood pressure, body temperature, and pulse) and 12-lead ECG (AN-R participants only) will be measured approximately 1.5 to 2 hours after the initial dose. The on-site study physician will review results to determine approval of the supplemental dose administration. If the ED-P prefers not to have the supplemental dose, or it’s determined that it is contraindicated, the therapy team will document the reason.
  - Transient increases in blood pressure can be anticipated from the initial MDMA administration. If the blood pressure measurement is at or above 140/90 mmHg, the ED-P should be given time to relax before the site physician repeats the blood pressure measurement up to two additional times to assess further and document the reason for the elevated blood pressure. If the appropriately repeat blood pressure measurements are consistently out of range the site physician will assess if the participant presents symptoms and clinical features that would determine the supplemental dose to be contraindicated. If the supplemental dose is contraindicated due to blood pressure increases, the Safety Committee will review and make a determination if the ED-P can continue in the study with future visits. If the Safety Committee agrees that the participant may continue, they may propose an evaluation by a cardiologist before continuing in the study where indicated.
  - If an AE requiring medical attention has occurred between the initial and supplemental dose, the site physician will determine whether the supplemental dose is contraindicated. If medical attention is needed, the site physician will provide further instruction or consult the Medical Monitor.
- A supplemental half-dose will be administered with a glass of electrolyte-containing fluid approximately 1.5 to 2 hours after the initial dose, unless contraindicated.
- Food, or meal replacements (e.g., BOOST® Nutritional Drink), will be provided during the latter part of the session.
- For AN-R participants, the ECG may be repeated post supplemental dose if clinically indicated.
- If there is an approved support-person attending the session, that person may arrive as agreed upon but will wait in the waiting room until a member of the therapy team brings them to the session room. Alternatively, the support-person may arrive after the session has ended.

End of Experimental Session

- The therapy team will administer Since Last Visit C-SSRS.
- The therapy 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, and the attendant or support-person has arrived.
• The therapy team or site physician shall remain available to participants via 24-hour cellular phone for integration, as needed.
• The ECG results for AN-R participants should be submitted to the study’s central physician for evaluation post Experimental Session.

Overnight Stay

• ED-Ps will remain overnight at the study site in an appropriately furnished room, or at nearby accommodations, such as a hotel approved by the research team, after each Experimental Session. With prior approval of the therapy team, a support-person may accompany the ED-P during the overnight stay. The overnight stay is an opportunity for rest and integration in a relaxed and comfortable environment away from the distractions of home, and to facilitate the logistics of participation in the integrative visit at the site on the day following the Experimental Session. The overnight stay is not required for medical reasons, but in case of emergencies, the therapists and study physician are on-call for all sites.
• If a support-person cannot be identified to stay with the ED-P, an attendant on the site study team will stay with the participant during the evening and overnight. The attendant will check in periodically on the participant during the overnight stay, will monitor the ED-P’s condition, and will help the ED-P relax during the overnight stay. The attendant will be an individual with some previous training in managing psychological distress and will be supportive but not intrusive. If there is an emergency or the ED-P needs additional support, the attendant can contact the therapy team.
• The ED-P and a support-person (if applicable) will receive information that will allow them to contact the therapy team during the overnight stay in the case of an emergency or to request for additional support.
• ED-Ps will be encouraged to use much of the time during their overnight stay for rest and as a period of reflection and integration in a quiet atmosphere.
• ED-Ps must not operate a vehicle for at least 24 hours after the initial MDMA dose administration. If there is necessity to drive the ED-P to their overnight location, and/or back to the study site for the Integrative Session the following day, a driver (such as a taxi) should be arranged by the participant or by site personnel prior to Experimental Session.

8.5.2 Telephone Contact After Experimental Sessions for the ED Participant

The goal of the telephone contact is to assess health changes, ensure participant safety, and offer support. The therapy team will follow-up with the ED-P by telephone on the second and seventh day after each Experimental Session, with two additional telephone contacts in between. Each call will last on average 5 to 15 minutes but could be longer to address participant concerns and to adequately assess wellbeing. Additional telephone contact can be initiated at the request of the therapy team or ED-P.

At each telephone contact, the therapy team will:

• Inquire about any possible changes in health, assess the ED-Ps mental health and the status of any previously recorded AEs, and record AEs as described in the Safety Section 13.3 of this protocol.
• Inquire about concomitant medication use and adherence.
• Offer support in accordance with the Treatment Manual.
• Administer the Since Last Visit C-SSRS.

8.5.3 Integrative Sessions

After each Experimental Session, three Integrative Sessions will take place as follows:

• Next Day Integrative Session: Individual Integrative Sessions (Visits 5, 9, and 13) for both the ED-P and the CG-P will occur the morning after each Experimental Session.
  o ED-Ps will complete the following measures prior to the start of these visits: EBI, ED-15, and SCS.
  o CG-Ps will complete the DERS-16 measure prior to the start of these visits.
• Second Dyadic Integrative Session: A second dyadic Integrative Session (Visits 6, 10, and 14) including both the ED-P and the CG-P will occur 7 to 12 days after the Next Day Integrative Session. The therapists and ED-P will have discretion regarding the appropriateness of the dyadic session. If the therapists and the ED-P determine not to have this as a dyadic session, individual Integrative Sessions should occur for both the ED-P and the CG-P at this time.
  o ED-Ps will complete the following measures prior to the start of Visit 6 only: CIA, BDI-II, DERS-16, EDEQ, EDI-3, EES, RMQ, RSES, and STAI.
  o ED-Ps will complete the ED-15 measure prior to the start of Visits 10 and 14.
• Third Integrative Session: A third Integrative Session for the ED-P will occur 7 to 12 days after the previous dyadic Integrative Sessions. This visit will be individual for the ED-P for visits 7 and 11, which serve two purposes at these visits: to continue integration and to prepare for the next Experimental Session. Visit 15 will be a required dyadic visit for both the ED-P and CG-P.
  o ED-Ps will complete the following measures prior to the start of Visit 11 only: CIA, BDI-II, DERS-16, EDEQ, EDI-3, EES, RMQ, RSES, and STAI.
  o ED-Ps will complete the ED-15 measure prior to the start of Visits 7 and 15 only.

Each Integrative Session with the ED-P will consist of 90 minutes of psychotherapy, while individual CG-P Integrative Sessions may be 60 minutes consisting of follow-up, therapy, and support. The therapy team will perform the following at all ED-P Integrative Sessions:

• Record the session to audio and video.
• Inquire about any possible changes in health for ED-Ps. Assess the ED-P’s mental health and the status of any previously recorded AEs.
• Record AEs as described in the Safety Section 13.3 of this protocol for ED-Ps.
• Inquire about concomitant medication use and adherence for ED-Ps.
• Administer Since Last Visit C-SSRS to determine suicidal risk for ED-Ps.
• Discuss and review events that occurred with the ED-P during the Experimental Session, including thoughts, feelings, and memories. If necessary, the therapy team will help the ED-P and CG-P (as applicable) to reduce any residual psychological distress they are experiencing. The therapy teams will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in Experimental Sessions to emotionally threatening everyday situations. The therapy teams will be supportive, validate the experience, and facilitate understanding and emotional clearing.
• Be accessible for additional support via phone or telemedicine if needed.
8.6 Study Termination

The Study Termination Visit (STV), Visit 16, will occur 7 to 12 days after the last Integrative Session (Visit 15) and is the Primary Endpoint of the study. This is a required dyad visit to be performed on site. Participants who have withdrawn from treatment but have continued for follow-up will also complete this assessment immediately upon withdrawal.

The site team will:

- Inquire about any possible changes in health for ED-Ps. Assess the ED-P’s mental health and the status of any previously recorded AEs.
- Record AEs as described in the Safety Section 13.3 of this protocol.
- Inquire about concomitant medication use and adherence for ED-Ps.
- Administer Since Last Visit C-SSRS for ED-Ps.
- Measure height and weight to calculate BMI for ED-Ps.
- Administer the EDE to assess eating disorder primary outcome.
- Provide and discuss a study Plan for Moving Forward for ED-Ps.
- Actively support participant in completion of Study Termination measures:
  - ED Participants: ASQ-SF, CIA, BDI-II, DERS-16, EDI-3, EES, LEC-5, MFFS, RMQ, RSES, SCS, STAI, FQ, and WHOLQOL-BREF
  - CG Participants: CASK, CTS, DERS-16, MFFS, EDSIS, and WHOLQOL-BREF

After all Study Termination measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life. The study team will provide a plan for moving forward, which may include a referral for additional medical or therapeutic care, as described in Plan for Moving Forward for the ED Participant Section 8.6.1.

8.6.1 Plan for Moving Forward for the ED Participant

At Study Termination, ED participants will be provided with a plan for moving forward. This plan will summarize treatments completed, current medications, and contact information for more information about the study if needed. EDP’s will be notified that MDMA is investigational and cannot be administered after study completion. ED-Ps may request a referral for further therapeutic or medical care if appropriate. Enrolled ED-Ps who terminate the study early will be provided a plan for moving forward at their last contact. ED-Ps who have screen failed will be provided a referral if requested.

9.0 Investigational Product

9.1 Description of Active Compounds

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA (as hydrochloride salt). This ring-substituted phenethylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and re-uptake inhibitor. Its direct actions on serotonergic, adrenergic, and other receptors are considerably lower. Refer to the IB for a comprehensive review of the pharmacology, effects and proposed mechanisms of action of the IMP. Mannitol and magnesium stearate will serve as inactive excipients.
9.1.1 Doses

This study will examine the safety and feasibility of three open-label Experimental Sessions of psychotherapy assisted by flexible doses of MDMA in ED participants, along with associated non-drug preparatory and integrative psychotherapy. Initial doses per Experimental Session include 80 mg or 120 mg MDMA HCl compounded with mannitol and magnesium stearate followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg MDMA HCl). Total amounts of MDMA HCl to be administered per Experimental Session range from 80 mg to 180 mg. All drug is encapsulated with HPMC capsules. Refer to Table 4: Dose Regimen of MDMA.

9.1.2 Dose Modifications

In the first Experimental Session, the initial dose will be 80 mg MDMA HCl for all ED-Ps. In the second and third Experimental Sessions, the initial dose will remain 80 mg MDMA HCl for participants weighing ≥45 kg and <48 kg, however may be increased to 120 mg MDMA HCl for participants weighing ≥48 kg unless contraindicated. For those participants, the choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the therapy team in consultation with the site physician based on observed response, safety and tolerability of the previously administered dose, and discussion with the ED participant. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the ED participant will be administered a supplemental half-dose unless contraindicated (which also includes observed response, safety and tolerability of the previously administered dose, and discussion with the participant). If an AE requiring medical attention occurs between the initial and supplemental dose this will be evaluated as a potential contraindication by the site physician. If an ED participant does not take the supplemental dose, the reason will be documented.

9.1.3 Stability

IMP is manufactured and packaged according to Good Manufacturing Practices (GMP). 6-month accelerated stability studies will be completed for the IMP along with an ambient stability study that will remain ongoing throughout the duration of the study. All required Chemistry Manufacturing and Control (CMC) submissions will be made to the IND.

9.2 Handling

9.2.1 Encapsulation, Packaging, and Labeling

Drug substance in bulk is sent from Onyx Pharmaceuticals, Inc., a current Good Manufacturing Practices (cGMP) drug substance manufacturer in the United Kingdom to Recipharm AESICA Queenborough Ltd via proper measures for encapsulation of the API with excipients to make drug product in hydroxypropyl methylcellulose (HPMC) capsules. After manufacture, the final encapsulated drug product will then be shipped via appropriate import/export permits to a Schedule I controlled substance-licensed cGMP drug product manufacturer or distributor to ensure that the final finished IMP is labeled and shipped to sites.

The IMP is packaged in 40 mg and 60 mg MDMA bottles. The 40 mg bottles will contain 9 capsules and the 60 mg bottles will contain 2 capsules. Each participant will be assigned to (1) 40 mg and (1) 60 mg bottle during their participation to account for flexible dosing regimens if they weigh 48 kg or higher. If the ED-P weighs less than 48 kg, they will only use the 40 mg bottle assigned to them. ED-Ps will not be eligible to receive Investigational Product if their weight falls below 45 kg. Bottles are 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 trial use only. All labels will comply with local, state/provincial, and federal regulations.

9.2.2 Accountability

Forms will be provided to track IMP accountability and administration throughout the study. IMP accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all local, state, and federal regulations and forms pertaining to the use of controlled substances will be maintained by the appropriate controlled substance license holder or delegate.

9.2.3 Storage

MDMA is a controlled substance and will be stored and handled in compliance with all relevant federal and state/provincial regulations. In accordance with these requirements, the appropriate license holder or designee will be responsible for storing, dispensing, and administering the MDMA. It will be stored securely in accordance with federal, state/provincial, and local regulations.

9.2.4 Administration

IMP will only be removed for a single Experimental Session at a time and will be administered orally at the study site. All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each Experimental Session. Supplemental doses should be administered unless contraindicated. Each dose (initial and supplemental) will be administered with a glass of electrolyte-containing fluid.

A person at the site authorized to manage and administer controlled substances will dispense the appropriate container for each Experimental Session. If a supplemental dose is not administered, the unused IMP will be kept for accountability.

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant federal and state/provincial regulations.

9.2.5 Treatment Compliance

Compliance to protocol required doses will be guaranteed by the person licensed to manage and administer controlled substances for Experimental Sessions at each site. All administered doses will be recorded for IMP accountability. The IMP will be stored securely per regulations.

10.0 Participant Numbering

Every potential participant who is prescreened by telephone according to the IRB/EC approved script will be assigned a nine-character alphanumeric Screening Number and recorded on the Screening Log. This Screening Number will be represented as follows:

- Beginning with ‘SE’ (for ED participants) or ‘SC’ (for CG participants) to identify that it is a Screening Number
- The next two digits will represent the site number (e.g., ‘11’)
- The next two digits will indicate the sequential number of the participant in the ED-P/CG-P screening set (e.g., ‘02’ for the second C-GP who is screened for the ED-P in this set)
• The last three digits will indicate the sequential number of the participant set screening at the site (e.g., ‘005’ for the fifth set screened at the site).

For example, the first ED-P/CG-P set to be screened at site 11 will be SE1101001 and SC1101001. If this CG-P screen-failed, the second CG-P to be screened for this first EDP/CGP set will be SC1102001.

Each participant who passes Screening and is enrolled in the trial at Visit 0 will be assigned a nine-character Participant Number. This Participant Number will be represented as follows:

• Beginning with ‘11’ (for ED participants) or ‘22’ (for CG participants) to identify that it is a Participant Number
• The next two digits will represent the site number (e.g., ‘11’)
• The next two digits will indicate the sequential number of the participant in the ED-P/CG-P enrolling set (e.g., ‘02’ for the second CG-P who is enrolled for the ED-P in this set)
• The last three digits will indicate the sequential number of the participant set enrolling at the site (e.g., ‘005’ for the fifth set enrolled at the site)

For example, the fifth ED-P/CG-P set to be enrolled at site 12 will be 111201005 and 221201005. If this CG-P withdraws before the ED-P’s first Experimental Session and is replaced by another CG-P, their Participant Number will be 221202005.

11.0 Bias Minimization

Eligibility will be determined by review of screening by the CI/QI, site team and the sponsor Medical Monitor prior to enrollment. To further minimize bias in measuring efficacy, the sponsor will use a centralized, reliable IR pool to administer the MINI measure (ED-P and CG-P) and the SCID-5-PD (ED-P) via live video interviews.

12.0 Risks

12.1 Non-drug Related Risks

12.1.1 Medical Assessments for ED Participants

In preparation for MDMA-assisted psychotherapy sessions, blood draws and a full medical examination, including a physical examination, ECG with 1-minute rhythm strip, and laboratory tests, are required for ED-Ps to establish eligibility for the study. Additional laboratory blood tests are required for AN-R participants up to 3 days prior to each Experimental Session for continued safety monitoring. Additional ECG testing is required for AN-R participants prior to initial and supplemental dosing at each Experimental Session. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. ECG testing risks are minimal and rare but include possible discomfort. If an ED-P warrants additional nuclear exercise testing at screening (to ensure they do not have evidence of significant vascular or other cardiac disease) there is a low radiation exposure from the tracer that is injected into the vein.

Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility and monitor safety for the study, they cannot be omitted from the protocol.
12.1.2 Eating Disorder Symptoms, Suicide Risk and Psychotherapy

During Screening, throughout the psychotherapy sessions, and during assessment of study measures, ED and CG participants will be asked to think about and discuss their thoughts and emotions which may relate to traumatic events. They may experience intense emotional responses. ED participants may also experience suicidal ideation as a result of recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing trauma and/or the eating disorder can produce distress and exacerbate suicidal ideation during and immediately after psychotherapy sessions. Eating disorder symptoms (such as skipping meals or binging) may also arise for ED-Ps. Psychotherapy is conducted as part of this study, and ED-Ps and CG-Ps undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable. Therapy teams will provide emotional support to all participants during any psychological distress.

The therapy team will minimize risks of eating disorder symptoms for ED-Ps by monitoring their weight and symptoms, and by assessing the ED measures throughout study participation. Ketone levels, which is a marker of starvation, will also be measured prior to all Experimental Sessions. If eating disorder symptoms, rapid weight loss, or other medical or psychological issues arise which deem it unsafe for the ED-P’s continuation in the study, they will be withdrawn from the study according to the Withdrawal Criteria for Enrolled Participants Section 5.3.3 of this protocol.

The therapy team will minimize risks of suicidal behavior for ED-Ps by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. ED-Ps will be enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician, therapy team, and Medical Monitor.

A qualified individual will administer the C-SSRS according to Table 5: ED Participant Time and Events-Study Measures, and as needed depending on clinical presentation of the ED-Ps, to monitor for development and intensity of suicidal ideation and/or behavior. The therapy team will implement the following plan to assess elevated or imminent suicide risk.

C-SSRS assessment is performed only once for CG participants at the time of screening. If the CG-P expresses any type of suicidal behavior or attempts of their own during psychotherapy sessions, they will be withdrawn from the study as a CG-P according to the Withdrawal Criteria for Enrolled Participants Section 5.3.3 of this protocol.

12.1.3 Recorded Content

All psychotherapy sessions, including CG-P only remote psychotherapy sessions, will be recorded to audio and video for research and training purposes. Participants may feel uncomfortable with having their sessions recorded. The recordings are necessary for developing the experimental treatment. Any requests for use of video outside of research and training requests will result in participants receiving information on the request (both the ED-P and the CG-P must agree to the use of their video for combined psychotherapy sessions with separate consent). The participants will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

Recorded content will be stored on secure servers hosted by the sponsor for up to 25 years. The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach. The sponsor is committed to taking preventative measures to avoid such
an event. In the case of a security breach, the participant(s) will be notified, and all efforts will be made to minimize the dissemination of recorded content.

12.2 Risks of Receiving MDMA for ED Participants

Study procedures and eligibility criteria have been developed based on Phase 3 PTSD clinical trials to exclude potential ED participants with pre-existing exclusionary medical conditions that would exacerbate risk. In addition to this criteria, extreme cases of AN-R and BED are excluded from participation, as precautionary measures to mitigate potential medical risks in these populations.

The therapy teams and site physicians will be available via mobile phone throughout the study if any problem occurs when an ED-P is not at the site. In the event of a medical emergency or any other medical problem during an Experimental Session, the site physician will be immediately available by telephone, and based on assessment of the situation, they will make the decision to either evaluate the participant themselves at the site, have the therapy team call EMS to transport the participant to the emergency department, or instruct the therapy team to take the participant to the emergency department.

Further information on the risks associated with MDMA can be found in the IB and risk mitigation procedures are described by risk category below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

12.2.1 High Level Risks

High Risk does not indicate an event is more likely to happen but indicates per the RACT assessment that new and or more complex procedures are required in the study to ensure screening is adequate to eliminate or manage the risk in the patient population. No high level risks have been identified in this study.

12.2.2 Medium Level Risks

Medium Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that new or many procedures, which are not complex, are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

12.2.2.1 Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. Participants with PTSD in MAPS-sponsored Phase 2 studies do not appear to differ from healthy individuals in this sympathomimetic, physiological response. 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 studies of MDMA-assisted psychotherapy detected a dose-dependent increase in systolic blood pressure but not diastolic blood pressure. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure will be addressed by excluding people (as described in Exclusion Criteria for ED Participants Section 3.2).
Blood pressure, body temperature, and pulse rate will be monitored before and after IMP administration in Experimental Sessions, and at any time the therapy team determines necessary. The therapy team 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) during Experimental Sessions. 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. The therapy team will notify the site physician for evaluation if this occurs.

If any participant has neurological deficits, as assessed by the site physician, whether or not they are associated with hypertensive crisis, they will be monitored, as described above and transported to the hospital if medically indicated. If evaluation at the hospital reveals an acute ischemic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the 2019 American Heart Association/American Stroke Association (AHA/ASA) guidelines [121, 122].

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, the site physician will be contacted immediately, and the participant will be taken to an emergency room by ambulance as expeditiously as possible to assess the patient and act in accordance with the assessment of the expert on site supported by national and local guidelines. Pending transport to the hospital the site team may take any measures ordered by the site physician including administering medication such as aspirin or nitroglycerin or providing supplemental oxygen per local standards. If further evaluation at the hospital reveals that the participant has had an AMI, they will be well within the time frame required for definitive therapy. Any participant who experiences such medical complications during an Experimental Session will not be given another Experimental Session.

During study participation, QTcF interval will be evaluated for AN-R participants at each Experimental Session (prior to the initial dose, and again 1.5 to 2 hours post initial dose and prior to the supplemental dose). QTcF interval will also be evaluated for AN-R participants in the event of a hospitalization for management of cardiovascular or cerebrovascular events.

12.2.2.2 Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [60, 123]. Psychological distress from MDMA could arise from the first indications of MDMA effects until the last effects have dissipated or even later. Anxiety or distress during the session may last for as little as 5 minutes or for as long as 5 hours or more. In addition, psychological distress could arise following an Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting and have responded well to reassurance from the therapy team, with occasional use of benzodiazepines for anxiety. In this study, ED-Ps will have the intention of confronting and working through traumatic experiences. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties that ED-Ps might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it.
• Preparatory Sessions of non-drug psychotherapy before the Experimental Session.
• Creating an atmosphere of trust during the Experimental Session.
• Close monitoring.
• Phone contact with ED-Ps during the week after the Experimental Session.
• Integrative Sessions.
• Having qualified site personnel, or an ED-Ps support person, available during the evening of the Experimental Session and overnight to respond to the needs of the participant. Attendants or support persons who stay with the ED-P will be instructed to contact the therapy team upon request, at the appearance of any medical issues, emotional distress, or if they fear of the participant’s safety.

During the Preparatory Sessions, ED-Ps will be made aware of the fact that difficult emotions, including grief, rage, fear, or panic, may arise during Experimental Sessions. Every effort will be made to help ED-Ps resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the Experimental Session, including empathic listening on the part of the therapy team and performance of diaphragmatic breathing by participants.

If the ED-P is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a psychotherapy session, at least one member of the therapy team will remain with the ED-P for at least 2 more hours. The caregiver should also be contacted to assist with ED-P support. During this time, the therapy team will employ affect management techniques, will talk with the ED-P to help them gain cognitive perspective of their experiences, and will help the ED-P implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the ED-P remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and therapy team will decide between the following options:

1. If severe distress occurs at the end of an Experimental Session, a psychiatric nurse, therapeutic assistant, physician, or therapy team member will stay with the ED-P until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The therapy team will then meet with the ED-P daily until the period of destabilization has passed.
2. If the ED-P experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, a licensed therapy team member or the site physician may prescribe a benzodiazepine (specifically, lorazepam) and/or sleep aid (e.g., zolpidem). The route, frequency, and dose should be determined by the site physician. If these medications are stocked on site, they should be stored according to applicable national and local regulations. This medication will be captured on the Concomitant Medications eCRF.
3. If an ED-P should become psychotic, arrangements will be made to stabilize them or transfer them to the ED if hospitalization is necessary. Any ED-P who is hospitalized after a severe psychological reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator and/or site physician will carefully evaluate the participant’s emotional status.

For those ED-Ps engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the ED-P’s outside therapist(s) will be involved in the management of any psychiatric complications. For those ED-Ps engaged in an ongoing psychotherapeutic relationship with the investigator or member of the therapy team, the management of any psychiatric complications will be undertaken by them in their capacity as the participant’s therapist.
12.2.3 Low Level Risks

Low Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no new or complex procedures are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

12.2.3.1 Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [123]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 studies for participants with PTSD, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1 degree Celsius (°C) above Baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1°C above Baseline.

Ambient temperature will be kept at a comfortable level during Experimental Sessions. If an ED-P’s temperature rises more than 1°C or the ED-P 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 ED-P. If at any time the temperature rises more than 1.5°C above Baseline despite these efforts, the site physician will be consulted for further evaluation and treatment.

12.2.3.2 Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. ED-Ps will not be allowed to drink more than three liters of electrolyte-containing fluids over the course of the Experimental Session and fluid intake will be spread out appropriately during the session. If an ED-P exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an Experimental Session, they will not receive another Experimental Session unless it is approved by the investigator, site physician, and the Medical Monitor.

12.2.3.3 Reproductive and Developmental Risks and Mitigation

Risks posed by MDMA to pregnant people are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [124, 125].

Pregnant and lactating people will be excluded from participation in the study. ED-Ps who are able to become pregnant must have a negative pregnancy screen prior to enrollment and before undergoing each Experimental Session. They must also agree to use adequate birth control for the duration of the study during the Treatment Period. Due to the limited number of single-dose exposures being studied in this trial, the chance of birth defects are low. Procedures described in the Pregnancy for ED Participants Section 13.4 of this protocol have been put in place to mitigate risk of reproductive or developmental exposure to the IMP.

12.2.4 Minimal Risks

Minimum Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no procedures are needed beyond basic monitoring to ensure screening is adequate to eliminate or manage the risk in the patient population.
12.2.4.1 Common AEs

Common AEs are typically observed during IMP administration, but are transient and diminish as the IMP is metabolized and excreted over the next 72 hours after dosing. Common AEs most frequently reported during Experimental Sessions include muscle tightness in the jaw, lack of appetite, dizziness, and nausea. During the week following treatment, lack of appetite, muscle tightness in the jaw, restlessness, weakness, dry mouth, thirst, impaired gait/balance, and sensitivity to cold may be reported. Severe anxiety, insomnia, fatigue, and depressed mood are commonly reported in PTSD studies in both placebo and MDMA groups. Common AEs are typically self-limiting. Elevations in anxiety and poor sleep respond to management with short-acting low dose benzodiazepines (specifically, lorazepam) or sleep aids as needed, per clinical judgment of the site physician.

12.2.4.2 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [126]. However, these claims are based on studies that employed inappropriately high doses of MDMA utilized in animal studies and on human studies comparing the effects of repeated use of Ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work and found only modest evidence of neurotoxicity [127, 128]. The sponsor has carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. It does not appear that MDMA-assisted psychotherapy negatively impacts cognitive function. Neurotoxicity and neurocognitive effects of MDMA were studied in the sponsor’s Phase 2 PTSD studies and provided sufficient data to conclude that limited exposures to MDMA allowed for adequate time for reversibility of any effects at the synaptic level. Furthermore, limited dosing of MDMA has shown to have no effect on neurocognitive functioning.

12.2.4.3 Abuse Liability

Findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens,” like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. In sponsor-supported Phase 2 PTSD studies in 107 participants treated with MDMA-assisted psychotherapy in a controlled clinical setting, 29.9% (32 of 107) of participants had tried Ecstasy at least 6 months prior to enrollment, with U.S. samples demonstrating a higher prevalence of use than international studies. Participants reported using Ecstasy an average of 2.3 (SD:1.43) times. Due to the known association of substance use disorders and PTSD, this sample was likely not representative of the general healthy volunteer population but is congruent with the PTSD population. At long-term follow-up across six Phase 2 studies, 8.7% of participants (eight of 92) reported “Ecstasy” use across studies, with five participants indicating single and not repeated use and three participants indicating two uses. Six of these eight subjects had used Ecstasy prior to study participation. Of these participants, most were attempting to recreate a therapeutic experience, and most did not indicate a desire to repeat this. In addition to self-report data, urine drug screens specific for MDMA were performed at random and 2, 6, and 12 months after the final Experimental Session during one study (MP2, N=12). All were negative, supporting the observation that study participants did not seek out MDMA or Ecstasy after taking part in the study [72, 129]. In addition to data on Ecstasy use at follow-up, AEs were reviewed across Phase 2 PTSD studies.
and the sponsor found an absence of clinically significant AEs supporting drug dependence, intentional drug misuse, and substance abuse, and a low rate (<2%) of secondary terms that reflect acute intoxication.

Based on current information, it does not appear that MDMA-assisted psychotherapy demonstrates signals associated with known abuse liability patterns in a PTSD population when administered in a therapeutic setting under continuous observation in three single-dose sessions. Any abuse potential and diversion is further limited since the IMP is not supplied to the participant to take home and is administered in a restrictive setting. Each investigator responsible for dispensing or administration of the IMP will maintain current registration with authorities with oversight of controlled substances. IMP will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies. See the Safety Section 13.3 of this protocol for AESI terms.

13.0 Safety

The safety of all participants enrolled in the MED1 study will be monitored by the sponsor’s internal safety team and the assigned Medical Monitors. Additionally, a Safety Committee will perform safety review of the study data based on enrollment and on an ongoing basis for the duration of the study.

13.1 Medical Monitors

The name and contact information for the Medical Monitors are:

Sara Garcia Velazquez, M.D.
Medical Monitor

Alia Lilienstein, M.D., M.P.H.
Medical Director

13.2 Safety Committee

A Safety Committee for the MED-1 study will include members of the sponsor's internal safety team, the study's Qualified and Clinical Investigators, the study’s Coordinating Investigator (who is a subject matter expert in the treatment of eating disorders), as well as an independent external physician not involved in the conduct of the clinical trial. The Safety Committee is set-up to provide a timely and appropriate review of study data on an ongoing basis for the duration of the study and has the right to halt enrollment or experimental sessions in the study if there is a newly identified safety concern.

The Safety Committee will review study data within four weeks following the first Experimental Sessions for the first two study participants. After this review, the Safety Committee will meet on a quarterly basis or more often as needed. Additionally, the Safety Committee will meet after the first two mild or moderate AN-R participants complete their first Experimental Sessions at a research site to assess any clinically significant concerns prior to the site enrolling any participant with severe AN-R. If the Safety Committee deems that there are no safety concerns, they may give permission to the research site to enroll severe AN-R participants.

If there are contraindications for an ED-P to receive their initial or supplemental doses during an Experimental Session due to increases in blood pressure, the Safety Committee will determine if the participant may continue safely in the study and will notify the QI or CI. The Safety
Committee may propose an evaluation by a cardiologist before continuing in the study where indicated.

### 13.3 Adverse Events

In accordance with guidance for the specific study site, Health Canada Clinical Safety Data Management Definitions and Standards for Expedited Reporting International Conference on Harmonisation (ICH) Topic E2A: Guidance for Industry or FDA Safety Reporting Requirements for Investigational New Drugs (INDs) and bioequivalent/bioavailability (BA/BE) Studies, an Adverse Event (AE) is defined as any medical occurrence in a participant, including any abnormal sign (e.g., abnormal and clinically significant physical exam, laboratory finding, ECG, or vital sign), symptom, or disease, temporally associated with the participant’s involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

Events related to planned treatments or physician visits for Baseline conditions collected in the medical history will not be collected, unless there is an exacerbation of the condition, in which case they will be actively followed until resolution.

An unexpected AE is one that is not listed in the current IB (for ED-Ps) or an event that is by nature more specific or more severe than a listed event.

The site physician will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapy teams will collect AEs for ED-Ps during study visits from Enrollment (Visit 0) through Study Termination (Visit 16). Participants will be asked directly how they are feeling during each contact, and AEs may be captured spontaneously during psychotherapy sessions, telephone calls, or other correspondence. Completed measures may create suspicion that an AE occurred; in this case, the site staff should follow-up with the participant.

All AEs will be monitored by the therapy team until resolution or, if the AE becomes chronic, a cause can be identified. If an AE is unresolved when a participant terminates from the study, a clinical assessment will be made by the site physician, investigator, and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” eCRF will be determined by the site physician as:

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

The relationship of the study treatment to an AE will be determined by the Clinical Investigator or qualified designee 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.

13.3.1 Adverse Events of Special Interest for ED Participants

In accordance with the guidance for a specific study site location, Health Canada 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 involving cardiac function 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. The subset of AEs involving suicide risk under the following terms are also of special interest: suicides, suicide attempts, self-injurious behavior associated with suicidal ideation and suicidal ideation judged to be serious or severe. These AEs will be marked in the eCRF with the denotation “Adverse Event of Special Interest” (AESIs) whether serious or non-serious.

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” (material represented 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 ED-Ps dropped out of the study will be assessed for presence of AESIs.
- Qualitative urine drug test data will be collected prior to each Experimental 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 an SAE or if it involves suicide risk, it should be reported to the sponsor with a narrative via the eCRF within 24 hours of the site’s awareness of the event.

13.3.2 Serious Adverse Events

In accordance with guidance for the specific study site, Health Canada 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, an SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the event causes substantial disruption of a person’s ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent permanent impairment or damage.
• Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe Adverse Event need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as a study-related SAE, unless, in the view of the site physician, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the participant was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or elective abortion does not result in an SAE report, unless, in the view of the site physician, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

All SAEs will be collected for ED-Ps from enrollment through Study Termination. All SAEs which occur during the course of the trial, whether considered to be associated with IMP for ED-Ps or not, must be reported to the sponsor within 24 hours of the site staff’s awareness of occurrence. Reporting procedures will be provided to the site. All SAEs will be assessed for relationship, expectedness and any required actions to address safety at the time of reporting of the event. SAEs will be evaluated by the site physician and Medical Monitor to determine if it is appropriate for the participant to continue treatment or to be withdrawn from the study and complete the Study Termination Visit.

13.4 Pregnancy for ED Participants

13.4.1 Definition of Childbearing Potential

A participant is considered of childbearing potential if they were assigned female at birth and are post-menarche. A participant is considered not of childbearing potential if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), or postmenopausal. Caregiver participants may be pregnant during study participation if they can commit to all eligibility criteria, including being willing to commit to Preparatory and Integrative Sessions, completion of evaluation instruments and other study procedures, and being contacted for all necessary telephone contacts.

13.4.2 Contraception Guidelines

CG participants will not be required to practice birth control. ED participants of childbearing potential are required to adhere to adequate birth control methods which include the following:

• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal
• Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide)
• Double barrier method (at least two of the following: condom, diaphragm, and spermicide)
• Vasectomized sole partner
• Abstinence from penile-vaginal intercourse
  o The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the participant in case they decide to engage in penile-vaginal intercourse during the course of the study.

For questions about acceptable birth control methods, contact the Medical Monitor.

13.4.3 Pregnancy Follow-up Requirements

Details of all pregnancies in ED participants will be collected after Enrollment (Visit 0) and collected through 10 days after the last Experimental Session. Pregnancies should be reported to the sponsor via telephone or email within 24 hours of site staff awareness.

In the event of a pregnancy, the ED participant will discontinue Experimental Sessions and be withdrawn from study participation following the Withdrawal Criteria for Enrolled Participants Section 5.3.3 of this protocol.

The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported on an optional Pregnancy eCRF. Any termination, elective or spontaneous, will be reported. Abnormal pregnancy outcomes, such as spontaneous abortion, fetal death, stillbirth, congenital abnormalities, or ectopic pregnancy, will be reported as SAEs.

14.0 Concomitant Medications for ED Participants

14.1 Tapering Instructions

The site physician will record concomitant medications during Screening. If the prospective ED-P is taking medications that are prohibited on this study at enrollment, the prospective participant will be encouraged to discuss medication tapering with their outside treating physician, if any, and will be required to give the site physician permission to do so as well. If required, the medications will then be tapered in an appropriate fashion to avoid withdrawal effects and will be discontinued at least five half-lives plus one additional week for stabilization before the first Experimental Session to avoid the possibility of any interaction.

The site physician will consult the prescribing physician to initiate medication tapering for prohibited medications. The prescribing physician’s opinion about medication discontinuation will be documented either in writing from the prescribing physician, or in writing by the site physician documenting phone contact with the prescribing physician. Tapering will follow a time course appropriate for the medication based on its half-life, with the first Experimental Session (Visit 4) scheduled to occur after complete washout (five half-lives plus at least 1 week for stabilization).

The therapy team will request information about any changes in medication at each contact. The site physician will be responsible for reviewing and confirming all medications collected during the study.

All medications, non-prescription and prescription, will be collected from Screening through 7 days after the last Experimental Session. From 7 days after the last Experimental Session through Study Termination, only prescription or non-prescription medications taken to treat AEs will be collected. Throughout the protocol, all medications used to treat AEs will be collected, and all
changes including discontinuations or additions to medications will be collected. The study team will also inquire about concomitant medication adherence and document all information on the Concomitant Medications eCRF.

Participants may return to taking prohibited medications and discontinue birth control after the final Study Termination Visit if necessary.

14.2 Allowed Concomitant Medications

The site physician may prescribe necessary and appropriate medications in accordance with local and state/provincial regulations during the study to treat AEs that do not respond to other management outlined in the Treatment Manual.

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

14.3 Prohibited Medications

To be enrolled in the study, ED participants must:

- Refrain from the use of any psychoactive medication not approved by the research team from the first Experimental Session through Study Termination (with the exception of gabapentin for pain control).
- Be willing to comply with all medication requirements per protocol. Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.
- Agree that, for 1 week preceding each Experimental Session they will refrain from:
  - Taking any specified herbal supplement (except with prior approval of the research team).
- Agree that, for 5 half-lives of the medication preceding each Experimental Session they will refrain from:
  - Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) unless with prior approval of the research team.
  - Taking any prescription medications (with the exception of birth control, thyroid hormones, or other medications approved by the research team).

15.0 Clinical Laboratory Assessments for ED Participants

The site physician will confirm laboratory assessments gathered in screening for assessing eligibility. The site physician will use a 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.

The following laboratory assessments will be performed as a part of Screening:

- Serum electrolytes and metabolic profile
  - Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)
  - Albumin:globulin (A:G) ratio
  - Albumin, serum
• Alkaline phosphatase, serum
• Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT)
• Bilirubin, total
• Blood urea nitrogen (BUN):creatinine ratio
• Calcium, serum
• Carbon dioxide
• Chloride, serum
• Creatinine, serum
• C-reactive protein (CRP)
• Globulin, total
• Glucose, serum
• Potassium, serum
• Protein, total, serum
• Sodium, serum

• Complete Blood Count (CBC)
  • Hematocrit
  • Hemoglobin
  • Mean corpuscular volume (MCV)
  • Mean corpuscular hemoglobin (MCH)
  • Mean corpuscular hemoglobin concentration (MCHC)
  • Red cell distribution width (RDW)
  • Percentage and absolute differential counts
  • Red blood cell (RBC) count
  • White blood cell (WBC) count

• Urinalysis
  • Color
  • Appearance
  • Specific gravity
  • pH
  • Protein
  • Glucose
  • Ketones
  • Occult blood
  • Leukocyte esterase
  • Nitrite
  • Bilirubin
  • Urobilinogen

• Thyroid function
  • Thyroid-stimulating hormone (TSH) high sensitivity (if abnormal, free T3 and T4 will also be tested)

• HCV if indicated
• HIV serology
• Urine-dip pregnancy test for participants of childbearing potential will be performed at the site
• Urinary drug test will be performed at the site

The following laboratory assessments will be performed within 3 days prior to each Experimental Session for AN-R participants only:

• Magnesium
• Phosphorus
• Complete Blood Count (CBC)
  o Hematocrit
  o Hemoglobin
  o Mean corpuscular volume (MCV)
  o Mean corpuscular hemoglobin (MCH)
  o Mean corpuscular hemoglobin concentration (MCHC)
  o Red cell distribution width (RDW)
  o Percentage and absolute differential counts
  o Red blood cell (RBC) count
  o White blood cell (WBC) count

• Comprehensive metabolic profile
  o Sodium
  o Potassium
  o Chloride
  o Bicarbonate
  o Glucose
  o Blood urea nitrogen (BUN)
  o Creatinine
  o Calcium
  o Protein, total
  o Albumin
  o Globulin, total
  o Bilirubin, total
  o Alkaline phosphatase
  o Aspartate aminotransferase (AST)
  o Alanine aminotransferase (ALT)

The following laboratory assessments will be performed just prior to each Experimental Session at the research site:

• Urine-dip ketone testing (AN-R participants only)
• Urine-dip pregnancy test for participants of childbearing potential
• Urinary drug test

Laboratory assessments (with the exception of urine pregnancy, drug, and ketone tests performed just prior to each Experimental Session), will be performed by a qualified clinical laboratory near the research site. Clinical laboratories for each site will be specified in a separate document. Laboratory compliance certificates and normal ranges will be stored in the site’s Investigator Site File (ISF). Laboratory records will be kept with the participant’s Source Records but will not be captured in the electronic Case Report Form (eCRF). Abnormal laboratory values, however, will be recorded in the medical history portion of the participants Source Record and eCRFs, if clinically significant.

16.0 Statistical Considerations

Key personnel, MAPS, and the biostatistician will agree on a Statistical Analysis Plan at the beginning of the study, which will provide more detail about analyses than provided in this protocol. An overview of the statistical analyses that will be performed is provided in the following sections.
16.1 Power Considerations

MED1 is an exploratory one-arm safety and feasibility study. This is a pilot study intended to collect estimates of effect size for statistical power calculations for future adequately powered studies. Due to their exploratory nature, pilot studies are often not powered for detection of the desired effect. Thus, no power nor sample size calculations were conducted.

16.2 Statistical Analyses

Every effort will be made to ensure complete, accurate and timely data collection and to avoid missing data, to ensure the completeness of the data which can impact the integrity and accuracy of the final study analysis. The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.4 or higher. In general, nominal variables will be described in terms of frequencies and percentages. Ordinal and non-normal continuous variables will be described using sample median and range.

Approximately normal variables will be described using sample mean and standard deviations and analyzed by summary statistics. All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered evidence for future research. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as<0.0001. Data not subject to analysis according to this plan will not appear in any tables or graphs, but will be included in the data listings. Selected results may be presented graphically using standard graphical software.

Effect size estimates will be generated for all effectiveness measures using Cohen’s D One Group Pretest Posttest methods. There may be an interim analysis before all participants have been enrolled for safety and effectiveness, in order to allocate subsequently enrolled participants between eating disorder subtypes.

Descriptive statistics will be computed overall for MDMA, as well as by initial MDMA dose received, for all available data from outcome measures, time course of onset of treatment effect and including minimum, maximum, average, median, and standard deviation.

The following analysis sets are defined for this study:

- All Enrolled: all ED and CG participants who sign informed consent and are initially enrolled.
- Analysis Population: all ED participants who receive IMP in at least one Experimental Session and have at least one follow-up EDE assessment post-treatment. All CG participants who have completed Visit 1.
- Per Protocol (PP): all ED participants who meet eligibility criteria, who receive IMP in three Experimental Sessions, and complete all follow-up EDE assessments post-treatment. All CG participants who meet eligibility criteria and completed all follow-up assessments from Visit 16.
- Not Per Protocol (NPP): all participants who are included in the analysis population set but not the PP set.
- Safety: all ED participants who receive any IMP.

16.2.1 Safety Analyses

Safety data for ED-Ps will be summarized by exposure to IMP, unsolicited AEs, concomitant medications, AEs of Special Interest (AESIs), and vital signs overall. If a participant has more
than one AE mapped to the same PT, that AE will be reported once using the highest severity at the subject level. AEs that occur on Day 0 (Experimental Session), Day 1, Day 2 after IMP administration will be presented separately. Incidence of AEs during Experimental Sessions such as clinical signs and symptoms, such as chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that may be indicative of a medical complication of the IMP will be tabulated. The effect of MDMA on cardiac repolarization will be analyzed using change in ECG parameters to derive QTcF.

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by analysis set and category. Concomitant medications taken on Day 0 (Experimental Session), Day 1, Day 2 after IMP administration will be presented separately. Any psychiatric concomitant medications will be tabulated by period (Preparatory, Treatment Period, Follow-up Period). Vital signs (heart rate, blood pressure, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IMP administration, prior to the supplemental dose, and at the end of each Experimental Session.

17.0 Study Governance

The sponsor, MAPS, holds the IND for MDMA and has delegated the primary responsibility of trial organization to MAPS PBC, including designing, initiating, managing, coordinating, continuing, and concluding the clinical trial. MAPS PBC is tasked with maintaining the quality of study conduct through ongoing monitoring of data and participating in writing study publications. MAPS PBC contracts with independent entities who represent clinical sites to accomplish these goals. Collectively, MAPS and MAPS PBC are referred to as sponsor throughout this document.

17.1 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including the US Code of Federal Regulations Title 21 and Canada’s Food and Drugs Act and Regulations) and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the ICF must be reviewed and approved by a properly constituted institutional review board (IRB) or ethics committee and national regulatory agency (FDA or Health Canada) before study start. Signed and dated documentation of approvals must be provided to the sponsor. Prior to study start, the investigator is required to sign a signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

17.1.1 Financial Disclosure

Investigators will adequately and accurately disclose financial interests to the sponsor prior to study start, during the study if financial interests change, and 1 year after study completion if financial interests change. The sponsor will submit necessary disclosures to the appropriate regulatory bodies.
17.1.2 Informed Consent

The investigator and therapy team are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering participants into the trial. Potential participants may be sent the ICF to review prior to the initial phone screen. Preferably, informed consent will be obtained by the therapy team that will treat the participant. Information about the study must be given orally and in an understandable written ICF. The informed consent discussion must be conducted by a person who is qualified according to federal, state/provincial, or local regulations. The participant should have the opportunity to inquire about details of the study and to consider participation.

The therapy team may meet with the potential participant via telemedicine for ICF review and signing prior to in person screening if necessary for scheduling of screening activities. If this is completed by telemedicine visit, the team will ensure the ICF is thoroughly explained and reviewed just as it would be at an in-person visit. If the potential participant is still interested after review, they will sign the consent during that telemedicine visit. The participant will then bring their signed copy of the ICF to their next in person visit where study staff will then counter sign the ICF, copy the ICF for the participant and file the original at the site.

In addition to the explanation of study visits, the information should include that access to original medical records (for ED-Ps) and processing of coded personal information must be authorized. A written release is needed to give permission to site staff to request and view the ED-P’s medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes:

- **ED-Ps**: past medical history, psychiatric interview, physical examination, and clinical laboratory tests.
- **CG-Ps**: psychiatric interview

Eligible participants may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol beyond phone screening). The process of obtaining informed consent should be documented in the participant’s source records. The study staff will provide a copy of the signed ICF to the participant and will maintain the original in the ISF.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant’s consent. Any revised ICF and written information should receive approval from an IRB or EC before use. The participant should be informed in a timely manner if new information becomes available that may affect the decision to take part or continue in the study. The communication of this information should be documented. Participants can withdraw consent at any time without prejudice. If an ED-P withdraws consent but does not revoke applicable authorizations in their country (e.g., the Health Insurance Portability and Accountability Act (HIPAA) in the U.S.), the study team will have full access to their medical records, including Study Termination Visit information. If an ED-P revokes only the HIPAA authorization, the study team will have full access to all medical records prior to the date and time of revocation.

If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.
17.2 Study Monitoring, Auditing, and Documentation

Investigators, therapy teams, and all study staff will be trained prior to study start for each site. Study sites will be monitored by site visits and telephone calls by representatives of the sponsor. In addition, critical data and systemic issues will be subject to centralized monitoring via the EDC system to develop and evaluate strategies for correction across sites. Sites will be monitored as appropriate for the rate of enrollment to comply with GCP guidelines and to ensure validity of study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on eCRFs, source records, and IMP accountability records. An eCRF collation will be completed for each participant enrolled within the EDC system.

Videos from selected sessions may be reviewed for research and training purposes by Supervisors in the MDMA Therapy Training Program. Findings from video reviews may be discussed with therapy teams as needed to ensure continued adherence to the protocol.

During or after the study, the regulatory authorities, the IRB or EC, and/or representatives of the sponsor may request access to all source documents, eCRFs, and other protocol documentation for monitoring visits, audits, or inspections. Monitoring and auditing procedures will be supplied in a separate document.

17.2.1 Source Records

Source records contain all primary evidence of existence of the participant and document all study procedures. Source records may include but are not limited to medical records, measures, checklists, notes, emails, and laboratory reports. All data reported in the eCRF are transcribed from primary source documents and must be consistent. These documents are maintained at the study site securely.

17.3 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants. Despite this, privacy cannot be guaranteed. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data. Except for the Screening Log, the Informed Consent, previous medical records, emails with the participant, and a Contact Information Sheet that will be stored separately from other documents, all source data will be identified only by the participant’s initials and participant ID number. If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. In accordance with the guidance for a specific study site location, Health Canada Guidance for Records Related to Clinical Trials (GUIDE-0068) or FDA E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), all assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators who are directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Audiovisual recordings are necessary for sponsor oversight of therapy processes. Any requests for use of audiovisual recordings outside of research and training requests will result in participants receiving information on the request. Participants will have control over any
presentation of audiovisual recordings beyond viewing by authorized researchers, sponsor staff, or regulatory agencies. The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach. The sponsor is committed to taking preventative measures to avoid such an event. In the case of a security breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

Clinical trial data other than audiovisual recordings will be hosted on an EDC system that is compliant with ICH-GCP and FDA guidance. All data entered into this system will be de-identified. Participants will only be referred to by numbers and a secondary identifier code. Source Records and identifying information will be retained at clinical sites per GCP. The sponsor will train the study staff on EDC procedures. Each study staff member with access to the data will be given an individual password.

The sponsor has developed a feature that will allow participants to create a password and enter their self-report questionnaire data directly into the EDC using the electronic Participant Reported Outcome (ePRO) feature. Participants will be reminded by email to enter the data. Participant emails will be treated as Protected Health Information (PHI) in the database. Participants will receive a welcome email and reminder emails to ensure that they provide all necessary data.

### 17.4 Costs to Participants

There will be no costs to the study participants for participation. The sponsor will cover all direct costs of study procedures required for participation, including any assessments or tests performed solely for the purpose of the study. Charges for treatment of a participant’s condition that are unrelated to the research study or any unrelated procedures will not be covered by the sponsor. Participants who previously received therapy from a therapy team member prior to the study, and who will continue to receive ongoing treatment outside of the study from that therapist, are responsible for those non-study related costs. Participants may be reimbursed for reasonable expenses incurred for study participation, such as local travel to the treatment site; this will be specified in each site’s consent.

### 17.5 Treatment and Compensation for Study Related Injury

Some study-related emergencies can be treated by the site physicians. If the site physicians cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital. Treatment of a study-related emergency would first be billed to a participant’s health insurance provider. If the participant's private or employer health insurance plan does not cover clinical trial-related claims, then the sponsor will cover any treatment costs directly related to the study. The sponsor will not cover costs of ongoing treatment unrelated to the study due to pre-existing conditions, or the cost of the participant's time spent obtaining treatment for pre-existing conditions before receiving treatment in the study. In the event of a suit against the sponsor, the sponsor carries third-party insurance that will cover bodily injury claims and will pay for applicable legal defense if needed/warranted.

### 17.6 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP, FDA regulations, and Health Canada Guidance for Records Related to Clinical Trials (GUIDE-0068) in a secure and safe facility. The investigator must consult a representative of the sponsor before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the
responsibility of the sponsor to inform the investigator or institution when these documents no longer need to be retained.

17.7 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. For multi-center studies, 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 or Qualified 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 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 or Qualified 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.

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.

18.0 Interruptions and Accommodations Due to the COVID-19 Pandemic or Any Other Unforeseen Emergency at Clinic Locations

Accommodations may be required for study continuation and the safety of participant and study site staff due to the Coronavirus Disease 2019 (COVID-19) pandemic or any other unforeseen emergency in the future. These accommodations may be necessary and will be evaluated on a case-by-case basis by the investigator and Medical Monitor. These may include, but not limited to the following:

- Delaying medication tapering after enrollment and the subsequent Treatment Period
- Delaying Experimental Sessions and associated Integrative Sessions

These above accommodations, or others, which deviate from protocol requirements must be approved by the Medical Monitor. Deviations from the protocol which are allowed by the Medical Monitor will be captured and noted as deviations in the Clinical Study Report as COVID-19 or relevant emergency deviations.

For any participant with COVID-19 related illness, continued trial 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.
References


64. Adamson, S., Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances. 1985, San Francisco CA: Four Trees Publications.


