EAMP1 Protocol and Synopsis

Original Protocol Version 1: 11 January 2019
Amendment 1 Version 1: 15 April 2019
Amendment 2 Version 1: 10 June 2019
Amendment 3 Version 1: 02 August 2019
Amendment 4 Version 1: 19 November 2019

An Intermediate-size Multi-site Expanded Access Program for MDMA-assisted Psychotherapy for Patients with Treatment-resistant PTSD

SPONSOR
Multidisciplinary Association for Psychedelic Studies (MAPS)
1115 Mission Street
Santa Cruz, CA 95060

SPONSOR REPRESENTATIVE
Rick Doblin, Ph.D.
Executive Director
MAPS

SPONSOR DELEGATE & TRIAL ORGANIZER
MAPS Public Benefit Corporation
1115 Mission Street
Santa Cruz, CA 95060

SPONSOR DESIGNEE
Amy Emerson
Executive Director, Head of Clinical Development & Regulatory Affairs
MAPS Public Benefit Corporation

CLINICAL INVESTIGATOR
Multi-site Study

MEDICAL MONITORS
Michael C. Mithoefer, M.D.
Alia Lilienstein, M.D., M.P.H.

USE
In conjunction with relevant Food and Drug Administration (FDA) guidance
Expanded Access Protocol Synopsis

Full protocol begins on page 8

Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in patients with posttraumatic stress disorder (PTSD). Data from a series of Phase 2 studies of MDMA-assisted psychotherapy conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, is treatable with up to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy.

MAPS has initiated Phase 3 studies with anticipated enrollment of 200 to 300 total subjects, but over 20,000 people with PTSD have contacted MAPS asking to be informed about possible enrollment in Phase 3. This open-label Expanded Access study will provide treatment refractory PTSD patients with early access to MDMA-assisted psychotherapy. Patients may not be eligible for another ongoing MDMA-assisted psychotherapy clinical trial in order to participate in this study.

PTSD is a serious debilitating disorder that negatively impacts a person’s daily life, and can result in diminished cognitive and psychosocial functioning, fractured relationships, inability to maintain employment, substance abuse, high-cost healthcare utilization, increased depression, and suicide risk. People who suffer from PTSD relive their traumatic experience(s) through nightmares and flashbacks, have difficulty sleeping, and feel detached or estranged. Symptoms can be severe and long lasting. MDMA is a monoamine releaser and re-uptake inhibitor with indirect effects on neurohormone release. The combined neurobiological effects reduce defenses and fear of emotional injury, enhance communication and introspection, and can increase empathy and compassion. MDMA may enhance fear extinction learning in humans. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process.

Study Design

This multi-site, open-label, intermediate-size Expanded Access study under a Treatment Investigational New Drug (IND) will provide access to treatment to patients with treatment-resistant PTSD for whom it wasn’t possible to participate in Phase 3 studies. This study will provide supportive data on safety and tolerability of MDMA-assisted psychotherapy in treatment-resistant patients with PTSD. This study will be conducted at multiple Expanded Access study sites. There will be at least one, but usually more, co-therapy pairs at each study site.

A flexible dose of MDMA, followed by a supplemental half-dose unless contraindicated, is administered during the Treatment Period with manualized psychotherapy in up to three open-label Experimental Sessions. During the Treatment Period, each Experimental Session is preceded by three 90-minute Preparatory Sessions and followed by three 90-minute Integrative Sessions of non-drug psychotherapy. Experimental Sessions will be followed by an overnight stay.

In the Phase 3 protocol the Experimental Sessions are scheduled roughly 3 to 5 weeks apart but in this Expanded Access protocol there could be longer times between the Experimental Sessions though all Experimental Sessions and associated non-drug psychotherapy sessions must be completed within 8 months.
For each patient, the study will consist of:

- **Screening Period**: phone screen, informed consent, eligibility assessment, and enrollment of eligible patients
- **Preparatory Period with Enrollment Confirmation**: medication tapering, Preparatory Sessions, and Baseline assessments
- **Treatment Period**: Up to three Experimental Sessions and associated Integrative Sessions within 8 months
- **Study Termination**: Completed after last integrative visit

**Study Design Overview**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Visit Duration/ Visit Timing/ (Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Multiple visits/ After phone screen/ Before enrollment</td>
<td>At initial visit, obtain Informed Consent and assess all screening measures (including PCL-5, Lifetime C-SSRS, MINI), medical history, and pre-study medications. Contact outside providers and order medical records, physical exam, clinical labs, on site qualitative pregnancy and drug tests, ECG, and 1-minute rhythm strip. Once all results and records are obtained, review along with notes from all screening visits and measures. Results will be confirmed by clinical observation during the Preparatory Period. Screening may take place over multiple visits.</td>
</tr>
<tr>
<td>Enrollment</td>
<td>~0.5 hours by phone</td>
<td>Prior to enrolling: review all screening measures, medical history, discussion with outside providers, and any clarification phone calls with patient. Sponsor will provide eligibility review. Visit is 0.5 hours to inform patient of eligibility and medical tapering plan. If enrolled, begin taper, (5 half-lives plus 1 week for stabilization). Adverse Event (AE) collection begins.</td>
</tr>
</tbody>
</table>

**Preparatory Period**

<table>
<thead>
<tr>
<th>Study Visit/ Visit #</th>
<th>Visit Duration/ Visit Timing/ (Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory Period</td>
<td>1.5-hour Preparatory Session. Target visit timing on tapering needs. If needed, schedule calls between V1 and V2 if indicated for tapering, safety, or further questions about medical history.</td>
<td></td>
</tr>
<tr>
<td>Preparatory Session 2 (Visit 2)</td>
<td>1.5-hour Preparatory Session/ongoing assessment. If tapering is complete or not needed, check eligibility and schedule V3 and V4. If tapering is ongoing, schedule post taper call for ongoing assessment.</td>
<td></td>
</tr>
<tr>
<td>Phone Call End Taper</td>
<td>0.5 hour/ Within 2 weeks of taper end</td>
<td>If needed, confirm medication taper and stabilization is complete and patient is eligible for dosing. Schedule V3 and V4.</td>
</tr>
</tbody>
</table>
## Preparatory Period
From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 3): 2 to 8 weeks

<table>
<thead>
<tr>
<th>Study Visit/Visit #</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory Session 3 (Visit 3)</td>
<td>2.5 hours: (~43 minutes of measures, 1.5 hours of therapy) Within 2 weeks (±1 week) of V2</td>
<td>Complete Baseline self-report measures. Complete 2.5-hour Preparatory Session (~43 minutes of measures, 1.5-hour therapy) and schedule V4.</td>
</tr>
</tbody>
</table>

## Treatment Period
From Experimental Session 1 (Visit 4) to Integrative Session 3.3 (Visit 15): Up to 32 weeks

<table>
<thead>
<tr>
<th>Study Visit/Visit #</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental Session 1 (Visit 4)</td>
<td>8 hours/After V3 and before V5</td>
<td>First Experimental Session lasts 8 hours with an overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 1.1 (Visit 5)</td>
<td>1.5 hours/Morning after V4</td>
<td>V5 is a 1.5-hour Integrative Session on the morning after V4. Followed by 4 phone check-ins over the 7 days post V4.</td>
</tr>
<tr>
<td>Integrative Session 1.2 (Visit 6)</td>
<td>1.5 hours/After V5 and before V7</td>
<td>V6 is a 1.5-hour Integrative Session.</td>
</tr>
<tr>
<td>Integrative Session 1.3 (Visit 7)</td>
<td>1.5 hours/After V6 and before V8</td>
<td>V7 is a 1.5-hour Integrative Session. Administer measures: Since Last Visit LEC-5, PCL-5, SDS, and C-SSRS.</td>
</tr>
<tr>
<td>Experimental Session 2 (Visit 8)</td>
<td>8 hours/At least 3 weeks after V4</td>
<td>Second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg with supplemental half-dose unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 2.1 (Visit 9)</td>
<td>1.5 hours/Morning after V8</td>
<td>V9 is a 1.5-hour Integrative Session the morning after V8. Followed by 4 phone check-ins over 7 days post V8.</td>
</tr>
<tr>
<td>Integrative Session 2.2 (Visit 10)</td>
<td>1.5 hours/After V9 and before V11</td>
<td>Approximately 2 weeks after V8, a 1.5-hour Integrative Session (V10) is completed.</td>
</tr>
<tr>
<td>Integrative Session 2.3 (Visit 11)</td>
<td>1.5 hours/After V10 and before V12</td>
<td>V11 is a 1.5-hour Integrative Session. Administer measures: Since Last Visit LEC-5, PCL-5, SDS, and C-SSRS.</td>
</tr>
<tr>
<td>Experimental Session 3 (Visit 12)</td>
<td>8 hours/At least 3 weeks after V8</td>
<td>Third Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 3.1 (Visit 13)</td>
<td>1.5 hours/Morning after V12</td>
<td>V13 is a 1.5-hour Integrative Session the morning after V12. Followed by 4 phone check-ins over 7 days post V12.</td>
</tr>
<tr>
<td>Integrative Session 3.2 (Visit 14)</td>
<td>1.5 hours/After V13 and before V15</td>
<td>Within 2 weeks after V12, a 1.5-hour Integrative Session (V14) is completed.</td>
</tr>
<tr>
<td>Integrative Session 3.3 (Visit 15)</td>
<td>1.5 hours/Within 8 months of V4</td>
<td>V15 is a 1.5-hour Integrative Session. Administer C-SSRS</td>
</tr>
</tbody>
</table>
Dose Selection

This study will evaluate the effect of up to three open-label manualized Experimental Sessions of psychotherapy assisted by flexible doses of MDMA as described in the table below, along with associated non-drug preparatory and integrative psychotherapy. Similar MDMA doses to those proposed in this study have been safely used in previous Phase 2 and 3 studies sponsored by MAPS.

Dose Regimen of MDMA

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

* Unless contraindicated

Protocol Objective

The primary objective of this Expanded Access study is to provide MDMA-assisted psychotherapy on a compassionate basis to treatment-resistant PTSD patients. The study will also provide supportive data on the safety and tolerability of open-label MDMA-assisted psychotherapy in clinical settings to patients with treatment-resistant PTSD.

Safety Objectives

The overall safety objective is to assess severity and incidence of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy in a clinical practice setting:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), 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.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and 2 days after IP administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and 2 days after IP administration.
7. Assess incidence of SAEs.
8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and 2 days after IP administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of each Experimental Session.

**Recruitment and Patient Population**

Co-therapy pairs will treat at least one and potentially more open-label patients in this study. Patients will be enrolled with a confirmed diagnosis of PTSD per the Mini-international Neuropsychiatric Interview (MINI) at Screening with symptoms that persist despite receiving PTSD treatment of adequate dose and duration in the clinician’s judgement. Patients will be persons aged 18 or older, with a confirmed diagnosis of PTSD. Patients would not be excluded for having more than one traumatic event. Patients must be in good physical health and without major medical disorders that could affect the safety or tolerability of MDMA. Patients will be recruited through print and internet advertisements, referrals from other psychiatrists, psychotherapists, or physicians, and by word of mouth.

The sponsor’s Phase 3 co-therapy pairs can begin enrollment for this Expanded Access protocol only after they have met their individual Phase 3 enrollment requirements and completed treatment of their expected Phase 3 participants.
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1.0 List of Abbreviations

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<tr>
<td>°C</td>
<td>Degrees Celsius</td>
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<tr>
<td>A:G</td>
<td>Albumin:Globulin</td>
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<td>ACE</td>
<td>Adverse Childhood Experiences Questionnaire</td>
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<td>Adverse Event of Special Interest</td>
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<td>Acute Myocardial Infarction</td>
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<td>Basic Life Support</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<td>Clinician-Administered PTSD Scale for DSM-4</td>
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<td>Clinical Research Associate</td>
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<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
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<tr>
<td>ED</td>
<td>Emergency Department</td>
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<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
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<tr>
<td>EMDR</td>
<td>Eye Movement Desensitization and Reprocessing</td>
</tr>
<tr>
<td>EMS</td>
<td>Emergency Medical Services</td>
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<tr>
<td>ePRO</td>
<td>Electronic Patient Reported Outcome</td>
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<tr>
<td>EQ-5D-5L</td>
<td>EuroQol Five Dimensions - Five Levels Questionnaire</td>
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<td>FDA</td>
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<td>Good Clinical Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>Health Insurance Portability and Accountability</td>
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<td>Investigational New Drug</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>ISF</td>
<td>Investigator Site File</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>ITT</td>
<td>Intent-to-Treat</td>
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<td>IUD</td>
<td>Intrauterine Device</td>
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<td>IUS</td>
<td>Intrauterine Hormone-releasing System</td>
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<td>LEC-5</td>
<td>Life Events Checklist</td>
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<tr>
<td>LTFU</td>
<td>Long-term Follow-up</td>
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<tr>
<td>MAPS</td>
<td>Multidisciplinary Association for Psychedelic Studies</td>
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<tr>
<td>MAOI</td>
<td>Monoamine Oxidase Inhibitor</td>
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<tr>
<td>MCH</td>
<td>Mean Corpuscular Hemoglobin</td>
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<td>MCHC</td>
<td>Mean Corpuscular Hemoglobin Concentration</td>
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<td>MCV</td>
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<td>3,4-methylenedioxyamphetamine</td>
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<tr>
<td>mg</td>
<td>Milligram</td>
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<tr>
<td>MINI</td>
<td>Mini-international Neuropsychiatric Interview</td>
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<tr>
<td>mmHg</td>
<td>Milligrams of Mercury</td>
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<tr>
<td>MPBC</td>
<td>MAPS Public Benefit Corporation</td>
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<tr>
<td>ms</td>
<td>Millisecond</td>
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<td>PCL-5</td>
<td>PTSD Checklist for DSM-5</td>
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<td>Protected Health Information</td>
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<td>PTCA</td>
<td>Percutaneous Transluminal Coronary Angioplasty</td>
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<td>Posttraumatic Stress Disorder</td>
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<td>RACT</td>
<td>Risk Assessment and Categorization Tool</td>
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<td>Red Blood Cell</td>
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<td>Red Cell Distribution Width</td>
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<td>Serious Adverse Event</td>
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<td>SDS</td>
<td>Sheehan Disability Scale</td>
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<td>SGOT</td>
<td>Serum Glutamic Oxaloacetic Transaminase</td>
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<tr>
<td>SNRI</td>
<td>Serotonin-norepinephrine Reuptake Inhibitor</td>
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<td>SGPT</td>
<td>Serum Glutamic Pyruvic Transaminase</td>
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<td>Self-reported Nicotine Use</td>
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<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<td>SUBJID</td>
<td>Subject Identifier</td>
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<td>TEAE</td>
<td>Treatment Emergent Adverse Event</td>
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<tr>
<td>TSH</td>
<td>Thyroid-stimulating Hormone</td>
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<tr>
<td>UFEC</td>
<td>Utilization of Facility-based and Emergent Care</td>
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<td>United States</td>
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<td>U.S. Department of Veterans Affairs</td>
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<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
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<td>WHO</td>
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2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain marketing approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in patients with posttraumatic stress disorder (PTSD). Controlled Phase 1 studies, nonclinical studies, and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA under Investigational New Drug (IND) #063384. MAPS-sponsored studies are implemented through MAPS’ wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (MPBC).

FDA has granted MDMA Breakthrough Therapy Designation for treatment of PTSD. Phase 2 studies support a positive benefit/risk ratio based on data from an international series of Phase 2 pilot studies conducted by the sponsor that provide preliminary evidence that chronic PTSD, independent of cause, is treatable with up to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy.

2.1 Rationale

MAPS has initiated Phase 3 studies with anticipated enrollment of between 200 to 300 total subjects but over 20,000 people with PTSD have contacted MAPS asking to be informed about possible enrollment in Phase 3. This open-label Expanded Access study will provide treatment refractory PTSD patients with early access to MDMA-assisted psychotherapy. PTSD is a serious debilitating psychiatric disorder with unmet medical need, despite available medications.

2.1.1 PTSD

PTSD is associated with increased mortality and cardiometabolic morbidity. PTSD is a stress-related psychiatric condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, and accidents. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares. PTSD negatively impacts a person’s daily life, resulting in fractured relationships, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization, and increased depression and suicide risk. People who suffer from PTSD often relive the experience through nightmares and flashbacks, have poor sleep quality, and feel detached or estranged. Confronting overwhelming internal distress and frightening external environments can also lead to high levels of depersonalization and derealization, which led clinicians to identify a dissociative subtype of PTSD in the DSM-5. Adaptations in normal brain function have been observed in imaging studies of patients with PTSD that underlie alterations in emotional processing and regulation, cognition, and many aspects of behavior, though clinical symptoms and changes in brain activity are not homogenous across patients [1]. The dissociative subtype occurs in 12 to 30% of people with PTSD and is characterized by detachment and emotional numbing and visualized in the brain as overmodulation of affect mediated by midline prefrontal inhibition of limbic regions, while the non-dissociative subtype presents symptoms of hyperarousal and re-experiencing, an emotional undermodulation mediated by the failure of prefrontal inhibition of the same limbic regions [2, 3]. Patients suffering from the dissociative subtype of PTSD typically have early childhood trauma and appear to be particularly difficult to treat, with mixed response to existing evidence-based treatments.
Approximately 7% of the population in the United States (U.S.) will have PTSD sometime in their life, but this figure jumps to 10.8% to 13% of veterans with combat experience [4]. For soldiers returning from Iraq and Afghanistan, the incidence of PTSD is 17.1% with 400,000 to 500,000 U.S. Iraq/Afghanistan veterans reportedly having PTSD. In 2004, the Defense Department and U.S. Department of Veterans Affairs (VA) spent $4.3 billion on PTSD disability payments to approximately 215,000 veterans [5]. Beyond disability payments, in 2012 alone the VA spent $294 million and $3 billion, respectively, on care for veterans with the disorder and disability payments, and even with this funding the demand for services far outweighed the availability of VA doctors and services. As of June 30, 2016, more than 868,000 veterans with a diagnosis of PTSD were receiving disability compensation for service-connected mental disorders, with an estimated cost of about $17 billion per year [6]. There are an estimated 20 to 22 suicides a day by veterans [7, 8].

Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration, which indicates a need to develop treatments targeting durable remission of PTSD. The Food and Drug Administration (FDA) has approved only two pharmacotherapies for PTSD, both of which are selective serotonin reuptake inhibitors (SSRIs). Paroxetine and sertraline (Paxil and Zoloft) both demonstrated statistically significant superiority over placebo on the CAPS in 12-week confirmatory clinical trials with daily dosing, but some studies were less effective in treating combat-related PTSD and sertraline demonstrated gender differences with minimal efficacy in men [9-11]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which fully return upon discontinuation of treatment. Adverse effects of maintenance SSRI treatment that contribute to discontinuation include sexual dysfunction, weight gain, and sleep disturbance. Variable SSRI treatment outcomes have led to recommendations of trauma-focused psychotherapy as routine first-line treatment by the VA’s National Center for PTSD in the U.S., as well as by the World Health Organization (WHO). An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but have only small effect sizes in reducing PTSD symptoms. PTSD brings a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [12, 13]. Given the chronicity of PTSD, low compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients suffer from unmet medical need.

One treatment approach is to develop medications and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and Eye Movement Desensitization and Reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [14, 15], although some patients may need more than one type of treatment to reduce or resolve those symptoms. A meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective with PTSD [16]. In the past decade, there has been a growing amount of research into medications and other methods that may augment the effectiveness of psychotherapy for PTSD (see [17] for a review). Examples of these are virtual reality-assisted exposure therapy [18, 19] and D-cycloserine-assisted psychotherapy [20]. MDMA-assisted psychotherapy is another such approach.

2.1.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [21, 22]. Similar to SSRIs, MDMA binds to the serotonin
transporter, but has additional effects on carrier-mediated release and reuptake inhibition of norepinephrine and to a lesser extent in humans, dopamine [23-29]. MDMA also increases levels of affiliative neurohormones oxytocin and vasopressin, which increases trust and attenuates reactivity to threatening cues, and some researchers have suggested a role for oxytocin in treating PTSD. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, which would treat the core psychopathology of PTSD for a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the 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. Unlike approved PTSD medications, therapeutic effects of MDMA have a rapid onset, and do not require daily dosing or a steady state in the blood to be effective. Thus, the effects of MDMA are distinct from and go well beyond anxiolytics and SSRIs. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [30, 31]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [32]. Hence, MDMA may have moderate abuse potential. See the Investigator’s Brochure (IB) for a more detailed explanation.

2.1.3 MDMA-assisted Psychotherapy for PTSD

Many psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in psychotherapy with an appropriate level of emotional engagement [15]. To be effective, exposure must be accompanied by a degree of emotional engagement or “fear activation” while avoiding dissociation or overwhelming emotion [33], which has been referred to as working within the “optimal arousal zone” or “window of tolerance” [34-36].

The combined neurobiological effects of MDMA increase compassion, reduce defenses and fear of emotional injury, and enhance communication and introspection. MDMA produces anxiolytic and prosocial effects, which counteract avoidance and hyperarousal in the context of therapy. PTSD increases amygdala activity, causing heightened encoding of fearful memories and decreasing blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [37], and there is some indication that MDMA may increase activity in the prefrontal cortex [38]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [37]. This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [39-41]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapy team during and after the MDMA experience. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process. MDMA is capable of inducing unique psychopharmacological effects, including decreased fear and increased wellbeing, sociability, interpersonal trust, acceptance of self and others, and ability to address these issues without extreme disorientation or ego loss due to alert state of consciousness. These factors taken together can provide the opportunity for a corrective emotional experience.

A combined treatment of MDMA and psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one’s emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [42-45]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to
information about them [46]. Patients are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-assisted psychotherapy may enable patients to restructure their intra-psychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

The therapeutic method is described in further detail in the Treatment Manual of MDMA-Assisted psychotherapy, which the study sites and co-therapy pairs will be trained on prior to the study.

2.1.4 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 [47], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [47, 48]. MDMA was found to robustly influence human emotional status in a unique way [47] without adversely affecting physiological functions or perception, such as visual perception or cognition [49-52]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [53]. Legal therapeutic use continued until its placement on the U.S. list of Schedule 1 substances in 1985 [43, 46, 54]. An estimated 500,000 doses of MDMA were administered during psychotherapy and personal growth sessions in North America prior to its scheduling [43, 55]. A few uncontrolled human studies of MDMA assessing safety in a therapeutic setting occurred in the 1980s [56, 57]. 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 [58, 59]. Starting in 2000 in Spain, MAPS funded a Phase 2 investigator-initiated dose-response effect and safety pilot study in patients with PTSD that was terminated early due to political pressure. This study enrolled six patients, with four receiving a single session of MDMA-assisted psychotherapy without any safety concerns and with some PTSD symptom reduction [45]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS 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 (Clinician-Administered PTSD Scale for DSM-4 [CAPS-4] score: 50+), with at least 6 months of symptoms. Patients were not excluded for having more than one traumatic event, or for having tried, not tolerated, or refused an 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 (LTFU) conducted an average of 3.8 years after the final MDMA-assisted psychotherapy session (MP1) [44, 60] and one in Switzerland (MP2) [61, 62]. MP1 was followed by a small open-label extension study examining the treatment of relapse in three patients 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 study 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 patients 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 October 1, 2016, with 154 individuals exposed to MDMA in the sponsor’s development program across various indications and at least 1130 patients in MDMA research studies conducted without sponsor support, the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted psychotherapy. Across Phase 2 studies, 75 mg-125 mg MDMA was statistically superior to 0 mg to 40 mg MDMA based on a t-test of difference in CAPS-4 severity scores from Baseline, 2 months after two blinded Experimental Sessions (p<0.001). The dropout rate across studies was 7.5% (8 of 107). Large effect size estimates (0.9), initial indications of efficacy, and favorable safety outcomes support expanding the research initiative to encompass a larger sample of patients with PTSD in the future Phase 3 program and Expanded Access program.

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

3.0 Protocol Objectives

The primary objective of this Expanded Access study is to provide MDMA-assisted psychotherapy on a compassionate basis to treatment-resistant PTSD patients. The study will also provide supportive data on the safety and tolerability of open-label MDMA-assisted psychotherapy in clinical settings to patients with treatment-resistant PTSD.

3.1 Safety Objectives

The overall safety objective is to assess severity and incidence of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy in a clinical practice setting:

1. 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.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and 2 days after IMP administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination. Assess
incidence of psychiatric concomitant medications taken during an Experimental Session and 2 days after IMP administration.

7. Assess incidence of SAEs.
8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and 2 days after IMP administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of each Experimental Session.

3.2 Exploratory Objectives

These objectives may be explored to characterize patients receiving MDMA-assisted psychotherapy:

1. Explore changes in:
   - PTSD Symptom Severity (PCL-5)
   - Functional Impairment (SDS)
   - Depression (BDI-II)
   - Chronic pain (CPGS)
   - Quality of life (EQ-5D-5L)
   - Addictive behaviors, including: alcohol use (AUDIT), drug use (DUDIT), and nicotine use (SRNU)
   - Eating habits (EAT-26)
   - Workplace productivity (HPQS)
   - Healthcare utilization (UFEC)

4.0 Eligibility Criteria

4.1 Inclusion Criteria

At the completion of Screening, patients must meet all eligibility criteria and agree to all lifestyle modifications to be enrolled. Each patient will then enter the Preparatory Period which includes medication tapering, if needed, and non-drug Preparatory Sessions. Patients will be confirmed for dosing if they have completed medication tapering, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria.

Potential patients are eligible to enroll in the protocol if they:

1. At Screening, meet criteria for PTSD diagnosis
2. Have had at least two unsuccessful attempts at treatment for PTSD. Treatment attempts can consist of adequate dose and duration of medication treatment (at least 3 months of Paroxetine or Sertraline or other SSRI at dosages recommended in the package insert) or adequate duration of psychotherapy treatment (at least 12 sessions of psychotherapy) or any combination of these two categories.
3. Are at least 18 years old.
4. Are fluent in speaking and reading a recognized language of the study site.
5. Are able to swallow pills.
6. Agree to have study visits recorded, including Experimental Sessions and non-drug psychotherapy sessions.
7. Must provide a contact (relative, spouse, close friend or other support person) who is willing and able to be reached by the investigators in the event of a patient becoming suicidal or unreachable.

8. Must agree to inform the investigators within 48 hours of any medical conditions and procedures.

9. 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. Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, abstinence, oral, vaginal, or transdermal hormones plus a barrier contraception, vasectomized sole partner or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e. condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom). Not of childbearing potential is defined as permanent sterilization, postmenopausal, or assigned male at birth.

10. Agree to the following lifestyle modifications (described in more detail below under Lifestyle Modifications): 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 after each Experimental Session and be driven home on the following day, and commit to medication dosing, therapy, and study procedures.

11. May have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening within the past year to rule out significant underlying cardiovascular disease.

12. May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed.

13. May have a history of or current Diabetes Mellitus (Type 2), if the patient passes additional screening to rule out significant underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval of the site physician and Medical Monitor.

14. May have hypothyroidism if taking adequate and stable thyroid replacement medication.

15. May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.

4.2 Exclusion Criteria

Potential patients are ineligible to enroll in the protocol 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. Are pregnant or nursing, or able to bear children and are not practicing an effective means of birth control.
4.3 Lifestyle Modification

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

- Are willing to commit to medication dosing, psychotherapy sessions, follow-up sessions, completing evaluation instruments, and all necessary telephone contact.
- Agree to not participate in any other interventional clinical trials during the duration of this study.

Leading up to Experimental Sessions

- Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each Experimental Session.
- Refrain from the use of any psychoactive medication not approved by the study site team from Baseline through Study Termination.
- Agree not to use caffeine or nicotine for 2 hours before and at least 6 hours after the initial dose during each Experimental Session.
- Are willing to comply with medication requirements per protocol (refer to Section 12.0 Concomitant Medications). Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.
- Are able to decrease dose of allowable opiates (per Section 12.0 Concomitant Medications), if used for pain management, leading up to the Experimental Session in order to avoid taking the medication for at least 12 hours prior to the initial IMP administration and 24 hours after. During this period, the patient will be allowed to take the medication if needed for intolerable pain flare-ups.
- Agree that, for 1 week preceding each Experimental Session to refrain from taking any herbal supplement (except with prior approval of the study site team).
- Agree that, for 5 half-lives of the medication or active metabolite, to refrain from:
  - Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen unless with prior approval of the study site team).
  - Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the study site team).

Post Experimental Session

- Are willing to remain overnight at the study site after each Experimental Session until after the Integrative Session the next morning.
- Are willing to be driven home on the morning after each Experimental Session after the Integrative Session, either by a driver arranged by the participant, site personnel, or taxi.

5.0 Protocol Design

5.1 Study Design Overview

This multi-site, open-label, Expanded Access study under a Treatment IND will provide access to treatment to patients with treatment-resistant PTSD for whom it wasn’t possible to participate in Phase 3 studies. This study will provide supportive data on safety and tolerability of MDMA-assisted psychotherapy in treatment-resistant patients with PTSD. This study will be conducted at multiple Expanded Access study sites. There will be at least one, but usually more, co-therapy pairs at each study site. The sponsor’s Phase 3 co-therapy pairs can begin enrollment for this Expanded Access protocol only after they have met their individual Phase 3 enrollment requirements and completed treatment of their expected Phase 3 participants.
A flexible dose of MDMA, followed by a supplemental half-dose unless contraindicated, is administered during the Treatment Period with manualized psychotherapy in up to three open-label Experimental Sessions. During the Treatment Period, each Experimental Session is preceded by three 90-minute Preparatory Sessions and followed by three 90-minute Integrative Sessions of non-drug psychotherapy. Experimental Sessions will be followed by an overnight stay.

In the Phase 3 protocol the Experimental Sessions are scheduled roughly 3 to 5 weeks apart but in this Expanded Access protocol there could be longer times between the Experimental Sessions though all Experimental Sessions and associated non-drug psychotherapy sessions must be completed within 8 months.

For each patient, the study will consist of:

- **Screening Period**: phone screen, informed consent, eligibility assessment, and enrollment of eligible patients.
- **Preparatory Period with Enrollment Confirmation**: medication tapering, Preparatory Sessions and Baseline assessments.
- **Treatment Period**: Up to three Experimental Sessions and associated Integrative Sessions within 8 months.
- **Study Termination**: Completed after last integrative visit.
## Study Design Overview

### Screening Period
From Consent to Enrollment (Visit 0): Within 6 weeks

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Multiple visits/After phone screen/Before enrollment</td>
<td>At initial visit, obtain Informed Consent and assess all screening measures (including PCL-5, Lifetime C-SSRS, MINI), medical history, and pre-study medications. Contact outside providers and order medical records, physical exam, clinical labs, on site qualitative pregnancy and drug tests, ECG, and 1-minute rhythm strip. Once all results and records are obtained, review along with notes from all screening visits and measures. Results will be confirmed by clinical observation during the Preparatory Period. Screening may take place over multiple visits.</td>
</tr>
<tr>
<td>Enrollment</td>
<td>~0.5 hours by phone</td>
<td>Prior to enrolling: review all screening measures, medical history, discussion with outside providers, and any clarification phone calls with patient. Sponsor will provide eligibility review. Visit is 0.5 hours to inform patient of eligibility and medical tapering plan. If enrolled, begin taper, (5 half-lives plus 1 week for stabilization). Adverse Event (AE) collection begins.</td>
</tr>
</tbody>
</table>

### Preparatory Period
From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 3): 2 to 8 weeks

<table>
<thead>
<tr>
<th>Study Visit/Visit #</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory Session 1 (Visit 1)</td>
<td>1.5 hours/Within 2 weeks of V0</td>
<td>1.5-hour Preparatory Session. Target visit timing on tapering needs. If needed, schedule calls between V1 and V2 if indicated for tapering, safety, or further questions about medical history.</td>
</tr>
<tr>
<td>Preparatory Session 2 (Visit 2)</td>
<td>1.5 hours/Within 3 weeks of V1</td>
<td>1.5-hour Preparatory Session/ongoing assessment. If tapering is complete or not needed, check eligibility and schedule V3 and V4. If tapering is ongoing, schedule post taper call for ongoing assessment.</td>
</tr>
<tr>
<td>Phone Call End Taper</td>
<td>0.5 hour/Within 2 weeks of taper end</td>
<td>If needed, confirm medication taper and stabilization is complete and patient is eligible for dosing. Schedule V3 and V4.</td>
</tr>
<tr>
<td>Preparatory Session 3 (Visit 3)</td>
<td>2.5 hours: (~43 minutes of measures, 1.5 hours of therapy) Within 3 weeks of V2</td>
<td>Complete Baseline self-report measures. Complete 2.5-hour Preparatory Session (~43 minutes of measures, 1.5-hour therapy) and schedule V4.</td>
</tr>
</tbody>
</table>
# Treatment Period
From Experimental Session 1 (Visit 4) to Integrative Session 3.3 (Visit 15): Up to 32 weeks

<table>
<thead>
<tr>
<th>Study Visit/Visit #</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental Session 1 (Visit 4)</td>
<td>8 hours/After V3 and before V5</td>
<td>First Experimental Session lasts 8 hours with an overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 1.1 (Visit 5)</td>
<td>1.5 hours/Morning after V4</td>
<td>V5 is a 1.5-hour Integrative Session on the morning after V4. Followed by 4 phone check-ins over the 7 days post V4.</td>
</tr>
<tr>
<td>Integrative Session 1.2 (Visit 6)</td>
<td>1.5 hours/After V5 and before V7</td>
<td>V6 is a 1.5-hour Integrative Session.</td>
</tr>
<tr>
<td>Integrative Session 1.3 (Visit 7)</td>
<td>1.5 hours/After V6 and before V8</td>
<td>V7 is a 1.5-hour Integrative Session. Administer measures: Since Last Visit LEC-5, PCL-5, SDS, and C-SSRS.</td>
</tr>
<tr>
<td><strong>Treatment 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental Session 2 (Visit 8)</td>
<td>8 hours/At least 3 weeks after V4</td>
<td>Second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg with supplemental half-dose unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 2.1 (Visit 9)</td>
<td>1.5 hours/Morning after V8</td>
<td>V9 is a 1.5-hour Integrative Session the morning after V8. Followed by 4 phone check-ins over 7 days post V8.</td>
</tr>
<tr>
<td>Integrative Session 2.2 (Visit 10)</td>
<td>1.5 hours/After V9 and before V11</td>
<td>Approximately 2 weeks after V8, a 1.5-hour Integrative Session (V10) is completed.</td>
</tr>
<tr>
<td>Integrative Session 2.3 (Visit 11)</td>
<td>1.5 hours/After V10 and before V12</td>
<td>V11 is a 1.5-hour Integrative Session. Administer measures: Since Last Visit LEC-5, PCL-5, SDS, and C-SSRS.</td>
</tr>
<tr>
<td><strong>Treatment 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental Session 3 (Visit 12)</td>
<td>8 hours/At least 3 weeks after V8</td>
<td>Third Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.</td>
</tr>
<tr>
<td>Integrative Session 3.1 (Visit 13)</td>
<td>1.5 hours/Morning after V12</td>
<td>V13 is a 1.5-hour Integrative Session the morning after V12. Followed by 4 phone check-ins over 7 days post V12.</td>
</tr>
<tr>
<td>Integrative Session 3.2 (Visit 14)</td>
<td>1.5 hours/After V13 and before V15</td>
<td>Within 2 weeks after V12, a 1.5-hour Integrative Session (V14) is completed.</td>
</tr>
<tr>
<td>Integrative Session 3.3 (Visit 15)</td>
<td>1.5 hours/Within 8 months of V4</td>
<td>V15 is a 1.5-hour Integrative Session.</td>
</tr>
</tbody>
</table>

# Study Termination
From last visit until Study Termination (Visit 16): same day as last visit or up to 4 weeks after last visit.

<table>
<thead>
<tr>
<th>Study Visit/Visit #</th>
<th>Visit Duration/Visit Timing/(Scheduling Window)</th>
<th>Brief Description of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Termination</strong> (Visit 16)</td>
<td>1 hour/Same day as last Integrative Session (+4 weeks)</td>
<td>Administer measures: Since Last Visit LEC-5, PCL-5, SDS, and C-SSRS. Patient completes self-report measures. Create an exit plan for patient.</td>
</tr>
</tbody>
</table>
5.2 Planned Duration of Study

Patients enrolled in this study completing through Treatment 3 will have a treatment duration of up to 8 months.

The minimum time that a patient who completes all study visits from Screening to Study Termination (three Experimental Sessions) is 13 weeks, and the maximum is 50 weeks. Any delays between visits outside of the protocol-defined windows may result in a corresponding extension of study duration. These out of window visits will not be considered protocol deviations because this Expanded Access protocol is intended to be identical to MDMA-assisted psychotherapy in clinical practice.

5.3 Discontinuation and Completion Criteria

5.3.1 Evaluable Patients

A patient is considered “Evaluable” and eligible for the safety analysis if they have completed at least one Experimental Session.

A patient is considered to be in good standing with the study site if, in the opinion of the investigator and/or co-therapy pair, the patient 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 patients who pass phone 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 patients who begin Screening will be tracked on a Screening Log, and reasons for Screen Failure will be recorded. Screen Failures are not considered evaluable.

Screen Failures may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the patient. Medical assessments may be repeated for confirmation. At any time during Screening, if a potential patient is deemed to be ineligible, classify as a Screen Failure, notify the potential patient that they are not eligible for the study, and do not schedule additional Screening assessments. Patients who fail Screening may be rescreened at a later date if deemed appropriate by the investigator but should sign a new copy of the Informed Consent Form (ICF). Screen Failures may request a referral to an outside therapist if needed. Screen Failures that were scheduled for a screening visit will be entered into the Electronic Data Capture (EDC) system.

5.3.3 Pre-Dosing Early Termination

“Pre-Dosing Early Terminations” are defined as patients who were deemed eligible and enrolled in the study at Visit 0 but are deemed ineligible prior to the first Experimental Session and do not have enrollment confirmed at Visit 4. These patients may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to Enrollment Confirmation or the study site may withdraw the patient for reasons described in Section 5.3.4 Early Termination from the Study). All enrolled patients will be maintained in the EDC system. Pre-Dosing Early Terminations are not considered evaluable.
Pre-Dosing Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the patient. At any time during the Preparatory Period, if a potential patient is deemed to be ineligible, classify as a Pre-Dosing Early Termination, notify the potential patient that they are not eligible for the study, and do not schedule additional assessments or visits.

5.3.4 Early Termination from the Study

Patients who are removed from the study after they are enrolled and receive IMP but do not complete the study may fall into one of these categories: Post-Dosing Early Termination or Dropout. If the patient has received IMP in at least one Experimental Session, they will be considered evaluable for safety analyses.

Patients can withdraw from treatment or withdraw consent at any time for any reason without judgment. If a patient decides to discontinue treatment after an Experimental Session, integrative therapy sessions are recommended before the Study Termination visit is complete. The study site team can withdraw a patient if, in their clinical judgment, it is in the best interest of the patient or if the patient cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the study site team makes the decision to terminate the patient from treatment or the study, they will explain the reason for withdrawal and document in the patient’s source records and Electronic Case Report Form (eCRF). If a patient develops any Exclusion Criteria that, in the opinion of the Medical Monitor or study site team, affects the safety of the patient, including psychiatric diagnosis, pregnancy, or requiring use of prohibited medications, the patient will discontinue treatment in Experimental Sessions but remain in the study for the associated Integrative Sessions. Any time a patient terminates from the study early, the study site team will attempt to obtain information about AE outcomes if appropriate, as determined by the site physician and Medical Monitor. The study site team will provide the patient with an Exit Plan as described in Section 8.4.1 Exit Plan:

- **Post-Dosing Early Termination**: Patients who discontinue study treatment but continue to participate in non-drug psychotherapy and complete study measures. Data collection will proceed to Study Termination visit procedures.
- **Dropout**: If a patient decides to withdraw consent, they will terminate without further follow-up. If the patient agrees, they will complete Study Termination visit procedures. These patients 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 study site staff. Data collected on study patients 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.

5.3.5 Lost to Follow-up

A patient will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the study site staff. If the patient has received IMP in at least one Experimental Session, they will be considered evaluable for safety analyses.

If a patient does not attend a scheduled visit, the study site must attempt to contact the patient to reschedule the visit as soon as possible and emphasize the importance of complying with the protocol specified visit schedule. The staff should determine if the patient is willing to comply with future visits.
If a patient does not respond to this initial contact, the study site staff must make multiple efforts to contact the study patient and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 1 week, 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 and support person the patient provides should be contacted. Lastly, a certified letter (or equivalent) should be sent to their last known mailing address. If the patient fails to respond to all of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up.

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 patient in the study or last scheduled procedure.

The sponsor has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform patients and will ensure they receive appropriate therapy, follow-up, and Exit Plan. 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 Phase 2 studies sponsored by MAPS. Phase 2 studies indicate that 75, 100 and 125 mg MDMA initial doses with the supplemental dose are active and effective in two to three Experimental Sessions. MDMA doses with an optimal risk-benefit ratio range from 75 mg (Cohen’s $d$ Independent Groups Pre-test Post-test [dIGPP]=2.73, N=7) to 125 mg (Cohen’s $d$IGPP=0.77, N=58) initial dose of MDMA with a 2-session treatment package. In Phase 2 studies, the sponsor observed a -36.4 point mean change in CAPS-4 scores among active dose patients receiving two Experimental Sessions (N=72) compared to a -44.2 point mean change after three Experimental Sessions (N=51). Although uncontrolled, the additional 7.8 point mean reduction observed after three Experimental Sessions compared to two, along with the observed favorable safety profile formed the basis for selection of a 3-session treatment package. A flexible dosing regimen has been previously explored in Phase 2 studies, where patients 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 patients and co-therapy pairs administering this treatment in Phase 2 studies, this flexible dosing regimen and three Experimental Sessions produced an optimal treatment response. Larger doses have been safely administered 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.

This open-label study will examine the effects of a flexible dose of 80 mg to 120 mg MDMA administered in up to three Experimental Sessions. Initial doses per Experimental Session range from 80 mg to 120 mg MDMA compounded with Magnesium Stearate and Mannitol, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg). A flexible dosing regimen was 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 range from 80 mg to 180 mg.

### Table 1: Dose Regimen of MDMA

<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 or 120 mg</td>
<td>40 or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
<tr>
<td>3</td>
<td>80 or 120 mg</td>
<td>40 or 60 mg</td>
<td>80 mg to 180 mg</td>
</tr>
</tbody>
</table>

Total Cumulative Dose: 240 mg to 480 mg

In the first Experimental Session, the initial dose will be 80 mg MDMA. In the second and third Experimental Sessions, the initial dose may be increased to 120 mg MDMA unless contraindicated in the opinion of the study site team. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the study site team based on observed response, tolerability to the previously administered dose, and discussion with the patient. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the patient will be administered a supplemental half-dose unless contraindicated.

### 6.0 Psychotherapy

#### 6.1 Description of Therapeutic Method

The largely non-directive therapeutic method of MDMA-assisted psychotherapy is described in detail in the Treatment Manual. All co-therapy pairs will be extensively trained by the sponsor in a multi-week MDMA Therapy Training Program prior to the study to ensure all patients are treated in a similar manner. The non-directive approach pertains to inviting inquiry and providing suggestion rather than directing the patient in the therapeutic approach, which 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 patient’s spontaneous experience.

#### 6.2 Study Team Qualifications

The study team will consist of a co-therapy pair and Schedule I license holder who may or may not be one of the co-therapy pair. Each study site will have one or more designated site physicians who may or may not be a Schedule I license holder. Study sites must ensure that the minimum requirements below are met:

- Co-therapy pairs must complete the sponsor’s MDMA Therapy Training Program including clinical supervision.
- All Schedule I license holders and site physicians will have medical license in good standing and applicable DEA and state-controlled substance registrations.
- One person per co-therapy pair is required to be licensed to provide psychotherapy according to state and local requirements and should have doctoral-level (PH.D./M.D.-level, or equivalent) qualifications.
- The co-facilitator is required, at a minimum, to have a bachelor’s degree and be trained in mental health (including students in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments), or that they have completed 1000 hours of behavioral health experience prior to co-facilitating sessions as a part of a co-therapy pair.
- If one person on the co-therapy pair is unlicensed, they will work under the direct supervision of the licensed team member.
Investigator is not on the FDA debarment list.

The following licenses and certifications are current throughout the study:
  - Good Clinical Practices Certification
  - Columbian-Suicide Severity Rating Scale (C-SSRS) training certification
  - Basic Life Support (BLS) Certification for at least one of the co-therapist pairs
  - License to practice psychotherapy for the lead facilitator for each co-therapy pair

6.3 Training

6.3.1 MDMA Therapy Training Program

The sponsor’s MDMA Therapy Training Program is designed to teach competency in applying MDMA-assisted psychotherapy. Therapy team members will receive specific training in the MDMA-assisted psychotherapy method, protocol, and latest version of the IB. Training in the psychotherapy method consists of reading the Treatment Manual, completing an online training module, and participating in an in-person training program that includes watching and discussing videos of selected study visits which include psychotherapy. The required elements of the therapy are defined in the Treatment Manual of MDMA-assisted psychotherapy for treatment of PTSD. In addition to this specific training, it is required that participating therapy team members have the proper background, education, and experience.

All Expanded Access co-therapy pairs who have not previously completed clinical supervision requirements will be required to have clinical supervision during the treatment of at least one participant. These co-therapy pairs will be required to be cleared by the sponsor’s MDMA Therapy Training Program supervisors before treating any additional patients. Co-therapy pairs in the process of receiving clinical supervision may be required to record audio and video of all therapy sessions, both those conducted in-person and via video call. Co-therapy pairs must obtain written patient consent to record sessions and to use recordings for supervision. Recordings are handled appropriately and securely.

7.0 Measures

The following eligibility, exploratory, and safety measures will be used in the study, in accordance with the study protocol.

7.1 Screening Measures

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 [68], is now compatible with DSM-5 and will be administered by a trained study site staff to screen for Axis I psychiatric conditions per DSM-5. 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 [69]. 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 [69, 70] Testing on nonpsychiatric samples did not create false positives [68].
7.2 Safety Measures

C-SSRS (Columbia-Suicide Severity Rating Scale)
The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [66]. It consists of a Lifetime version and a Since Last Visit version that assess suicidal ideation, ideation intensity, and behavior. The C-SSRS consists of a series of questions, and can be administered during a face-to-face interview or over the telephone. The Lifetime version will only be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. Patients who are discontinuing medications to participate in the study will complete the C-SSRS before and after medication washout. 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 [67].

7.3 Exploratory Measures

ACE (Adverse Childhood Experiences Questionnaire)
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 [72]. 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 [73-76]. The scoring method has been used in archival research, finding an association between increased scores and health problems in several generations [75].

LEC-5 (Life Events Checklist for DSM-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 [71].

PCL-5 (PTSD Checklist)
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 [74]. 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).

BDI-II (Beck Depression Inventory II)
The BDI-II is a revision of the BDI, a 21-item self-report measure [77, 78] that will serve as a measure of depression symptom severity [79]. 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 [79]. 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 [79, 80]. Higher scores indicate more severe depressive symptoms.
CPGS (Chronic Pain Grade Scale)
The CPGS is a seven-item measure of pain. Responses to six of the seven items are made on a 10-point Likert scale, and a response on the other item is the number of days in the past 3 to 6 months when pain prevented the respondent from carrying out everyday activities [81]. Responses to questions are used to attain a rating (grade) for pain from 0 (no pain) to five (high disability, severely limiting). The instrument has three scale scores: pain severity, pain intensity, and pain-related disability. Estimated time to complete is 3 to 5 minutes. The CPGS is a validated scale with high internal consistency (Cronbach’s alpha = 0.90) and correlated with other instruments assessing pain [82].

EQ-5D-5L (EuroQol Five Dimensions - Five Levels Questionnaire)
The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions; mobility, self-care, usual activities, pain-discomfort and anxiety-depression, and one visual analog scale (VAS). Responses are made on each dimension by checking one of five statement that best reflects their health on the day of measure completion, from the healthiest or fewest problems (e.g., “I have no trouble walking about”) to the most trouble (e.g., “I am unable to walk about”) [83, 84]. In the second part of the EQ-5D-5L, current degree of health (“your health today”) is indicated by marking a 20 cm line marked form one to 100, with 100 considered “the best health you can imagine” and one “the worst health you can imagine.” The EQ-5D-5L does not sum responses, but treats each response on a dimension as a scale score, and the VAS is the location of the mark in centimeters. The scale can permit comparison across groups on health profiles, and an index can be derived from matching the five dimension scores and the VAS response with nation-specific datasets and calculator software or statistical software syntax designed for the measure. The EQ-5D-5L began as part of the EuroQoL measure, published in 1990 [85]. The instrument has been validated in populations from eight countries. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation [86]. The EQ-5D-5L takes about 3 minutes to complete.

AUDIT (Alcohol Use Disorders Identification Test)
The AUDIT is a ten-item self-report test. Respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) [87]. The ninth item addresses occurrence of injury of self or other as a result of drinking and the tenth addresses others’ concerns about the respondent’s drinking, with only three responses provided (0=No, 2=Yes, but not during the last year, 3=Yes, during the last year). The measure can readily detect alcohol abuse disorders in a wide array of individuals [88].

DUDIT (Drug Use Disorders Identification Test)
The DUDIT is an 11-item measure designed to assess presence of substance use disorders [89]. Responses to items are made on a 5-point scale with exact responses varying across questions. When present, use can be described in monthly or less than monthly versus four times a week or daily. A list of substances is provided at the end of the measure. The DUDIT is reliable, with a Cronbach’s alpha of 0.80. When compared with an interview based on ICD 10, the DUDIT had a sensitivity to detecting substance use disorders of 90% and a specificity of 80% [89]. The English translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.
SDS (Sheehan Disability Scale)
The SDS is a clinician-rated assessment of functional impairment [64]. The items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on an eleven-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely). The SDS takes 1 to 2 minutes to complete. The measure can be scored for each of the three domains. The SDS has high internal consistency and accurately identified 80% of a sample of primary care patients with mental disorders [65].

SRNU (Self-reported Nicotine Use)
The SRNU is a sponsor-developed measure that will assess patient’s use of nicotine, including approximate frequency of use in the last month and attitudes towards quitting. The measure will take less than 3 minutes to complete.

EAT-26 (Eating Attitudes Test)
The EAT-26 is a 26-item self-report measure that assesses attitudes about eating and food and is used to assess presence of eating disorders. Responses are made on a six-point scale (1=Always to 6=Never), and gathers information on gender, age, height, and weight. The EAT-26 produces a total score and can be used to generate a “referral score.” The 27th item addresses the occurrence and frequency of specific eating behaviors, such as binge eating. Estimated time to complete is 4 to 8 minutes. Items on the EAT-26 have high reliability coefficients (Cronbach alpha of 0.83 to 0.90) and has concurrent validity [90].

HPQSF (Health and Work Performance Absenteeism and Presenteeism Short Form)
The HPQSF is a short form of a larger measure of health and work performance that has selected items referring to absenteeism and work performance [91]. The larger measure was created by the WHO as part of the Global Burden of Disease initiative. It consists of eight questions selected from the larger Health and Work Performance Questionnaire, with one question containing five additional items. Items include questions concerning hours worked during an average week, number of whole and partial days missed during a 4-week period, and items that rate average coworker and self-work performance on a ten-point Likert scale (1=Worst performance to 10=Top performance). Hours spent in work over a 4-week period and over the last 7 days can be used to estimate absenteeism, and the HPQSF can also score presenteeism, a measure of actual performance in relation to possible performance. Self-reports on measure appear to match employer records of presence or absence [92], and the HPQSF appears to be reliable between one time point and another (reliability of 0.52) and is sensitive to change [91].

UFEC (Utilization of Facility-based and Emergent Care)
The UFEC is a sponsor-developed measure assessing patient health events, including hospitalization and use of healthcare facilities, including in-patient hospitalization, rehabilitation facilities and other health care facilities for a set period prior to study entry.

8.0 Study Procedures
All assessments must be performed by qualified study staff delegated these duties on the Site Responsibilities Log. The Clinical Research Associate (CRA) should be notified of any delays or deviations to study procedures and Medical Monitor consulted if necessary.
8.1 Screening Period

8.1.1 Initial Screening

Prospective patients will be pre-screened by telephone according to an Institutional Review Board (IRB)-approved script to ascertain if they meet basic eligibility criteria. All individuals who are pre-screened should be assigned a Screening Number and recorded on the Screening Log. Data from potential patients who do not pass telephone screening will not be entered in the eCRF but reason of ineligibility will be documented on the Screening Log. At any time during Screening, if a potential patient is deemed ineligible, they will be classified as a Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments.

If deemed potentially eligible, the potential patient will receive a copy of the ICF for review and invited to the study site for in-person screening. Medical and psychiatric records are required for the site physician to obtain a well-characterized medical history and assess eligibility.

Study site staff (preferably the co-therapy pair who would be treating this potential patient) will explain and obtain written informed consent using the IRB-approved ICF. Written consent must be obtained prior to performing any tests or evaluations for the study. Discussion about the ICF may take place over a video call or at the first in-person visit. If a patient fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

Screening will take place over multiple visits and will be completed in-person, via video call, 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.
- Medical Assessments, including labs, electrocardiogram (ECG), and physical exam.
- The trained study site staff will complete initial measures throughout screening.

The sponsor recommends the following order of assessments:

*Initial Eligibility*
Qualified study site staff will:

- Support the patient during completion of the LEC-5 with PCL-5 to confirm PTSD severity. Support is needed to ensure proper identification of the index trauma on the PCL-5. Symptom severity is assessed in relation to the index trauma.
- Administer the Lifetime C-SSRS to assess history of suicidal behavior and ideation.
- Trained study site staff will administer the MINI.
- Review past and current medications and adherence to prescriptions.
- Assess childbearing potential and discuss requirement for commitment to adequate birth control for the duration of the study. Perform urine pregnancy test for patients who are of childbearing potential.
- Perform a urine drug test.
- Direct patient to complete self-reported Screening measures.
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, potential patient will be provided with instructions (and appointments, if applicable) for a physical exam, laboratory assessments, an
electrocardiogram (ECG), and 1-minute rhythm strip. Some or all of these assessments may be at outside facilities.

**Medical Assessments**

The physical exam must be performed by a qualified physician and lab assessments must be completed at a designated lab. Medical assessments will include:

- Blood pressure, pulse, and body temperature measurement.
- Height and weight, which will be used to calculate Body Mass Index (BMI).
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities.
- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes, and cerebellar function).
- ECG and 1-minute rhythm strip.
- Clinical laboratory assessments, per Section 13.0 Clinical Laboratory Assessments. The clinical laboratory values will not be captured in the eCRF, but will be used to establish eligibility and will be kept with the patient’s source record. Clinically significant abnormal values will be captured as medical history.
- If there is evidence of 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 patient 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 patient 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 patient may be enrolled, if there are no other contraindications.

Additional visits (in person, by telephone, or via video call may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential patient.

Once all results are obtained, the study 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 patient permission as needed.

### 8.1.2 Enrollment

In advance of Visit 0, the study site team will review all notes from Screening visits, medical assessments, measures, notes, discussions, and medical records against eligibility criteria. The sponsor will also provide enrollment review. If the patient is eligible, medication tapering and concomitant medications dose adjustments will be discussed, if applicable. The site physician will consult the prescribing physician to initiate medication tapering for patients. For all details on concomitant medications, tapering, allowed, and prohibited medications refer to Section 12.0 Concomitant Medications.

At study onset at each study site, if a potential patient is eligible, the study site team will contact the Medical Monitor and send a summary of the medical history for approval to enroll the potential patient. After the Medical Monitor establishes confidence in the enrollment procedures
at each study site, the Medical Monitor will inform the study site that for future patients they need only contact the Medical Monitor if they have questions about further patients’ eligibility. If a patient is approved by the sponsor, the patient will be notified of enrollment at Visit 0 in-person, via video call, or by telephone. Medical history and medication information will be reviewed for completeness. A medication tapering plan will be discussed with the patient, if applicable. If agreeable, the patient will be enrolled in the study. Once enrolled, AE collection requirements begin (refer to Section 11.0 Safety).

8.2 Preparatory Period

Patients will undergo three Preparatory Sessions (Visits 1, 2, and 3) lasting approximately 90 minutes with the co-therapy pair prior to the first Experimental Session. The Preparatory Period will be initiated within 2 weeks of Visit 0 and last up to 8 weeks, depending on duration of medication tapering. The minimum time to complete the Preparatory Period is 2 weeks. In these visits, the co-therapy pair will work with the patient to prepare for MDMA-assisted psychotherapy, begin building therapeutic alliance, and promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts. Each Preparatory Session may be conducted at a mutually agreeable setting appropriate for therapy practices.

8.2.1 Preparatory Sessions 1 and 2

Preparatory Sessions during the Preparatory Period will focus on psychoeducation about PTSD, building safety for the therapeutic relationship, developing the therapeutic alliance, obtaining the background for the trauma, and preparing the patient for the first Experimental Session. Telephone calls may be scheduled between visits if indicated for tapering, safety, or any further questions about medical history.

- Preparatory Session 1 (Visit 1) will occur within 2 weeks of Visit 0. The visit timing should take into account appropriate times for monitoring medication tapering.
- Preparatory Session 2 (Visit 2) will occur within 3 weeks of Visit 0 and after Visit 1. The visit timing should take into account appropriate times for monitoring medication tapering.

If tapering is ongoing at Preparatory Session 2 (Visit 2), the study site team will schedule a telephone phone call after tapering and stabilization are complete to confirm that the patient is eligible to continue. If tapering is complete or not needed, the study site team will confirm eligibility and schedule Preparatory Session 3 (Visit 3) as soon as possible.

At each 90-minute psychoeducation and psychotherapy Preparatory Session, the co-therapy pair will:

- Record the therapy session.
- Inquire about any possible changes in health to ensure the patient continues to meet all eligibility requirements. Record AEs as described in Section 11.0 Safety.
- Inquire about concomitant medication use and adherence.
- 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 [93].

If a patient would like a companion present during or after the Experimental Session, a meeting between the co-therapy pair and that individual will be scheduled prior to the first Experimental Session. There must be mutual agreement between the patient and co-therapy pair concerning the presence of the companion.
During one of the Preparatory Sessions, if possible, the co-therapy pair will introduce the patient to the attendant who will remain with the patient during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress. The study site will make all attempts to have the same attendant for each Experimental Session for a given patient, but it is not guaranteed. Patient will be escorted to and from the study site after Experimental Sessions. The support person is not required to be the same as the escort for the patient. An escort who is responsible only for transportation need not meet with the co-therapy pair to perform that role.

At any time during the Preparatory Period, if a potential patient is deemed to be ineligible, the study site team will classify them as an Enrollment Confirmation Failure, notify the potential patient that they are unfortunately not eligible for the study, and not schedule additional assessments.

**8.2.2 Preparatory Session 3 & Enrollment Confirmation**

Prior to Preparatory Session 3 (Visit 3), the study site team will review the results of the screening measures and ensure that the patient continues to meet eligibility criteria. Visit 3 should be scheduled within 3 weeks of Preparatory Session 2 (Visit 2). Experimental Session 1 (Visit 4) should be scheduled as close to Visit 3 as possible, but not on the same day.

If the patient continues to be eligible for the study, enrollment will be confirmed (after approval from the Medical Monitor for the initial patients until confidence is established). If any requirements are not met before or during Visit 3, the patient will be considered a Pre-Dosing Early Termination.

For eligible patients at Visit 3, qualified study site staff will ensure at least 3 hours are scheduled for the visit and:

- **Perform urine pregnancy test for patients who are of childbearing potential.**
- **Perform urine drug test.**
- **Administer Since Last Visit C-SSRS to determine suicide risk.**
- **Actively support patient in the completion of self-reported measures:**
  - SDS
  - ACE
  - BDI-II
  - CPGS
  - EQ-5D-5L
  - SRNU
  - EAT-26
  - HPQSF
  - UFEC

Completion of the measures does not need to be recorded.
• Complete the third 90-minute Preparatory Session (as described in Section 8.2.1 Preparatory Sessions 1 and 2) with the purpose of confirming all enrollment is met and completing final preparation for the first Experimental Session.
• Remind the patients of lifestyle modifications, including fasting and refraining from using psychoactive or non-approved medications, pertinent prior to the Experimental Session per Section 4.3 Lifestyle Modifications.
• Schedule Visit 4.

8.3 Treatment Period

During the Treatment Period, which occurs over a duration of up to 8 months (Visits 4 to 15). Patients will complete up to 3 Experimental Sessions. Each treatment consists of an Experimental Session, an Integrative Session the morning after, a second Integrative Session, and a third Integrative Session. The Experimental Sessions will be scheduled at least 3 weeks apart.

8.3.1 Experimental Sessions

There will be up to three open-label Experimental Sessions (Visits 4, 8, 12). 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.

- Experimental Session 1 (Visit 4) will occur after Preparatory Session 3 (Visit 3) The first Experimental Session will include 80 mg of IMP followed by a supplemental half-dose 1.5 to 2 hours after the initial dose, unless contraindicated.
- Experimental Session 2 (Visit 8) will occur at least 3 weeks after Experimental Session 1 (Visit 4) and after Integrative Session 1.3 (Visit 7) is completed. A dose of 80 or 120 mg MDMA will be administered. A supplemental half-dose will be administered 1.5 to 2 hours after the initial dose, unless contraindicated.
- Experimental Session 3 (Visit 12) will occur at least 3 weeks after Experimental Session 2 (Visit 8) and after Integrative Session 2.3 (Visit 11) is completed. A dose of 80 or 120 mg MDMA will be administered. A supplemental half-dose will be administered 1.5 to 2 hours after the initial dose unless contraindicated.

<table>
<thead>
<tr>
<th>Table 2: Schedule of Procedures for Experimental Sessions</th>
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<tbody>
<tr>
<td>Approximate Time</td>
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Pre-IMP Administration

- On the day of the Experimental Session, the patient will arrive approximately 30 to 60 minutes prior to IMP administration.
- The study site team will ensure the patient has not used caffeine or nicotine 2 hours prior, and fasted for 10 hours prior to IMP administration and complied with all other requirements per Section 4.3 Lifestyle Modifications.
• The study site team will inquire about any possible changes in health to ensure the patient continues to meet all eligibility requirements and record AEs as described in Section 11.0 Safety.
• The study site team will instruct the patient that they will not be able to use caffeine or nicotine at least 6 hours after the IMP administration.
• The study site team will complete urine drug screen, pregnancy test, and concomitant medication review.
  a. 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 patient from the study, based on Medical Monitor review.
  b. A positive pregnancy screen is cause for withdrawal from the protocol.
• The co-therapy pair will administer Since Last Visit C-SSRS.
• The co-therapy pair will review procedures for the Experimental Session with the patient and discuss the patient’s goals, intentions, and concerns and some of the commonly experienced effects of MDMA. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the co-therapy pair in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the patient.
• If the patient 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.

During the Experimental Session

• At approximately 10:00 AM and after starting the audio and video recording, a qualified staff member will administer the initial dose of IMP. The patient will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided for the patient if they wish to use them. Whenever they wish, patients may speak to the co-therapy pair, who will provide guidance and support, as needed.
• After the first hour, if the patient has not spoken spontaneously, the co-therapy pair will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the co-therapy pair will support and encourage the patient in emotional processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.
• Patients will be provided and encouraged to drink electrolyte-containing fluids throughout the Experimental Sessions but will not be allowed to exceed three liters overall.
• If suicidal ideation arises during Experimental Sessions, the co-therapy pair will explore and process the thoughts and emotions involved, and take advantage of the opportunity to work therapeutically with the underlying experiences driving the suicidal ideation.
• Blood pressure, body temperature, and pulse will be measured approximately 1.5 to 2 hours after the initial dose, before the supplemental dose is administered.
• The site physician will be contacted with a brief description of how the session is progressing and the recent vital signs. The site physician will approve or deny the administration of the supplemental dose. If medical attention is needed, the site physician will provide further instruction or consult the Medical Monitor.
• A supplemental half-dose will be administered orally approximately 1.5 to 2 hours after the initial dose, unless contraindicated.
• Food will be provided during the latter part of the session.
• If there is an approved companion, that person may arrive as agreed upon but will wait in the waiting room until a member of the co-therapy pair brings them to the session room. Alternatively, the companion may arrive after the session has ended.

End of Experimental Session

• The co-therapy pair will administer Since Last Visit C-SSRS.
• The co-therapy pair 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 patient is alert, ambulatory, and emotionally stable, and the night attendant has arrived.
• A member of the co-therapy pair or site physician shall remain available to patients via 24-hour cellular phone for integration, as needed.

Overnight Stay

At the end of each Experimental Session, the co-therapy pair and site physician will assess the patient’s condition to determine if they are physically and emotionally stable. If a patient is deemed not psychologically stable at the end of the Experimental Session, they will remain under the care of their co-therapy pair. The co-therapy pair will continue to evaluate the patient to make further disposition recommendations depending on the patient’s psychological condition, which could include: continued observation, psychological support and/or psychopharmacologic interventions; or further evaluation for potential transfer as appropriate.

• Patients will remain overnight in an appropriately furnished room at the study site.
• With prior approval of the co-therapy pair, a companion may accompany the patient during the overnight stay.
• An attendant will check in periodically on the patient during the overnight stay, even if a companion is present. The attendant will monitor patient condition and will help patients 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 patient needs additional support, the attendant can contact a member of the co-therapy pair.
• One person from the co-therapy pair or the site Clinical Investigator will remain on-call overnight to attend to any medical or psychological issues that may come up for the patient following an Experimental Session.
• Patients 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.
• In the morning after the Integrative Visit, the patient will be escorted to the study site via car, rideshare, or public transportation, as patients are not allowed to drive within 24 hours of administration of MDMA.

Orienting the Night Attendant

In advance of the appropriate Experimental Session, the night attendant staying with the participant overnight will be required to meet with the participant in person. The night attendant will receive printed instructions, including contact information of the study physician, therapists, Principal Investigator, and Study Coordinator and what to do in the case of an emergency.

The night attendant will not provide psychotherapy to the participant. Minimal discussion is acceptable, but only if initiated by the participant. The night attendant should not interpret the
participant’s experience or act as therapist. The therapy team will discuss this explicitly with the
night attendant and include this information in the written instructions.

The main roles of the night attendant include:

- Ensuring the participant has a comfortable place to sleep and discuss the plan for wakeup,
  breakfast, and travel time for the next day’s Integrative Session.
- Seeing to the participant’s needs for food and liquids, including providing dinner and
  breakfast in accordance with the participant’s dietary preferences.
- Eating with the participant unless they ask to be left alone.
- Cleaning up after the participant, including doing the dishes and handling bedding
- Keeping all participant information confidential.
- Ensuring the participant is safely transported to and from the study site as appropriate
  (may be completed by a separate support person).
- Ensuring that the participant does not leave the overnight site without accompaniment
  and does not leave the participant alone at the overnight site. The participant may have
  privacy at the overnight site.
- Supervising the participant to ensure they do not consume drugs or alcohol on the night
  of the Experimental Session and that phone/computer time is limited.
- Remaining sober throughout the entire overnight stay.
- Remaining available to participant’s needs throughout the night, but may sleep if the
  participant is sleeping.

8.3.2 Telephone Contact After Experimental Sessions

The goal of the telephone contact is to assess health changes, ensure patient safety, and offer
support. One member of the co-therapy pair will follow-up with the patient by telephone on the
second and seventh day after each Experimental Session, with two additional telephone contacts
on Day 3, 4, 5, or 6 after the Experimental Session. Each call will last on average five to 15
minutes but could be longer to address patient concerns and to adequately assess wellbeing.
Additional telephone contact can be initiated at the request of the co-therapy pair or patient.

At each telephone contact, a member of the co-therapy pair will:

- Inquire about any possible changes in health, assess the patient’s mental health and the
  status of any previously recorded AEs, and record AEs as described in Section 11.0
  Safety.
- Inquire about concomitant medication use and adherence.
- Offer support in accordance with the Treatment Manual.
- On the second and seventh contact day after an Experimental Session the co-therapy pair
  will administer the Since Last Visit C-SSRS.
  Administer the C-SSRS as needed (i.e. on Day 3, 4, 5, or 6 after the Experimental
  session) during telephone contact if there are any concerns regarding suicidal ideation or
  behavior. If the C-SSRS reveals any current serious suicidal ideation (scores of four or
greater) or positive suicidal behavior (scores of one or greater) the patient will be referred
  for further management as described in Section 10.1.2.

<table>
<thead>
<tr>
<th>Table 3: Schedule of Telephone Calls After Experimental Sessions</th>
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<tr>
<td><strong>Days after Experimental Session</strong></td>
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<td>Day 2</td>
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8.3.3 Integrative Sessions

After each Experimental Session, three Integrative Sessions will take place. Each session will consist of 90 minutes of psychotherapy. Integrative Sessions that do not directly follow or precede an Experimental Session may be completed through a video call (i.e. Integrative Sessions 1.2, 2.2, and 3.2) if logistics require it, but visits should be in person whenever reasonably possible. All Integrative Sessions both in-person and over video call will be required to record audio and video. Patients completing Integrative Sessions over video call must be in a private location. Integrative visits may also be completed at a mutually agreeable location suitable for therapy practices.

**Integrative Session 1**
- Integrative Session 1.1 (Visit 5): morning after Experimental Session 1 (Visit 4)
- Integrative Session 1.2 (Visit 6): After Integrative Session 1.1 (Visit 5) and before Integrative Session 1.3 (Visit 7)
- Integrative Session 1.3 (Visit 7): After Integrative Session 1.2 (Visit 6) and before Experimental Session 2 (Visit 8). Visit 7 serves two purposes: to continue integration and to prepare for the next Experimental Session. The patient will be administered the C-SSRS to assess suicidality.

**Integrative Session 2**
- Integrative Session 2.1 (Visit 9): morning after Experimental Session 2 (Visit 8)
- Integrative Session 2.2 (Visit 10): After Integrative Session 2.1 (Visit 9) and before Integrative Session 2.3 (Visit 11)
- Integrative Session 2.3 (Visit 11): After Integrative Session 2.2 (Visit 10) and before Experimental Session 3 (Visit 12). Visit 11 serves two purposes: to continue integration and to prepare for the next Experimental Session. The patient will be administered the C-SSRS to assess suicidality.

**Integrative Session 3**
- Integrative Session 3.1 (Visit 13): morning after Experimental Session 3 (Visit 12)
- Integrative Session 3.2 (Visit 14): After Integrative Session 3.1 (Visit 13) and before Integrative Session 3.3 (Visit 15)
- Integrative Session 3.3 (Visit 15): After Integrative Session 3.2 (Visit 14) and within 8 months of Experimental Session 1 (Visit 4)

During Integrative Sessions, the co-therapy pair will:

- Record the session.
- Inquire about any possible changes in health. Assess the patient’s mental health and the status of any previously recorded AEs. Record AEs as described in Section 11.0 Safety.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- Discuss and review events that occurred with the patient during the Experimental Session, including thoughts, feelings, and memories. If necessary, the co-therapy pair will
help the patient to reduce any residual psychological distress they are experiencing. The co-therapy pair will also encourage the transfer of states of acceptances, feelings of intimacy, closeness, and reduced fear experienced in Experimental Sessions to emotionally threatening everyday situations. The co-therapy pair will be supportive, validate the experience, and facilitate understanding and emotional clearing.

- Be accessible for additional support via phone or video call if needed.

**8.4 Study Termination**

The patient will complete Study Termination (Visit 16) after the last Integrative Session regardless of the number of Experimental Sessions they have completed. Patients may complete Study Termination on the same day as the last Integrative Session or up to 4 weeks later. Self-report and safety measures will be completed. Patients may complete Study Termination (Visit 16) over video call or in-person at a mutually agreeable location suitable for therapy practices.

Patients that have withdrawn from treatment after Experimental Session 1 (Visit 4) but prior to Integrative Session 3.3 (Visit 15) will still be asked to complete the self-report and safety measures during their Study Termination.

The study site team will:

- Inquire about any possible changes in health. Assess the patient’s mental health and the status of any previously recorded AEs. Record AEs as described in Section 11.0 Safety.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS.
- Measure weight (used to calculate BMI).
- Measure blood pressure.
- Provide and discuss a study exit plan.
- Review contact information and Informed Consent procedures for any additional needed communications with the co-therapy pair.
- Actively support patient in completion of Study Termination self-reported measures:
  - SDS
  - LEC-5
  - PCL-5
  - BDI-II
  - CPGS
  - EQ-5D-5L
  - AUDIT
  - DUDIT
  - SRNU
  - EAT-26
  - HPQSF
  - UFEC

Completion of the measures do not need to be recorded.

After all Study Termination measures and assessments are completed, the patient is considered terminated from the study. The patient may resume normal everyday life. A referral for additional medical or therapeutic care may be provided in the Exit Plan, as described in Section 8.4.1 Exit Plan.
8.4.1 Exit Plan

At Study Termination, patients will be provided with an Exit Plan. This Exit Plan will summarize treatments completed, current medications, and contact information for more information about the study if needed. Patients may request a referral for further therapeutic or medical care if appropriate. Enrolled patients who terminate the study early will be provided an Exit Plan at their last contact. Screen Failures will be provided a referral if requested.

9.0 Investigational Medicinal Product

9.1 Description of Active Compounds

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA HCl (referred to as MDMA throughout). 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. Magnesium Stearate and Mannitol will serve as an inactive excipients.

9.1.1 Doses

This study will provide expanded access to MDMA-assisted psychotherapy and supportive data on safety and tolerability with up to three open-label, manualized Experimental Sessions of psychotherapy assisted by flexible doses of MDMA. Initial doses per Experimental Session include 80 mg or 120 mg MDMA compounded with Magnesium Stearate and Mannitol, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg). Total amounts of MDMA to be administered per Experimental Session range from 80 mg to 180 mg. Each patient will have a total allowance of up to 480 mg MDMA split between three Experimental Sessions. Refer to Table 2: Dose Regimen of MDMA.

9.1.2 Dose Modification

In the first Experimental Session, the initial dose will be 80 mg MDMA. In the second and third Experimental Sessions, the initial dose may be increased to 120 mg MDMA unless contraindicated. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the co-therapy pair in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the patient. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the patient will be administered a supplemental half-dose unless contraindicated.

9.1.3 Stability

IMP will be manufactured and packaged according to Good Manufacturing Practices (GMP). Stability studies for the IMP will be ongoing during the course 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
All labels will comply with local, state, and federal regulations. Each package will be labeled with a unique container number, protocol number, IMP name, lot number, sponsor name and contact information, dosage form, route and directions for administration, storage conditions. Experimental Session number and a statement that the IMP is restricted to clinical trial use only will be labeled on each package.

Each package will be an open-label bottle that will be used as bulk presentation at each Expanded Access study site. Each dose of MDMA can be dispensed by the Schedule 1 license holder or designee. Additional doses of MDMA that are not administered to a patient, will be kept in the open-label bottles for administration in future sessions or to other patients.

9.2.2 Accountability

Forms will be provided to track IMP accountability and administration throughout the study. Open-label IMP accountability and administration logs will be reviewed by the sponsor. MDMA will be accounted for per capsule dispensed, based on the doses to be administered at each Experimental Session for any given patient.

IMP will be handled in accordance with all local, state, and federal regulations and forms pertaining to the use of schedule I controlled substances, and forms 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 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, and local regulations.

9.2.4 Administration

IMP 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 study 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 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 study site. All administered doses will be recorded for IMP accountability. The IMP will be stored securely per regulations.
9.3 Patient Numbering

Every potential patient who is prescreened by telephone according to the IRB-approved script will be assigned a seven-character alphanumeric Screening Number and recorded on the Screening Log. This number will begin with ‘S2’ to identify that it is a Screening Number. The next two digits represent the study site number (e.g., ‘11’), followed by a three-digit screening identifier starting with ‘201’. The screening identifier will be assigned to each prescreened patient at a study site sequentially. For example, the first Screening Number at Site 11 will be S211201 and first Screening Number at Site 12 will be S212201.

Each patient who passes Screening and is enrolled in the trial at Visit 0 will be assigned a seven-digit Patient Number. The first digits will be ‘32’. The next two digits represent the study site number (e.g., ‘12’), followed by a three-digit patient identifier starting with ‘001’. The patient identifier will be assigned to each enrolled patient at a study site sequentially. For example, the first Patient Number at Site 12 will be 3212001.

Eligible patients will be enrolled in the study and sequentially assigned an identification number. All patients will also be assigned a unique patient identifier within the database for use in analysis.

10.0 Risks

10.1 Non-drug Related Risks

10.1.1 Medical Assessments

In preparation for MDMA-assisted psychotherapy sessions, blood draws and a full medical examination, including a physical examination, ECG, 1-minute rhythm strip, and laboratory tests, are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

10.1.2 PTSD, Suicide Risk, and Psychotherapy

During Screening, throughout MDMA-assisted psychotherapy, and during assessment of study measures, patients will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress and exacerbate suicidal ideation during and immediately after psychotherapy sessions. Psychotherapy is conducted as part of this study, and people 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. The co-therapy pairs will provide emotional support to patients during any psychological distress.

The co-therapy pair will minimize risks by carefully evaluating all patients to determine if there is a current risk of suicidal behavior. Patients with a history of suicide attempts will not be excluded unless significant risk of suicidal ideation and/or behavior is detected, per Exclusion Criteria
described in Section 4.2. Patients will be enrolled according to the Eligibility Criteria based on
the clinical judgment of the site physician, co-therapy pair, and Medical Monitor.

If suicidal ideation arises during Experimental Sessions, any safety risk will be managed because
the co-therapy pair will be present, and the participant will be under continuous observation. The
approach to suicidal ideation during Experimental Sessions will be to explore and process the
thoughts and emotions involved, and to take advantage of the opportunity to work therapeutically
with the underlying experiences driving the suicidal ideation.

A qualified individual at the study site will administer the C-SSRS as defined by the study
protocol, and as needed depending on clinical presentation of the patients, to monitor for
development and intensity of suicidal ideation and/or behavior. The co-therapy pair will
implement the following plan to assess elevated or imminent suicide risk.

If the Since Last Visit C-SSRS reveals current serious Suicidal Ideation (scores of 4 or greater),
indicating risk at the time of the assessment, or positive Suicidal Behavior, the patient will be
referred for further management as described below:

1. If the patient has current suicidal ideation, but no specific plan to commit suicide
   (Suicidal Ideation Score=4), the individual administering the C-SSRS will ensure:
   a. The patient is evaluated by the investigator and/or site physician to determine an
      appropriate course of action. Findings will be discussed with the patient and their
      personal therapist, if applicable.
   b. Regular check-ins via phone or in-person will be continued until the patient has
      stabilized or a new course of action is taken based on changes in C-SSRS score
      and/or ongoing clinical assessment.
   c. Notification of the sponsor within 24 hours of this event and provide a narrative
      for the AE for expedited reporting to FDA. Increases in suicidality will be
      captured as an Adverse Event of Special Interest (AESI) per Section 11.1.1 and
      evaluated for seriousness. SAEs will be reported per regulatory guidance.
   d. Treatment would be continued when deemed appropriate by the investigator and
      Medical Monitor, unless it is determined that treatment should be discontinued,
      in which case the patient will enter follow-up.

2. If the patient has suicidal ideation, and a plan to commit suicide (Suicidal Ideation
   Score=5) or positive Suicidal Behavior, the individual administering the C-SSRS will
   assess whether the risk is imminent. A Suicidal Ideation score of 5 does not necessarily
   indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and
   deterrents are strong. If there is no imminent risk, the individual will follow the procedure
   described above. If there is imminent risk of suicidal behavior, the individual will ensure:
   a. Patients are evaluated by the investigator or site physician to determine an
      appropriate course of action, and a member of the co-therapy pair will contact the
      patient’s personal therapist, if there is one, who may be invited to come to the
      study site to assist, depending on their location.
   b. If it is determined that the patient is at imminent risk of suicide, the co-therapy
      pair will do one of the following:
      i. Escort the patient to the Emergency Department (ED)
      ii. Escort the patient to an appropriate mental health services facility (e.g.,
          hospital psychiatric unit)
      iii. Call Emergency Medical Services (EMS) and ensure that the patient is
           transferred to the responding medical personnel.
   c. If the patient will not comply and wishes to leave without consultation, call EMS.
      Explain that the patient is in immediate danger of committing suicide. Provide a
complete description of the patient and give any other needed details to ensure the patient’s safety.

d. Notification of appropriate members of the study site team and sponsor representatives within 24 hours, provide a narrative for the AE, for expedited reporting to FDA.

e. The event will be collected as an AESI per Section 11.1.1 and seriousness will be evaluated. SAEs will be reported per regulatory guidance.

f. Treatment would be continued when deemed appropriate by the investigator and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the patient will enter follow-up.

10.1.3 Recorded Content

All psychotherapy sessions may be recorded for research and training purposes. Any co-therapy pair member that has not fully treated a patient with MDMA-assisted psychotherapy will be required to undergo clinical supervision for their first patient in Expanded Access. Recordings of all sessions of a co-therapy pair’s first treated patient is required by the MDMA Therapy Training Team to accurately provide feedback about therapeutic techniques. Co-therapy pairs that have completed clinical supervision may also record all therapy sessions to continue development of the therapy methods and training materials. Any requests for use of audio and/or video, outside of research and training requests, will result in patients receiving information on the request. They will have control over any presentation of this material beyond viewing by researchers, training participants, sponsor personnel, or regulatory agencies.

Patients may feel uncomfortable with having audio and video of their sessions recorded and are allowed to request the recording be stopped if they would like to discuss sensitive information they do not want recorded. The co-therapy pair may ask the patient if they are comfortable with the audio and video recording being turned back on once the sensitive information has been discussed.

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 patient will be notified, and all efforts will be made to minimize the dissemination of recorded content (See Section 15.3).

10.2 Risks of Receiving MDMA

Study procedures and eligibility criteria have been developed based on Phase 2 clinical trials to exclude potential patients with pre-existing exclusionary medical conditions that would exacerbate risk. The co-therapy pairs and site physicians will be available via mobile phone throughout the study if any problem occurs when a patient is not at the study 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 patient themselves at the study site, have a member of the co-therapy pair call EMS to transport the patient to the ED, or instruct a member of the co-therapy pair to take the patient to the ED.

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).
10.2.1 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.

10.2.2 Medium 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.

10.2.2.1 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. Patients 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 patients with controlled hypertension is ongoing.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in Section 4.2 Exclusion Criteria. Before and after IMP administration in Experimental Sessions, the co-therapy pair will monitor vital signs. The co-therapy pair will attend to clinical signs and symptoms during Experimental Sessions, such as chest pain, shortness of breath, neurological deficit or confusion, and other potential indicators of end organ effects of hypertension that prompt additional vital sign measurements, and intervene if appropriate. The co-therapy pair will notify the site physician for evaluation if this occurs. If any patient 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, for rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). If a patient experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, they will be given 0.4 mg of sublingual nitroglycerin every 5 minutes as needed for chest pain pending transport to the hospital. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [94, 95].

If further evaluation at the hospital reveals that the patient has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [96]. Any patient who experiences such medical complications during an Experimental Session will not be given another Experimental Session, unless it is approved by the investigator, site physician, and the Medical Monitor.
As the characterization of QT effects for the API is ongoing, QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event. If at any time a patient develops a QT/QTc interval >500 ms or of >60 ms over Baseline during ECG evaluation, the patient will be discontinued from treatment.

10.2.2.2 Psychological Risk and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [50, 97]. 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 patients 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 co-therapy pair, with occasional use of benzodiazepines for anxiety. In this study, patients 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 patients 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 patients during the week after the Experimental Session.
- Integrative Sessions.
- Overnight stays at the study site or another appropriate location nearby for the night of each Experimental Session. Qualified personnel will be available during the overnight stay to respond to the needs of the patient. Attendants will be instructed to contact a member of the co-therapy pair upon request or at the appearance of signs of a potential Serious Adverse Event.

During the Preparatory Sessions, patients 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 patients 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 co-therapy pair and performance of diaphragmatic breathing by patients.

If the patient 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 co-therapy pair will remain with the patient for at least 2 more hours. During this time, the member of the co-therapy pair will employ affect management techniques, will talk with the patient to help them gain cognitive perspective of their experiences, and will help the patient implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the patient 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 co-therapy pair 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 a member of the co-therapy pair will stay with the patient until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The co-therapy pair will then meet with the patient daily until the period of destabilization has passed.

2. If the patient experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, a licensed member of the co-therapy pair or the site physician may prescribe a benzodiazepine (specifically, lorazepam) and/or sleep aid (e.g., zolpidem). This medication will be captured on the Concomitant Medications eCRF. The site physician should not prescribe an SSRI, SNRI, or monoamine oxidase inhibitor (MAOI) in this context, unless it has been determined that the patient will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the co-therapy pair.

3. If a patient should become psychotic, arrangements will be made to stabilize them or transfer them to the ED if hospitalization is necessary. Any patient 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 patient’s emotional status.

For those patients engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the patient’s outside therapist(s) will be involved in the management of any psychiatric complications. For those patients engaged in an ongoing psychotherapeutic relationship with the investigator or member of the co-therapy pair, the management of any psychiatric complications will be undertaken by them in their capacity as the patient’s therapist.

10.2.3 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.

10.2.3.1 Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [97]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 studies, it was found that compared to placebo, a higher percentage of patients 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 a patient’s temperature rises more than 1° C or the patient 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 patient. 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.
10.2.3.2 Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. Patients 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 a patient 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.

10.2.3.3 Genotoxicity Risk and Mitigation

To reduce the risk of metabolic activation and formation of nitroso-derivatives of MDMA due to interactions with nitrates or nitrites in food, patients are required to have fasted (no intake other than alcohol-free liquids) for 10 hours prior to IMP administration at Experimental Sessions.

10.2.3.4 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 [98, 99].

Pregnant and nursing people will be excluded from participation in the study. Patients who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session and must agree to use adequate birth control for the duration of the study during the Treatment Period. Procedures described in Section 11.3 Pregnancy have been put in place to mitigate risk of reproductive or developmental exposure to the IMP.

Paternal drug exposure studies show that exposure to MDMA was not a factor in adverse pregnancy outcomes, so partners of participants who were assigned male at birth will not be required to practice birth control. Due to the limited number of single-dose exposures being studied in this trial, the chance of birth defects are low.

10.2.4 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.

10.2.4.1 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.
10.2.4.2 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [100]. 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 [101]. 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.

10.2.4.3 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 patients treated with MDMA-assisted psychotherapy in a controlled clinical setting, 29.9% (32 of 107) of patients had tried Ecstasy at least 6 months prior to enrollment, with U.S. samples demonstrating a higher prevalence of use than international studies. Patients reported using Ecstasy an average of 2.3 (SD:1.43) times. Due to the known association of substance abuse 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 studies, 7.6% of patients (seven of 92) reported “Ecstasy” use, with five patients indicating single and not repeated use and two patients indicating two uses. Six of these seven patients had used Ecstasy prior to study participation. Of these patients, most were attempting to recreate a therapeutic experience, and none indicated 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 patients did not seek out MDMA or Ecstasy after taking part in the study [61]. In addition to data on Ecstasy use at follow-up, AEs were reviewed across Phase 2 studies, 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 patient 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 Section 11.1.1 for AESI terms.

Within-patient elevation in self-reported Ecstasy use post-treatment will be clinically assessed for signals of abuse and will be monitored during Expanded Access.
11.0 Safety

11.1 Adverse Events

An Adverse Event (AE) is defined as any medical occurrence in a patient, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the patient’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 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 co-therapy pairs will collect AEs during study visits from Enrollment (Visit 0) through Study Termination (Visit 16). Patients 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 study site staff should follow-up with the patient.

All AEs will be monitored by the co-therapy pair until resolution or, if the AE becomes chronic, a cause can be identified. If an AE is unresolved when a patient 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 each AE to the IMP will be determined via analysis and the opinion of the investigator will not be collected, with the exception of SAEs.

11.1.1 Adverse Events of Special Interest

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 in the opinion of the investigator. 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 of MDMA will be collected and coded as AESIs in the eCRF.
- Cases of noncompliance, protocol violations, patients lost to follow-up, and any other reasons why patients 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 a Serious Adverse Event (SAE) or it involves suicide risk, it should be reported to the sponsor with a narrative via the eCRF within 24 hours of the study site’s awareness of the event.

### 11.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the patient 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 patient 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 patient 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 from enrollment through Study Termination. All SAEs which occur during the course of the trial, whether considered to be associated with IMP or not, must be
reported to the sponsor within 24 hours of the study site staff’s awareness of occurrence. Reporting procedures will be provided to the study 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 patient to continue treatment or enter follow-up.

11.2 Other Significant Events

Significant life events that may occur during the course of the study, including death of a loved one, loss of employment, or other hardship, may have an impact on treatment outcome. The sponsor will capture these life events using the Since Last Visit LEC-5 measure. Such events will be entered as Comments in the eCRF and if appropriate, described in the Case Study Report for data outliers, if any.

11.3 Pregnancy

11.3.1 Definition of Childbearing Potential

A patient is considered of childbearing potential if they were assigned female at birth and are post-menarche. A patient is considered not of childbearing potential if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male at birth.

11.3.2 Contraception Guidelines

Adequate birth control methods are required for patients of childbearing potential and include:

- Intruterine 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
  - The reliability of abstinence should be evaluated carefully with the patient in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the patient in case they decide to engage in penile-vaginal intercourse during the course of the study.

Study participants who were assigned male at birth with partners of childbearing potential will not be required to practice birth control. For questions about acceptable birth control methods, contact the Medical Monitor.

11.3.3 Follow-up Requirements

Details of all pregnancies in study patients 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 study site staff awareness.

In the event of a pregnancy, the patient will discontinue Experimental Sessions but may continue with non-drug Integrative Sessions, the next PCL-5 assessment, and Study Termination.
procedures. At a minimum, prior to withdrawal from the study, efforts should be made to assess the final PCL-5 immediately and complete Study Termination procedures.

The investigator will collect follow-up information on the patient 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.

11.4 Medical Monitor

The name and contact information for the Medical Monitor is:

    Michael C. Mithoefer
    Alia Lilienstein

Medical Monitor contact information will be provided in a separate contact list.

12.0 Concomitant Medications

12.1 Tapering Instructions

The site physician will record concomitant medications during Screening. If the prospective patient is being treated with psychiatric medications at enrollment, the prospective patient 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. The medications will then be tapered in an appropriate fashion to avoid withdrawal effects, and discontinued at least five half-lives plus one additional week for stabilization before the first Experimental Session to avoid the possibility of any interaction. Additionally, patients who are taking prohibited opiates will be cross-tapered to an allowable opiate (hydrocodone, morphine, and codeine) under the care of their prescribing physician.

The site physician will consult the prescribing physician to initiate medication tapering for patients, as they must refrain from taking psychiatric medications throughout the study, with some exceptions (see Section 12.2 Allowable Concomitant Medications). The prescribing physician’s opinion about medication discontinuation will 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 scheduled to occur after complete washout (five half-lives plus at least 1 week for stabilization).

The co-therapy pair 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 site team will also inquire about concomitant medication adherence and document all information on the Concomitant Medications eCRF.
Patients may return to taking psychiatric medications and discontinue birth control after the final Study Termination visit if necessary.

12.2 Allowed Concomitant Medications

The site physician may prescribe necessary and appropriate medications in accordance with local and state regulations during the study to treat AEs that do not respond to other management outlined in the Treatment Manual. Examples include concomitant benzodiazepines for uncontrolled anxiety (specifically, lorazepam at modest doses and occasional use only to avoid withdrawal effects of discontinuation between Experimental Sessions) or sleep aids (excluding trazodone) in compliance with Section 12.3 Prohibited Medications. Sublingual nitroglycerin will be available on site in the case of emergency.

Gabapentin or certain opiates will be allowed when prescribed for pain management. The following opiates will be allowed during the study: hydrocodone, morphine, and codeine. Prior to receiving Investigational Product, patients who are taking opiates not included on this list will be cross-tapered to an allowable opiate under the care of their prescribing physician. Opiate medications may reduce the efficacy of MDMA and may prolong QT/QTc interval, but the opiates that are allowed during this trial have been selected because they have the lowest potential for QT/QTc interval prolongation and minimal serotonergic effects. Individuals using opiates for pain management will be asked to decrease the dose leading up to the Experimental Session in order to avoid withdrawal effects when they are required to refrain from taking the medication from 12 hours before IMP administration at the Experimental Session to 24 hours after. If a patient reports lack of analgesic effect during the sub-acute period following each Experimental Session, the site physician may cross-taper to a different allowed opiate medication.

If the patient is on stimulants for attention deficit/hyperactivity disorder (ADHD) at Baseline, they can continue to use them at the same dose and frequency, as long as they discontinue five half-lives before each Experimental Session and do not restart for 10 days after each Experimental Session.

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

12.3 Prohibited Medications

To be enrolled in the study, patients must:

- Refrain from the use of any psychoactive medication not approved by the study site team from Baseline through Study Termination (with the exception of gabapentin or certain opiates 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 to refrain from:
  - Taking any specified herbal supplement (except with prior approval of the study site team).
• Agree that, for 5 half-lives of the medication preceding each Experimental Session, they will refrain from:
  o Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) unless with prior approval of the study site team.
  o Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the study site team).

If an SSRI, SNRI, MAOI or medications with MAOI effects, or other antidepressant is used between Experimental Session 1 (Visit 4) and Study Termination (Visit 16), the patient will be withdrawn from treatment.

Opiates other than hydrocodone, morphine, and codeine are prohibited from Enrollment Confirmation to Study Termination. Patients taking prohibited opiates will be cross-tapered to an allowable opiate during the Preparatory Period.

13.0 Clinical Laboratory Assessments

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 patients are eligible for the protocol and will indicate justification for admitting patients 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
  o Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)
  o Albumin:globulin (A:G) ratio
  o Albumin, serum
  o Alkaline phosphatase, serum
  o Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT)
  o Bilirubin, total
  o Blood urea nitrogen (BUN):creatinine ratio
  o Calcium, serum
  o Carbon dioxide
  o Chloride, serum
  o Creatinine, serum
  o Globulin, total
  o Glucose, serum
  o Potassium, serum
  o Protein, total, serum
  o Sodium, serum

• 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

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

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

- HCV if indicated
- HIV serology
- %Carbohydrate deficient transferrin (%CDT) to detect heavy alcohol use
- Urine-dip pregnancy test for individuals of childbearing potential will be performed at the study site
- Urinary drug test will be performed at the study site

Laboratory assessments, with the exception of urine pregnancy and drug tests, will be performed at the nearest clinical laboratory to the study site or a clinical laboratory chosen by the patient. Clinical laboratories for each study site will be specified in a separate document. Certificates and normal ranges will be stored in the study site’s Investigator Site File (ISF).

### 14.0 Study Governance

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

### 14.1 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 US Code of Federal Regulations Title 21) 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) 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.

14.1.1 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. The sponsor will submit necessary disclosures to the appropriate regulatory bodies.

14.1.2 Informed Consent

The investigator and co-therapy pair are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the patient into the trial. Potential patients may be sent the ICF to review after the initial phone screen. Preferably, informed consent will be obtained by the co-therapy pair that will treat the patient. 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, or local regulations. The patient should have the opportunity to inquire about details of the study and to consider participation.

The co-therapy pair may meet with the potential patient via video call for ICF review and signing prior to in person screening if necessary for scheduling of screening activities. If this is completed by video call, the co-therapy pair will ensure the ICF is thoroughly explained and reviewed just as it would be at an in-person visit. If the potential patient is still interested after review, they will sign the consent during that video call. The patient 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 patient and file the original at the study site.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. A written release is needed to give permission to study site staff to request and view the patient’s medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible patients 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 patient’s source records. The study staff will provide a copy of the signed ICF to the patient and will maintain the original in the ISF.

The written ICF and any other written information to be provided to patients should be revised whenever important new information becomes available that may be relevant to the patient’s consent. Any revised ICF and written information should receive approval from an IRB before use. The patient 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. Patients can withdraw consent at any time without prejudice. If a patient withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the study site team will have full access to their medical records, including termination visit information. If a patient revokes only the HIPAA authorization, the study site team will have full access to all medical records prior to the date and time of revocation.
If a patient fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

14.2 Study Monitoring, Auditing, and Documentation

Investigators, co-therapy pairs, and all study site staff will be trained prior to study start at each site. Study sites will be centrally monitored using the EDC system and telephone or video calls by representatives of the sponsor. Source Data Verification will be conducted during at least one study site monitoring visit 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 patient enrolled within the EDC system. Self-reported exploratory measures will not be monitored as patients will provide these data through Electronic Patient Reported Outcome (ePRO) directly into the EDC system. Designated study site staff will be responsible for data entry of the safety measures into the associated eCRFs.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, eCRFs, and other protocol documentation for on-site audit or inspection. Monitoring and auditing procedures will be supplied in a separate document.

14.2.1 Source Records

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

14.3 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of patients. Despite this, privacy cannot be guaranteed. Removing identifying information from data and restricting access to researchers directly involved in assessing the patients should prevent the dissemination of confidential data. Except for the Screening Log, the Informed Consent, previous medical records, emails with the patient, and a Contact Information Sheet that will be stored separately from other documents, all source data will be identified only by the patient’s initials and subject identifier (SUBJID). If past medical records are needed, patients will sign forms for the release of information upon consent to permit screening for protocol enrollment. 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 patients 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 patient privacy. Electronic data is securely transferred to remote servers. Clinical trial data other than audiovisual recordings will be hosted on an EDC system that is FDA-compliant. All data entered into this system will be de-identified. Patients will only be referred to by numbers and a secondary identifier code. Source Records will be retained at study sites per GCP. The sponsor will train the study site staff on EDC procedures. Each study site staff member with access to the data will be given an individual password.
The sponsor has developed a feature that will allow patients to create a password and enter their self-report questionnaire data directly into the EDC system using the ePRO feature. Patients will be reminded by email to enter the data. Patient emails will be treated as Protected Health Information (PHI) in the database. Patients will receive a welcome email and reminder emails to ensure that they provide all necessary data.

Audiovisual recordings are necessary for sponsor oversight of therapy processes and to develop training materials to support the MDMA Therapy Training Program. 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 patient will be notified, and all efforts will be made to minimize the dissemination of recorded content.

Medical records, the consent form, data resulting from this study, and audiovisual records which identify the patient may be looked at and/or copied for research or regulatory purposes. These records may be reviewed by:

- The sponsor, affiliated companies, and the people they hire
- Researchers who cooperate with the sponsor to conduct further research
- People who conduct therapy trainings on behalf of the sponsor
- The FDA and similar regulatory agencies in other countries
- Governmental agencies in other countries
- The IRB

Any requests for use of audiovisual recordings outside of research and training requests will result in patients receiving information on the request. Patients will have control over any presentation of audiovisual recordings beyond viewing by authorized researchers, sponsor staff, or regulatory agencies.

14.4 Costs to Patients

Expanded Access patients will be covering all costs for MDMA-assisted psychotherapy treatment, including the cost of MDMA and psychotherapy. The Expanded Access study sites will function as a third-party payer to the sponsor for MDMA. The third-party payer may request reimbursement for MDMA from the patient. Proposal of cost recovery will be submitted to FDA for authorization prior to charging the third-party payer.

Expanded Access study sites may bill patients for subsequent costs incurred including psychotherapy, equipment costs, and costs for study-related procedures (e.g. screening assessments, labs). Patients may have costs of Expanded Access treatment covered under their insurance policy.

14.5 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 patients to the nearest hospital. Treatment of a study-related emergency would be billed to a patient’s health insurance provider. If the patient's private or employer health insurance plan does not cover related claims, the patient must cover all associated costs of any study-related emergencies. The sponsor will not cover costs of ongoing treatment unrelated to the study due to pre-existing conditions, or the cost of the patient's time spent obtaining treatment for pre-existing conditions before receiving treatment in the study. In the event of a lawsuit 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.

14.6 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP and FDA regulations in a secure and safe facility. The investigator must consult a representative of the sponsor before disposal of any 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.

14.7 Publication Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to patients 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 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 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.
15.0 References


