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**An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder**

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USE	In conjunction with relevant regulatory and ethical guidance

**CONFIDENTIAL**

## Protocol Amendment Summary of Changes

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Amendment Version #7	16Nov2022
Amendment Version #6	29March2022
Amendment Version #5	14Oct2019
Amendment Version #4	19Aug2019
Amendment Version #3	10June2019
Amendment Version #2	12Dec2018
Original Protocol Version 1	20Sep2018

## **MP18 Protocol Synopsis**

*Full protocol begins on Page 20*

### **Rationale**

MAPS Europe B.V. is a small or medium-sized enterprise (SME) 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). MAPS Europe B.V. is a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), a tax-exempt charity providing funding for the clinical development program. The Multidisciplinary Association for Psychedelic Studies (MAPS) Data from a series of Phase 2 studies of MDMA-assisted psychotherapy sponsored by MAPS provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy. This open-label Phase 2 study will serve as the lead-in to the planned Phase 3 study in Europe and to validate assumptions made for statistical power calculations supporting the planned Phase 3 clinical trial. This study will also provide cross-cultural validation data on the updated version of the Primary Outcome measure, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), which will be used in the Phase 3 study. In addition, the study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy while providing an opportunity for clinical supervision to planned Phase 3 therapy teams. This study will be the first multicenter study of MDMA-assisted psychotherapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated Phase 2 trials to confirm the Phase 3 study design.

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 may relive the traumatic experience 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 multicenter, open-label, lead-in study assesses the safety and effectiveness of MDMA-assisted psychotherapy in participants diagnosed with at least severe PTSD. All safety data will be included in the global safety database for MDMA maintained by MAPS. The study will be conducted in up to 40 participants who will complete the study in multiple countries in Europe. Some sites will participate in the imaging sub-study (see Appendix A).

A flexible dose of MDMA, followed by a supplemental half-dose unless tolerability issues emerge, is administered during the Treatment Period with manualized psychotherapy in two open-label Experimental Sessions spaced approximately a month apart. This 8-week Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug psychotherapy. The Primary Outcome measure, the change in CAPS-5 Total Severity Score from Baseline (V3) to Visit 14, is assessed by a centralized Independent Rater (IR) pool at 13 weeks post Baseline (V14). The CAPS-5 is also administered as an exploratory measure after Treatment 1 (V8). The

IR pool will be blinded to visit number and number of treatments received and will not have access to data collected by the sites during the active treatment period.

For each participant, the study will consist of the following periods:

- Screening Period: phone screen (where permitted), informed consent, eligibility assessment, and enrollment of eligible participants
- Preparatory Period with Enrollment Confirmation: medication tapering, Preparatory Sessions and Baseline assessments leading to Enrollment Confirmation
- Treatment Period: two monthly Experimental Sessions and associated Integrative Sessions over ~8 weeks plus one CAPS-5 assessment
- Follow-up Period and Study Termination: ~4 weeks with no study visits, followed by Primary Outcome CAPS-5 and Study Termination visit

The imaging sub-study (Appendix A) will include Magnetic Resonance Imaging (MRI) scanning to explore the effects of two experimental sessions, consisting of a baseline scan (one week before the first experimental session at MRI-1 V4.1), and the second scan will be conducted after the CAPS-5 outcome measure (at MRI-2 V14.1).

## Study Design Overview

<b>Screening Period</b> From Consent to Enrollment (Visit 0): ~4 weeks (+/-2 weeks)			
<b>Study Visit</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Screening	Screening	Multiple visits over 3 weeks (-2 weeks/+1 week)  7 to 28 days total	At initial visit, obtain Informed Consent and assess all screening measures (including LEC-5, PCL-5, Lifetime C-SSRS, AUDIT, DUDIT), medical history, and pre-study medications. Contact outside providers and order medical records, physical exam, labs (including 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. If eligible, send results of LEC-5 & CIPD-SR to IR. Screening may take place over 3 weeks at multiple visits.
	Independent Rater Screening	1 hour/ 2 days after initial eligibility established in Screening (+7 days)  2 to 9 days after initial eligibility established	After PCL-5, and initial eligibility are reviewed, an IR will conduct the Since Last Visit C-SSRS, CIPD, DDIS, and MINI via tele-assessment. Results will be confirmed by clinical observation during the Preparatory Period, but the CIPD, DDIS, and MINI will not be repeated.
Enrollment	Enrollment (Visit 0)	1.5 hours/ 2 days after (+12 days) Independent Rater Screening  2 to 14 days after IR Screening	Prior to enrolling: review all screening measures, medical history, discussion with outside providers and sponsor, and any clarification phone calls with participant. Visit is 1.5 hours to review eligibility and medical tapering plan. If enrolled, begin taper, (5 half-lives plus 1 week for stabilization). Adverse Event (AE) collection begins.

<b>Preparatory Period with Enrollment Confirmation</b> From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 4): ~6 weeks (+5/-4 weeks)			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Preparatory Period	Preparatory Session 1 (Visit 1)	1.5 hours/ Within 1 week (-7/+5 days) after Enrollment (V0)  0 to 12 days after Enrollment (V0)	90-minute 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.
	Preparatory Session 2 (Visit 2)	1.5 hours/ At least 2 days after Preparatory Session 1 (V1); within 3 weeks of Preparatory Session 1 (V1)  2 to 21 days after Preparatory Session 1 (V1)	90-minute 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.
	Phone Call End Taper	1 hour/ Within 1 week of planned taper end & stabilization off medications; before Baseline CAPS T1 (V3); within 8 weeks of V0  0 to 56 days after Enrollment (V0); within 7 days of the end of tapering and stabilization; prior to baseline CAPS T1 (V3)	If needed, confirm medication taper and stabilization is complete and participant is eligible for Baseline CAPS-5. Schedule V3 and V4.
Baseline & Enrollment Confirmation	Baseline CAPS-5 T1 (Visit 3)	1.5 hours/ Post Preparatory Session 2 (V2) & confirmation of Medication Taper and stabilization; before V4  At least 7 days after Preparatory Session 2 (V2)	CAPS-5, SDS, and DSP-I completed by an IR via tele-assessment after taper is complete. CAPS-5 scores sent ASAP to the therapy team/Principal Investigator.

	<p>Preparatory Session 3 &amp; Enrollment Confirmation (Visit 4)</p>	<p>3 hours: (90 minutes of measures, 90-minute therapy) Within 6 days of Baseline CAPS T1 (V3); within 4 days prior to Experimental Session 1 (V5) but not on the same day.</p> <p>3 to 6 days after Baseline CAPS T1 (V3); 1 to 4 days before Experimental Session 1 (V5). Both Baseline CAPS T1 (V3) and Preparatory Session 3 and Enrollment Confirmation (V4) must take place within 7 days prior to Experimental Session 1 (V5).</p>	<p>Prior to visit, ensure CAPS-5 confirms PTSD diagnosis and Total Severity Score of <math>\geq 35</math> and confirm enrollment by reassessing specified eligibility criteria. Complete Baseline self-report measures. Complete 3-hour Preparatory Session (~90-minute measures, 90-minute therapy) and schedule V5. If enrollment is not confirmed do not perform visit, complete termination.</p>
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<b>Treatment Period</b> From Experimental Session 1 (Visit 5) to Integrative Session 2.3(Visit 13): 8 weeks (-3/+4)			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Treatment 1	Experimental Session 1 (Visit 5)	<p>8 hours + overnight/ Within 1 week of Baseline CAPS-5 T1 (V3) and Preparatory Session 3 and Enrollment Confirmation (V4)</p> <p>4 to 7 days after Baseline CAPS-5 T1 (V3); 1 to 4 days after Preparatory Session 3 and Enrollment Confirmation (V4). Experimental Session 1 (V5) must occur within 7 days of the Baseline CAPS-5 T1 (V3) and after Preparatory Session 3 and Enrollment Confirmation (V4)</p> <p>At least 14 days after Preparatory Session 2 (V2); after Therapist Supervision Meeting</p>	First Experimental Session is within 1 week of the Baseline CAPS-5 (V3) and 2 weeks after Preparatory Session 2 (V2); it lasts 8 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless tolerability issues emerge with the first dose or the participant declines. Negative pregnancy test and drug test must be confirmed prior to dosing.
	Integrative Session 1.1 (Visit 6)	<p>1.5 hours/ Morning after Experimental Session 1 (V5)</p> <p>1 day after Experimental Session 1 (V5)</p>	V6 is a 90-minute Integrative Session the morning after V5. Followed by 4 phone check-ins over the 7 days post V5.
	Integrative Session 1.2 (Visit 7)	<p>1.5 hours/ At least 3 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.1 (V6); within 2 weeks after Experimental Session 1 (V5)</p> <p>3 to 14 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.1 (V6)</p>	Approximately 2 weeks after V5, a 90-minute Integrative Session (V7) is completed.

	CAPS-5 T2 (Visit 8)	1 hour/ 3 weeks (-3/+9 days) after Experimental Session 1 (V5); after Integrative Session 1.2 (V7) and before Integrative Session 1.3 (V9)  18 to 30 days after Experimental Session 1 (V5); between Integrative Sessions 1.2 and 1.3 (V7 & V9) but may be same day as either.	Between V7 and V9, CAPS-5, SDS, and DSP-I assessment completed by an IR via tele-assessment.
	Integrative Session 1.3 (Visit 9)	1.5 hours/ 3 to 5 weeks after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.2 (V7); may be the same day as CAPS-5 T2 (V8); 1 to 7 days before Experimental Session 2 (V10)  20 to 34 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.2 (V7); 1 to 7 days before Experimental Session 2 (V10)	90-minute Integrative Session post V8 and in preparation for V10. Can occur 1 to 7 days before V10. Measures include LEC-5, PCL-5, and Since Last Visit C-SSRS.

Study Visit/ Visit #		Visit Duration/ Visit Timing/ (Scheduling Window)	Brief Description of Events
Treatment 2	Experimental Session 2 (Visit 10)	8 hours + overnight/ 3 to 5 weeks after Experimental Session 1 (V5); at least 2 weeks after Integrative Session 1.3 (V9)  21 to 35 days after Experimental Session 1 (V5)  At least 14 days after Integrative Session 1.2 (V7); after Therapist Supervision Meeting	3 to 5 weeks after V5, and 2 weeks after Integrative Session 1.1 (V6). The second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose (80 mg + supplemental 40 mg -OR- 120 mg + supplemental 60 mg) unless tolerability issues emerge with the first dose or the participant declines. Negative pregnancy test and drug test must be confirmed prior to dosing.



	Integrative Session 2.1 (Visit 11)	1.5 hours/ Morning after Experimental Session 2 (V10)  1 day after Experimental Session 2 (V10)	V11 is a 90-minute Integrative Session the morning after V10. Followed by 4 phone check-ins over 7 days post V10.
	Integrative Session 2.2 (Visit 12)	1.5 hours/ At least 3 days after Experimental Session 2 (V10); at least 2 days after Integrative Session 2.1 (V11); within 2 weeks after Experimental Session 2 (V10)  3 to 14 days after Experimental session 2 (V10); at least 2 days after Integrative Session 2.1 (V11)	Approximately 2 weeks after V10, a 90-minute Integrative Session (V12) is completed.
	Integrative Session 2.3 (Visit 13)	1.5 hours/ 3 to 5 weeks after Experimental Session 2 (V10)  20 to 34 days after Experimental Session 2 (V10); at least 2 days after Integrative Session 2.2 (V12)	90-minute Integrative Session post V12. Measures include LEC-5, PCL-5 and Since Last Visit C-SSRS.
<b>Follow-up Period and Study Termination</b> From Integrative Session 2.3 (Visit 13) until Study Termination (Visit 15): 4 weeks (+/-2). After Integrative Session 2.3 (Visit 13), ~4 weeks with no scheduled study visits until the Primary Outcome is completed.			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Primary Outcome	Primary Outcome CAPS-5 T3 (Visit 14)	1 hour/ ~13 (+/-3) weeks after Baseline CAPS-5 T1 (V3) & 8 weeks (+/-2) after Experimental Session 2 (V10)  67 to 112 days post Baseline CAPS-5 T1 (V3); 42 to 70 days after Experimental Session 2 (V10)	Primary Outcome CAPS-5, SDS, and DSP-I assessment completed by an IR via tele-assessment. Although there are allowable windows for all visits throughout the protocol, this visit must be completed within the overall window. Other visits should be scheduled to ensure the timing of the Primary Outcome CAPS-5 T3 assessment is appropriate.

Study Termination	Study Termination (Visit 15)	2 hours ~13 (-3/+4) weeks after Baseline CAPS-5 T1 (V3) & 2 days (-1/+7 days) after Primary Outcome CAPS-5 T3 (V14)  68 to 121 days after Baseline CAPS-5 T1 (V3); 1 to 9 days after Primary Outcome CAPS-5 T3 (V14)	Complete self-reported and safety measures; create an exit plan for participant.
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Qualified IRs selected based on availability from the IR Pool will perform the CAPS-5 assessments as described in the following table.

### Primary Outcome (CAPS-5) Data Collection by Visit

CAPS Number	Visit	Description/Timing	Target Timing Post Baseline (V3)
Baseline CAPS-5 T1	V3	Baseline; between V2 and confirmation of end of tapering and stabilization of medications	0 days
CAPS-5 T2	V8	Post Experimental Session 1 (3 weeks -3/+9 days); between Integrative Sessions 1.2 and 1.3 (V7 & V9)	~6 weeks
Primary Outcome CAPS-5 T3	V14	Post Experimental Session 2 (8 weeks +/-2) after Experimental Session 2 (V10); after Integrative Session 2.3 (V13) (4 weeks +/-2).	~13 weeks

This study will compare the effects of two open-label manualized Experimental Sessions of psychotherapy assisted with a flexible divided-dose of MDMA as described in the table below, along with associated non-drug preparatory and integrative psychotherapy sessions. MDMA dose ranges proposed in this study have been safely used in previous Phase 2 studies sponsored by MAPS.

### Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
Total Cumulative Dose			160 mg to 300 mg

\* Unless tolerability issues emerge with the first dose or the participant declines

### Protocol Objective

The overall objective of this study is to use standard clinical measures to explore the safety and effectiveness of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with severe PTSD and to serve as an opportunity for training and supervision of therapy teams selected to conduct Phase 3 MDMA-assisted psychotherapy research.

## Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted psychotherapy for treatment of PTSD, as measured by the *estimand* of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

## Secondary Objective

The secondary objective is to evaluate the effectiveness of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline).

## Safety Objectives

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

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 through 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.
7. Assess incidence of SAEs.
8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and through 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-IP administration to end of each Experimental Session.

## Exploratory Objectives

These objectives may be explored to characterize participants receiving MDMA-assisted psychotherapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors (LEC-5) on the CAPS-5 Total Severity analyses
2. Explore changes within-participants in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline)

3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses
4. Explore changes in:
  - Dissociative symptoms associated with PTSD (DSP-I)
  - Depression (BDI-II)
  - Chronic pain (CPGS)
  - Quality of life (EQ-5D-5L)
  - Self-compassion (SCS)
  - Addictive behaviors including alcohol use (AUDIT), drug use (DUDIT), and nicotine use (SRNU)
  - Eating habits (EAT-26)
  - Healthcare utilization (UFEC) and economic productivity
  - Subjective effects (SE)

## **Recruitment and Participant Population**

Therapy teams that have been identified to work on the sponsor's planned Phase 3 study will treat at least one participant with open-label MDMA. Up to 40 participants with a confirmed diagnosis of at least severe PTSD will be enrolled. Participants will be recruited through referrals from other psychiatrists, psychotherapists, or physicians, print and internet advertisements, and by word of mouth. The sponsor will monitor demographics on an ongoing basis and encourage diversity in enrollment by communicating with sites.

Participants will be persons aged 18 or older, with a confirmed diagnosis of at least severe PTSD per the PTSD Checklist for DSM-5 (PCL-5) at Screening with symptoms present for at least 6 months. At Baseline, participants must qualify for a PTSD diagnosis per the CAPS-5 and have a Total Severity Score equal to or greater than 35 (severe). Participants would not be excluded for having more than one traumatic event or for having tried, not tolerated, or refused a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) prescribed for PTSD. Participants with confirmed diagnosis of specific psychological and personality disorders will be excluded. Participants must be in good physical health and without major medical disorders that could affect the safety or tolerability of MDMA.

## **Eligibility Criteria**

At the completion of Screening, participants must meet all eligibility criteria (except Inclusion Criterion #13 listed below) and agree to all lifestyle modifications to be enrolled. Each participant will then enter the Preparatory Period which includes medication tapering, if needed, and non-drug Preparatory Sessions. The Preparatory Period ends with Enrollment Confirmation. A participant's enrollment will be confirmed once they have completed medication tapering, have a confirmed PTSD diagnosis per the CAPS-5 assessment and a Total Severity Score of 35 or greater, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria.

## **Inclusion Criteria**

1. Are at least 18 years old.
2. Are fluent in speaking and reading the predominantly used or recognized language of the study site.
3. Are able to swallow pills.
4. Agree to have study visits video-recorded, including Experimental Sessions, Independent Rater assessments, and non-drug psychotherapy sessions.

5. 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 participant becoming suicidal or unreachable.
6. Must agree to inform the investigators within 48 hours of any medical treatments and procedures.
7. People able to become pregnant (PABP) (*i.e.*, assigned female at birth, fertile, following menarche and until becoming post-menopausal unless permanently sterile), must have a highly sensitive 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 hormones plus a barrier contraception, vasectomized sole partner (described in more detail in Section 10.3.2 Contraception Guidelines).
8. Agree to the following lifestyle modifications (described in more detail in Section 3.3 Lifestyle Modifications): comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not enroll 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 after, and commit to medication dosing, therapy, and study procedures.

#### *Medical History*

9. At Screening, meet DSM-5 criteria for current PTSD with a symptom duration of 6 months or longer.
10. At Screening, have at least severe PTSD symptoms in the last month based on PCL-5 total score of 46 or greater.
11. May have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease.
12. May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed.
13. At Baseline, have a confirmed diagnosis of PTSD per CAPS-5 and at least severe symptoms in the last month constituting a CAPS-5 Total Severity Score of 35 or greater.
14. May have alcohol or substance use disorder if participant is not in withdrawal or requiring detox. Participants must have a plan, agreed upon by investigator, therapy team, and Medical Monitor, to reduce use of alcohol or other substances and to manage symptoms without self-medicating. Enrollment will require that, in the judgment of the investigator, therapy team, and Medical Monitor, the plan for decreasing substance use is realistic and has a good chance of succeeding in order to prevent substance use from impacting the safety or efficacy of the investigational treatment.
15. May have a history of or current Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the Medical Monitor.
16. May have hypothyroidism if taking adequate and stable thyroid replacement medication.
17. May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.

## Exclusion Criteria

Potential participants are ineligible to enroll in the protocol if they:

1. Are not able to give adequate informed consent.
2. Are currently engaged in compensation litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders.
3. Are likely, in the investigator's opinion and via observation during the Preparatory Period, to be re-exposed to their index trauma or other significant trauma, lack social support, or lack a stable living situation.
4. Have used Ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first Experimental Session; or have previously participated in a MAPS-sponsored MDMA clinical trial.
5. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation.
6. Have hypersensitivity to any ingredient of the IMP (Investigational Medicinal Product).

### *Psychiatric History*

7. Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment.
8. Have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 assessed via MINI and clinical interview or dissociative identity disorder assessed via DDIS and clinical interview.
9. Have a current eating disorder with active purging assessed via MINI and clinical interview.
10. Have current major depressive disorder with psychotic features assessed via MINI.
11. Have a current alcohol or substance use disorder other than caffeine or nicotine that the investigators, therapy team, and/or Medical Monitor judge to be a safety concern for enrollment in the study or that could interfere with the therapeutic process or with other aspects of study participation. Any participant who is not able to agree or adhere to a plan to reduce use and manage symptoms will not be enrolled.
12. Have current Personality Disorders (paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive) assessed via CIPD. Diagnoses will be confirmed via clinical interview.
13. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to C-SSRS, and clinical judgment of the investigator will be excluded; however, history of suicide attempts is not an exclusion. Any participant who is likely to require hospitalization related to suicidal ideation and behavior, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the Baseline C-SSRS will be excluded:
  - Suicidal ideation score of 4 or greater within the last month of the assessment at a frequency of once a week or more.
  - Suicidal ideation score of 5 within the last 6 months of the assessment.
  - Any suicidal behavior, including suicide attempts or preparatory acts, within the last 6 months of the assessment. Participants with non-suicidal self-injurious behavior may be included if approved by the Medical Monitor.
14. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist.
15. Require ongoing concomitant therapy with a psychiatric medication with exceptions described in Section 11.0: Concomitant Medications.

### *Medical History*

16. Have a history of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate. This includes, but is not limited to, a history of myocardial infarction, cerebrovascular accident, or aneurysm. Participants with other mild, stable chronic medical problems may be enrolled if the site physician, PI, and Medical Monitor agree the condition would not significantly increase the risk of MDMA administration or be likely to produce significant symptoms during the study that could interfere with study participation or be confused with side effects of the IMP. Examples of stable medical conditions that could be allowed include, but are not limited to Diabetes Mellitus (Type 2), Human Immunodeficiency Virus (HIV) infection, Gastroesophageal Reflux Disease (GERD), etc. Any medical disorder judged by the investigator to significantly increase the risk of MDMA administration by any mechanism would require exclusion.
17. Have a diagnosis of uncontrolled hypertension, defined as repeated readings of  $\geq 140$  millimeters of mercury [mmHg] systolic or  $\geq 90$  mmHg diastolic. The diagnosis may be confirmed by repeated clinic measurements or home blood pressure monitoring if clinically indicated per European Society of Cardiology (ESC) guidelines.
18. Have a history of ventricular arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease.
19. Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation.
20. Have a history of arrhythmia, other than premature atrial contractions (PACs) or occasional PVCs in the absence of ischemic heart disease, within 12 months of screening. Participants with a history of atrial fibrillation, atrial tachycardia, atrial flutter or paroxysmal supraventricular tachycardia or any other arrhythmia associated with a bypass tract may be enrolled only if they have been successfully treated with ablation and have not had recurrent arrhythmia for at least one year off all antiarrhythmic drugs, and confirmed by a cardiologist.
21. Have a marked Baseline prolongation of QT/QTc interval (For purposes of eligibility, this is defined as repeated demonstration of a QT interval corrected using Fridericia's formula [QTcF]  $> 450$  milliseconds [ms]).
22. Have a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
23. Require use of concomitant medications that prolong the QT/QTc interval during Experimental Sessions. Refer to Section 11.0 Concomitant Medications.
24. Have symptomatic liver disease or have significant liver enzyme elevation.
25. Have history of hyponatremia (defined as outside of the normal range of 135 to 145 mmol/L) or hyperthermia.
26. Weigh less than 48 kilograms (kg).
27. Are pregnant or nursing or are able to become pregnant and are not practicing an approved means of birth control.
28. Have engaged in ketamine-assisted therapy or used ketamine within 12 weeks of enrollment.

## **Lifestyle Modifications**

All participants must agree to the following lifestyle modifications at time of signing the informed consent form and throughout the study. Participants are eligible to enroll in the study if they:

- Are willing to commit to medication and MDMA 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, without prior approval of the Medical Monitor.
- Agree to not begin a new form of mental healthcare during the screening or treatment phases of the trial, without first discussing with the PI in consultation with the Medical Monitor.
  - It is acceptable for participants to continue ongoing mental healthcare, if it is not increased in frequency or specifically excluded by the study protocol.
  - All ongoing therapies should be documented by the site and discussed with the Medical Monitor prior to enrollment to avoid confounding treatment effects. In some instances, the Medical Monitor may request that the participant delay enrollment until their planned course of therapy is complete and an integration period has elapsed.

### *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 research 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 11.0 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 11.0 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 IP administration and 24 hours after. During this period, the participant 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 research team)
  - Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen unless with prior approval of the research team).
  - Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the research team).

### *Post Experimental Session*

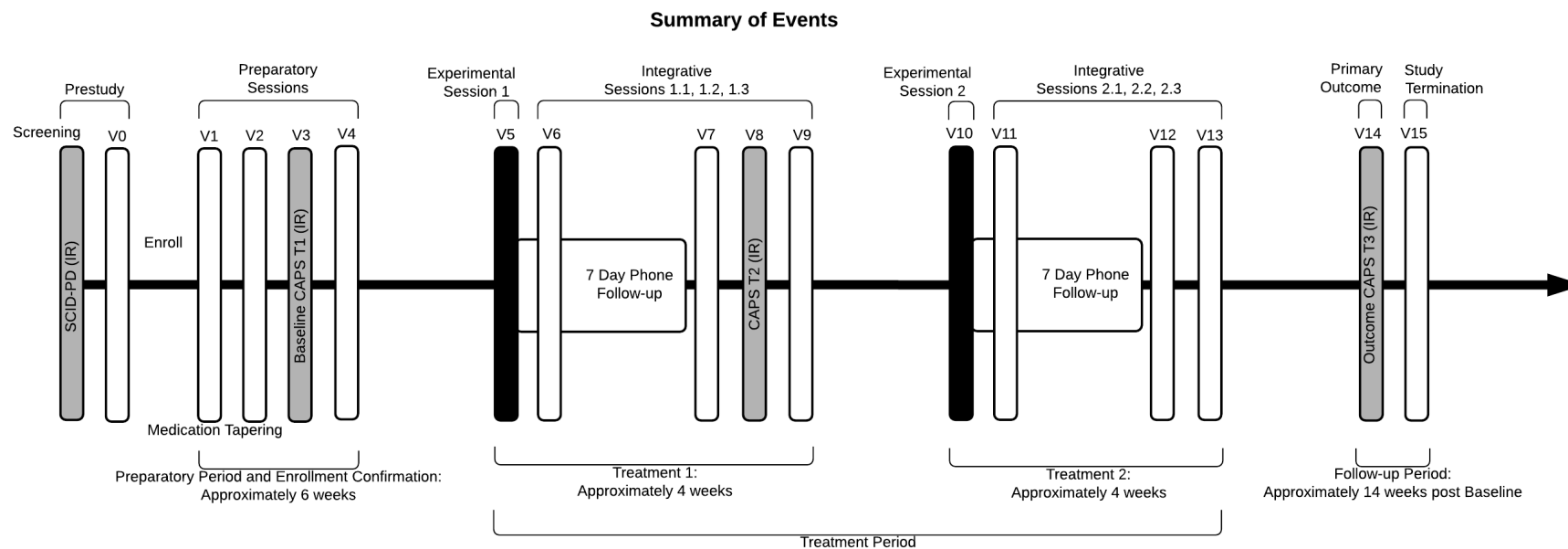
- Are willing to remain overnight at the study site after each Experimental Session until after the Integrative Session the next morning.
- Are willing to be driven home on the morning after the Experimental Sessions after the Integrative Session, either by a driver arranged by the participant, site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



## Statistical Analysis

The primary and key secondary endpoint analyses will be based on the *mITT* analysis set. The primary estimator of effectiveness will be the mean change in CAPS-5 Total Severity Scores from Baseline to 14 weeks after start of dosing (Visit 14). Least squares means from a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be used to estimate the change in CAPS-5 from baseline to each visit. The *mITT* analysis set will include all participants who receive IP in at least one Experimental Session and have at least one follow-up CAPS-5 assessment. Additional details of statistical analyses are described in the Statistical Analysis Plan (SAP).

## Study Structure Overview



**Protocol MP18**  
EudraCT # 2018-001718-13

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**Protocol Version 7.0: 22 November 2022**

**An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder**

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USE	In conjunction with relevant regulatory and ethical guidance

**CONFIDENTIAL**

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## List of Abbreviations

A:G	Albumin:Globulin
ACE	Adverse Childhood Events
ADHD	Attention Deficit Hyperactivity Disorder
AE(s)	Adverse Event(s)
AED	Automatic External Defibrillator
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory-II
BLS	Basic Life Support
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CAPS-4	Clinician-Administered PTSD Scale for DSM-4
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
%CDT	%Carbohydrate-deficient Transferrin
CIPD	Clinical Interview for Personality Disorders
CIPD-SR	Clinical Interview for Personality Disorders Self-Report
CMC	Chemistry Manufacturing and Control
CPGS	Chronic Pain Grade Scale
CRA	Clinical Research Associate
C-SSRS	Columbia-Suicide Severity Rating Scale
DDIS	Dissociative Disorders Interview Schedule
DID	Dissociative Identity Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> edition
DSM-4	Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> edition
DSP-I	Dissociative Subtype of PTSD Interview
DUDIT	Drug Abuse Disorders Identification Test
EAT-26	Eating Attitudes Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ePRO	Electronic Participant Reported Outcome
ESC	European Society of Cardiology
EQ-5D-5L	EuroQol Five Dimensions – Five Levels Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GERD	Gastroesophageal Reflux Disease
GMP	Good Manufacturing Practice

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
HPMC	Hydroxypropyl Methylcellulose
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICD-10	International Classification of Disease, 10 <sup>th</sup> edition
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IR	Independent Rater
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
kg	Kilogram
LEC-5	Life Events Checklist
LTFU	Long-term Follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-International Neuropsychiatric Interview
mg	Milligram
<i>mITT</i>	Modified Intent-to-Treat
mmHg	Milligrams of Mercury
MMRM	Mixed Model Repeated Measure
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
PABP	People Able to Become Pregnant
PAC	Premature atrial contraction
PCL-5	PTSD Checklist for DSM-5
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PVC	Premature ventricular contraction
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-4-PD	Structured Clinical Interview for DSM-4 Personality Disorders
SCS	Self-compassion Scale
SDS	Sheehan Disability Scale
SE	Subjective Effects
SGOT	Serum Glutamic Oxaloacetic Transaminase
SME	Small or Medium-sized Enterprise
SNRI	Serotonin-norepinephrine Reuptake Inhibitor



SPGT	Serum Glutamic Pyruvic Transaminase
SRNU	Self-reported Nicotine Use
SSRI	Selective Serotonin Reuptake Inhibitor
SUDS	Subjective Unit of Distress Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid-stimulating Hormone
UFEC	Utilization of Facility-based and Emergent Care
US	United States
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization

## 1.0 Introduction

MAPS Europe B.V. is a small or medium-sized enterprise (SME) 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). MAPS Europe B.V. is a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), a tax-exempt charity providing funding for the clinical development program. Controlled Phase 1 studies, nonclinical studies, and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA.

### 1.1 Rationale

PTSD is a serious, debilitating disorder that negatively impacts a person's daily life. MDMA has been shown to reduce defenses and fear of emotional injury, enhance communication, and increase empathy. MDMA may enhance fear extinction learning in humans. These subjective effects of MDMA create a productive psychological state that enhances the therapeutic process for the treatment of PTSD and other anxiety disorders. This novel treatment package consists of up to three Experimental Sessions spaced a month apart of psychotherapy combined with a flexible dose of MDMA, along with non-drug preparatory and integrative psychotherapy. This study design is supported by data from an international series of Phase 2 pilot studies of MDMA-assisted psychotherapy conducted by the sponsor that provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy sessions. The results from multiple independent studies in Phase 2 efficacy analyses demonstrate superiority of MDMA-assisted psychotherapy over psychotherapy with placebo or low dose MDMA. The acceptable risk-benefit safety ratio in early trials justifies further study.

This open-label, lead-in Phase 2 study is intended to gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy as a treatment for PTSD. The Primary Outcome measure, the change in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) from Baseline to V14, evaluates changes in PTSD symptom severity and is assessed by a centralized Independent Rater (IR) pool in this study and in planned Phase 3 clinical trials [\[1\]](#). This will be the first study of MDMA-assisted psychotherapy in Europe using the CAPS-5 as a primary outcome measure to confirm assumptions made for statistical power calculations using the Clinician-Administered PTSD Scale for DSM-4 (CAPS-4) which support planned Phase 3 clinical trials. This study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy as a treatment for PTSD and provide clinical supervision to planned Phase 3 therapy teams. This study will also be the first multi-site study of MDMA-assisted psychotherapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated trials in a multi-site format to further confirm the Phase 3 study design.

In this Phase 2 study, therapy teams without previous experience on a MAPS-sponsored MDMA-assisted psychotherapy study will have the opportunity for training and clinical supervision from the sponsor prior to participating in Phase 3 studies. The sponsor conducts training programs to teach therapy team members about techniques and procedures for conducting MDMA-assisted therapy for PTSD based on the MDMA-assisted therapy Treatment Manual. These programs are designed to support and expand the knowledge and skills of therapy team members who will be working on MDMA research studies.

## 1.2 Background

### 1.2.1 PTSD

PTSD is a serious debilitating disorder 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, 5<sup>th</sup> 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 [2]. 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 under modulation mediated by the failure of prefrontal inhibition of the same limbic regions [3, 4]. 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.

In Europe, lifetime PTSD prevalence ranges from 0.56% to 6.67% in the general population. The Netherlands was shown to be amongst the countries with the highest lifetime prevalence of PTSD next to the United Kingdom (UK), France and Germany [5]. The lifetime PTSD prevalence in the general population in the Netherlands is 7.4% [6], in the UK adult population, the lifetime prevalence is between 1.9 and 8.8% [7]. Occupational exposure to dangerous and high-risk situations increases the risk for PTSD. This applies to military personnel and police officers. In Dutch veterans the risk of developing PTSD is increased in the first 2 years after deployment [8] and the need for medical care is also increased [9]. In the UK, the cost of PTSD to the National Health Service and society is substantial, with a recent study in Northern Ireland estimating 150 million euro per year [10].

Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration. This 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 [11-13]. 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). Currently, there is evidence that the antidepressants paroxetine, venlafaxine, sertraline and fluoxetine can be effective in post-traumatic stress disorder, but the magnitude of effect is, unfortunately, small to medium [14] (Cohen's  $d$  0.13 – 0.43) and there is no evidence for augmenting trauma-focused psychotherapy (TFPT) with drugs, such as D-cycloserine, that have evidence for enhancing exposure therapy in other disorders [15]. An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but are minimally effective in reducing PTSD symptoms. PTSD carries a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [16, 17]. Given the chronicity of PTSD, low treatment compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients exhibit an unmet medical need.

One treatment approach is to develop medications and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical irregularities underlying 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 [18]. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in reducing symptoms of PTSD for some people [19, 20], although many patients 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 for PTSD [21]. In the past decade, there has been a growing amount of research into medications and other methods that may augment psychotherapy for PTSD (see [22] for a review). For example, virtual reality-assisted exposure therapy [23] and D-cycloserine combined with psychotherapy are under investigation [24]. MDMA-assisted psychotherapy is another novel approach.

### 1.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by Merck pharmaceutical company in 1912 [25, 26]. Similar to SSRIs, MDMA binds to the monoamine transporters, with the greatest affinity for the serotonin transport (SERT). MDMA also enhances synaptic levels of serotonin, and to a lesser extent norepinephrine and dopamine, by vesicular carrier-mediated release and reuptake inhibition of these neurotransmitters [27-33]. MDMA increases levels of affiliative neurohormones oxytocin and vasopressin, which is associated with increased trust and attenuation of reactivity to threatening cues, and cortisol and prolactin. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, which would treat the core psychopathology of PTSD for a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the 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 MDMA has 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 work through different mechanisms than anxiolytics and SSRIs. Furthermore, there is no evidence that limited doses of MDMA in controlled clinical settings creates a physical dependence or drug seeking behavior. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [34, 35]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often

than once a week [36]. Hence, MDMA is said to have moderate abuse potential in non-medical settings, and low abuse potential in clinical settings. See the Investigator's Brochure (IB) for a more detailed explanation.

### 1.2.3 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 [20]. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion [37]. This has been referred to as working within the "optimal arousal zone" or "window of tolerance" [38-40].

The combined neurobiological effects of MDMA increase compassion for self and others, 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 decreases blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [41], and there is some indication that MDMA may increase activity in the prefrontal cortex (PFC) [42]. Another study showed increased functional connectivity between the amygdala and hippocampus, and decreased connectivity between the amygdala and PFC [43]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [41], compatible with its reported reduction in fear or defensiveness, and counteracts the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [44-46]. 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 enhances perceived self-authenticity [47] and a naturalistic study suggests that it can increase self-compassion [48], effects that may support and contribute to 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 [49-52]. 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 [53]. Participants are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. In healthy controls, MDMA reduces reactivity to unpleasant memories [54]. 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 participants 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 sites and therapy teams will be trained on prior to the study.

### 1.2.4 Previous Clinical Experience with MDMA

MDMA-assisted psychotherapy is a novel treatment package that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct intended to enhance certain aspects of psychotherapy. Chemists Shulgin and Nichols were the first to report on the effects of MDMA in humans [55], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [55, 56]. MDMA was found to robustly influence human emotional status in a unique way [55] without adversely affecting physiological functions or perception, such as visual perception or cognition [57-60]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety, even though the drug had not been studied in controlled clinical trials [61]. Legal therapeutic use continued until its placement on the U.S. list of Schedule 1 substances in 1985 [50, 53, 62]. An estimated 500,000 doses of MDMA were administered during psychotherapy and personal growth sessions in North America prior to its scheduling [50, 63]. A few uncontrolled human studies of MDMA assessing safety in a controlled setting occurred in the 1980s [64, 65].

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 [66, 67]. Starting in 2000 in Spain, MAPS funded a Phase 2 investigator-initiated dose-response effect and safety pilot study in participants with PTSD that was terminated early due to political pressure. This study enrolled six participants, with four receiving a single session of MDMA-assisted psychotherapy without any safety concerns and with some PTSD symptom reduction [52]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS IND with FDA.

MAPS initiated an international series of Phase 2 clinical trials to develop the medical use of MDMA-assisted psychotherapy for patients with chronic, at least moderate PTSD (CAPS-4 score: 50+), with at least 6 months of symptoms. Participants were not excluded for having more than one traumatic event, or for having tried, not tolerated, or refused 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) [51, 68] and one in Switzerland (MP2) [69, 70]. MP1 was followed by a small open-label extension study examining the treatment of relapse in three participants with a single MDMA-assisted psychotherapy treatment and a 12-month follow-up (MP1E2). Three additional studies have completed treatments (MP8, MP9, MP12) and two international studies were terminated early for logistical reasons with partial datasets (MP3, MP4). These studies tested a range of designs, such as a placebo control (MP1, MP4), low dose MDMA comparator control (MP2, MP9), and three-arm dose response studies (MP8, MP12). Findings from a dose-comparison study at the same site in military veterans, firefighters and police officers (MP8) have now been published and confirm findings reported in the initial studies [71]. MP4 was terminated early due to delays in regulatory approval and enrollment timelines, with available efficacy data presented without a formal analysis. MP3 was terminated early by the sponsor due to inadequate data collection procedures at the site and insufficient therapy team training; efficacy data are not available for these reasons (MP3 is excluded from Phase 2 data).

Intent-to-treat (ITT) analysis of primary efficacy and safety data from six MAPS-sponsored MDMA PTSD Phase 2 clinical trials worldwide (MP1, MP2, MP4, MP8, MP9, MP12) consisting



of 107 blinded participants with chronic PTSD was completed in 2016. In these studies, PTSD, independent of cause, appears treatable with a two- to three-session treatment package of MDMA-assisted psychotherapy. As of 01 October 2021 with 358 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1799 participants 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 initial doses of 75 mg-125 mg MDMA were statistically superior to 0 mg to 40 mg MDMA based on a t-test of difference in CAPS-4 severity scores from Baseline to 1 to 2 months after two to three blinded experimental sessions ( $p < 0.001$ ). The dropout rate across studies was 7.5% (8 of 107). Large placebo-subtracted effect sizes (Cohen's  $d$  0.9), initial indications of efficacy, and favorable safety outcomes support expanding the research initiative to encompass a larger sample of participants with PTSD in a Phase 3 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.

## **2.0 Protocol Objectives**

The overall objective of this study is to use standard clinical measures to explore the safety and effects of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with severe PTSD, and to serve as an opportunity for supervision of therapy teams selected to conduct Phase 3 MDMA-assisted psychotherapy research.

### **2.1 Primary Objective and Primary End Point**

The primary objective of this study is to evaluate the effect of MDMA-assisted psychotherapy on PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

The primary endpoint is the change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

### **2.2 Secondary Objective and Secondary End Point**

The secondary objective is to evaluate the effect of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to 13 weeks post Baseline (Visit 14).

The secondary endpoint is the mean change in Sheehan Disability Scale (SDS) item scores from baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

### **2.3 Safety Objectives**

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs to support the package insert for MDMA-assisted psychotherapy. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy.

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 through 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.
  7. Assess incidence of SAEs.
  8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and through 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-IP administration to end of each Experimental Session.

## 2.4 Exploratory Objectives

These objectives may be explored to characterize participants receiving MDMA-assisted psychotherapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors (LEC-5) on the CAPS-5 Total Severity analyses
2. Explore changes within-participants in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline)
3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses
4. Explore changes in:
  - Dissociative symptoms associated with PTSD (DSP-I)
  - Depression (BDI-II)
  - Chronic pain (CPGS)
  - Quality of life (EQ-5D-5L)
  - Self-compassion (SCS)
  - Addictive behaviors including: Alcohol use (AUDIT), Drug use (DUDIT) and Nicotine use (SRNU)
  - Eating habits (EAT-26)
  - Healthcare utilization (UFEC) and economic productivity
  - Subjective effects (SE)

## 3.0 Eligibility Criteria

At the completion of Screening, participants must meet all eligibility criteria (except Inclusion Criterion #13 listed below) and agree to all lifestyle modifications to be enrolled. Each participant will then enter the Preparatory Period which includes medication tapering, if needed, and non-drug Preparatory Sessions. The Preparatory Period ends with Enrollment Confirmation. A participant's enrollment will be confirmed once they have completed medication tapering, have a



confirmed PTSD diagnosis per the CAPS-5 assessment and a Total Severity Score of 35 or greater, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria.

### 3.1 Inclusion Criteria

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

1. Are at least 18 years old.
2. Are fluent in speaking and reading the predominantly used or recognized language of the study site.
3. Are able to swallow pills.
4. Agree to have study visits video-recorded, including Experimental Sessions, Independent Rater assessments, and non-drug psychotherapy sessions.
5. 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 participant becoming suicidal or unreachable.
6. Must agree to inform the investigators within 48 hours of any medical treatments and procedures.
7. People able to become pregnant (PABP) (*i.e.*, assigned female at birth, fertile, following menarche and until becoming post-menopausal unless permanently sterile), must have a highly sensitive 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 hormones plus a barrier contraception, vasectomized sole partner (described in more detail in Section 10.3.2 Contraception Guidelines).
8. Agree to the following lifestyle modifications (described in more detail in Section 3.3 Lifestyle Modifications): comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not enroll 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 after, and commit to medication dosing, therapy, and study procedures.

#### *Medical History*

9. At Screening, meet DSM-5 criteria for current PTSD with a symptom duration of 6 months or longer.
10. At Screening, have at least severe PTSD symptoms in the last month based on PCL-5 total score of 46 or greater.
11. May have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease.
12. May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed.
13. At Baseline, have a confirmed diagnosis of PTSD per CAPS-5 and at least severe symptoms in the last month constituting a CAPS-5 Total Severity Score of 35 or greater.
14. May have alcohol or substance use disorder if participant is not in withdrawal or requiring detox. Participants must have a plan, agreed upon by investigator, therapy team, and Medical Monitor, to reduce use of alcohol or other substances and to manage symptoms without self-medicating. Enrollment will require that, in the judgment of the investigator, therapy team, and Medical Monitor, the plan for decreasing substance use is realistic and has a good chance of succeeding in order to prevent substance use from impacting the safety or efficacy of the investigational treatment.

15. May have a history of or current Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the Medical Monitor.
16. May have hypothyroidism if taking adequate and stable thyroid replacement medication.
17. May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.

### 3.2 Exclusion Criteria

Potential participants are ineligible to enroll in the protocol if they:

1. Are not able to give adequate informed consent.
2. Are currently engaged in compensation litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders.
3. Are likely, in the investigator's opinion and via observation during the Preparatory Period, to be re-exposed to their index trauma or other significant trauma, lack social support, or lack a stable living situation.
4. Have used Ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first Experimental Session; or have previously participated in a MAPS-sponsored MDMA clinical trial.
5. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation.
6. Have hypersensitivity to any ingredient of the IMP (Investigational Medicinal Product).

#### *Psychiatric History*

7. Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment.
8. Have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 assessed via MINI and clinical interview or dissociative identity disorder assessed via DDIS and clinical interview.
9. Have a current eating disorder with active purging assessed via MINI and clinical interview.
10. Have current major depressive disorder with psychotic features assessed via MINI.
11. Have a current alcohol or substance use disorder other than caffeine or nicotine that the investigators, therapy team, and/or Medical Monitor judge to be a safety concern for enrollment in the study or that could interfere with the therapeutic process or with other aspects of study participation. Any participant who is not able to agree or adhere to a plan to reduce use and manage symptoms will not be enrolled.
12. Have current Personality Disorders (paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive) assessed via CIPD. Diagnoses will be confirmed via clinical interview.
13. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to C-SSRS, and clinical judgment of the investigator will be excluded; however, history of suicide attempts is not an exclusion. Any participant who is likely to require hospitalization related to suicidal ideation and behavior, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the Baseline C-SSRS will be excluded:
  - Suicidal ideation score of 4 or greater within the last month of the assessment at a frequency of once a week or more.
  - Suicidal ideation score of 5 within the last 6 months of the assessment.

- Any suicidal behavior, including suicide attempts or preparatory acts, within the last 6 months of the assessment. Participants with non-suicidal self-injurious behavior may be included if approved by the Medical Monitor.
14. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist.
  15. Require ongoing concomitant therapy with a psychiatric medication with exceptions described in Section 11.0: Concomitant Medications.

### *Medical History*

16. Have a history of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate. This includes, but is not limited to, a history of myocardial infarction, cerebrovascular accident, or aneurysm. Participants with other mild, stable chronic medical problems may be enrolled if the site physician, PI, and Medical Monitor agree the condition would not significantly increase the risk of MDMA administration or be likely to produce significant symptoms during the study that could interfere with study participation or be confused with side effects of the IMP. Examples of stable medical conditions that could be allowed include, but are not limited to Diabetes Mellitus (Type 2), Human Immunodeficiency Virus (HIV) infection, Gastroesophageal Reflux Disease (GERD), etc. Any medical disorder judged by the investigator to significantly increase the risk of MDMA administration by any mechanism would require exclusion.
17. Have a diagnosis of uncontrolled hypertension, defined as repeated readings of  $\geq 140$  millimeters of mercury [mmHg] systolic or  $\geq 90$  mmHg diastolic. The diagnosis may be confirmed by repeated clinic measurements or home blood pressure monitoring if clinically indicated per European Society of Cardiology (ESC) guidelines.
18. Have a history of ventricular arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease.
19. Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation.
20. Have a history of arrhythmia, other than premature atrial contractions (PACs) or occasional PVCs in the absence of ischemic heart disease, within 12 months of screening. Participants with a history of atrial fibrillation, atrial tachycardia, atrial flutter or paroxysmal supraventricular tachycardia or any other arrhythmia associated with a bypass tract may be enrolled only if they have been successfully treated with ablation and have not had recurrent arrhythmia for at least one year off all antiarrhythmic drugs, and confirmed by a cardiologist.
21. Have a marked Baseline prolongation of QT/QTc interval (For purposes of eligibility, this is defined as repeated demonstration of a QT interval corrected using Fridericia's formula [QTcF]  $> 450$  milliseconds [ms]).
22. Have a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
23. Require use of concomitant medications that prolong the QT/QTc interval during Experimental Sessions. Refer to Section 11.0 Concomitant Medications.
24. Have symptomatic liver disease or have significant liver enzyme elevation.
25. Have history of hyponatremia (defined as outside of the normal range of 135 to 145 mmol/L) or hyperthermia.
26. Weigh less than 48 kilograms (kg).
27. Are pregnant or nursing or are able to become pregnant and are not practicing an approved means of birth control.
28. Have engaged in ketamine-assisted therapy or used ketamine within 12 weeks of enrollment.

### 3.3 Lifestyle Modifications

All participants must agree to the following lifestyle modifications at time of signing the informed consent form and throughout the study. Participants are eligible to enroll in the study if they:

- Are willing to commit to medication and MDMA 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, without prior approval of the Medical Monitor.
- Agree to not begin a new form of mental healthcare during the screening or treatment phases of the trial, without first discussing with the PI in consultation with the Medical Monitor.
  - It is acceptable for participants to continue ongoing mental healthcare, if it is not increased in frequency or specifically excluded by the study protocol.
  - All ongoing therapies should be documented by the site and discussed with the Medical Monitor prior to enrollment to avoid confounding treatment effects. In some instances, the Medical Monitor may request that the participant delay enrollment until their planned course of therapy is complete and an integration period has elapsed.

#### *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 research 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 11.0 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 11.0 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 IP administration and 24 hours after. During this period, the participant 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 research team)
  - Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen unless with prior approval of the research team).
  - Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the research 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 the Experimental Sessions after the Integrative Session, either by a driver arranged by the participant, site personnel or taxi.

## 4.0 Protocol Design

### 4.1 Study Design Overview

This multi-site, open-label study assesses the safety and effectiveness of MDMA-assisted psychotherapy in participants diagnosed with at least severe PTSD. This study will also serve as an experiential training opportunity for therapy teams who will be participating in the upcoming Phase 3 study. The sponsor will provide clinical supervision through the adherence raters and the therapy pair supervisors, who will review the therapy session videos to ensure adherence to the therapeutic method, consistency between sites and therapy pairs, and provide support and advice to the therapy pair..

The study will be conducted in up to 40 participants in multiple countries in Europe. Some sites will participate in the imaging sub-study (see Appendix A for additional details). This study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s). All data will be included in the sponsor's safety database.

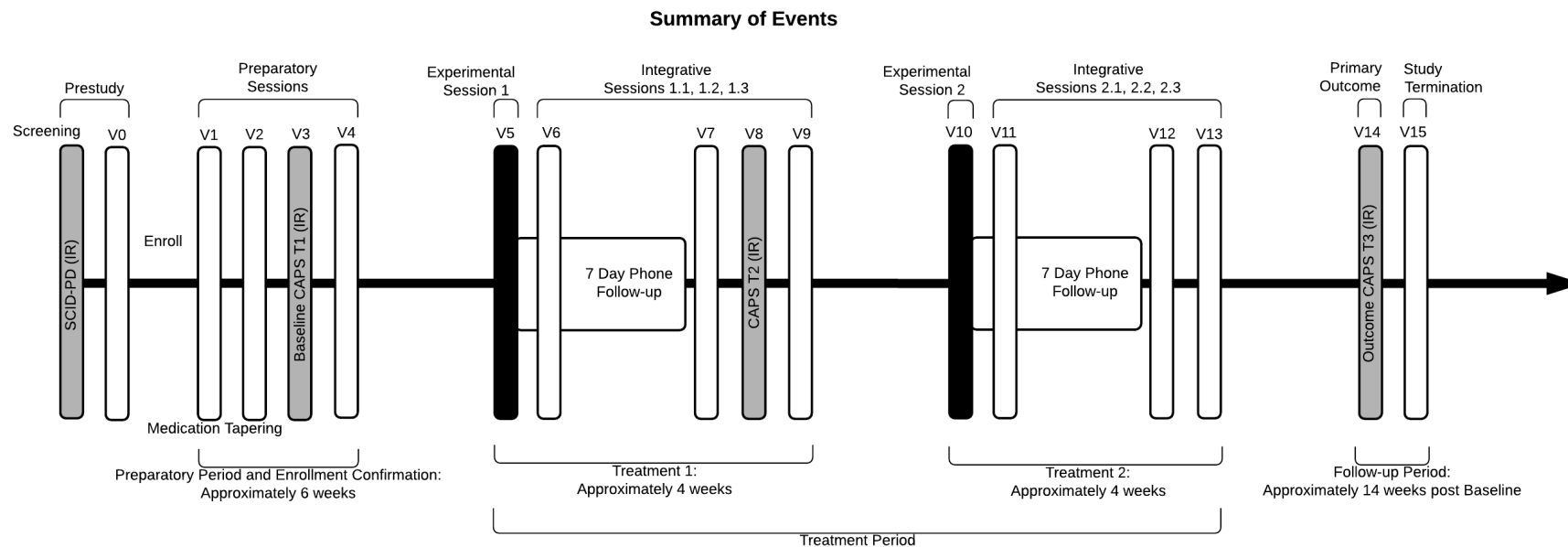
For each participant, the study will consist of:

- Screening Period: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants
- Preparatory Period with Enrollment Confirmation: medication tapering, Preparatory Sessions and Baseline assessments leading to Enrollment Confirmation
- Treatment Period: two Experimental Sessions spaced a month apart and associated Integrative Sessions over ~8 weeks plus one CAPS-5 assessment
- Follow-up Period and Study Termination: ~4 weeks with no study visits, followed by Primary Outcome CAPS-5 and Study Termination visit

The treatment consists of a flexible dose of MDMA, followed by a supplemental half-dose unless tolerability issues emerge with the first dose or the participant declines, administered with manualized psychotherapy in two open-label Experimental Sessions spaced a month apart. This ~8-week Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug psychotherapy. Experimental Sessions are followed by an overnight stay. Study design overview is shown in Table 1 and Figure 1.

Participants will have tele-assessment visits conducted by an Independent Rater (IR) from the IR Pool. All CAPS-5, SDS, MINI, DDIS, DSPI, and CIPD/SCID-PD assessments will be performed by an IR. All ratings will be video recorded. The Primary Outcome measure, the change in CAPS-5 from Baseline (V3), is assessed at 13 weeks post Baseline (V14). The CAPS-5 is also administered as an exploratory measure after Treatment 1 (V8). The IR pool will be blinded to visit number and number of treatments received and will not have access to data collected by the sites during the active treatment period.

**Figure 1: Study Structure Overview**



**Table 1: Study Design Overview**

<b>Screening Period</b> From Consent to Enrollment (Visit 0): ~4 weeks (+/-2 weeks)			
<b>Study Visit</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Screening	Screening	Multiple visits over 3 weeks (-2 weeks/+1 week)  7 to 28 days total	At initial visit, obtain Informed Consent and assess all screening measures (including LEC-5, PCL-5, Lifetime C-SSRS, AUDIT, DUDIT), medical history, and pre-study medications. Contact outside providers and order medical records, physical exam, labs (including 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. If eligible, send results of LEC-5 & CIPD-SR to IR. Screening may take place over 3 weeks at multiple visits.
	Independent Rater Screening	1 hour/ 2 days after initial eligibility established in Screening (+7 days)  2 to 9 days after initial eligibility established	After PCL-5, and initial eligibility are reviewed, an IR will conduct the Since Last Visit C-SSRS, CIPD, DDIS, and MINI via tele-assessment. Results will be confirmed by clinical observation during the Preparatory Period, but the CIPD-SR, DDIS, and MINI will not be repeated.
Enrollment	Enrollment (Visit 0)	1.5 hours/ 2 days after (+12 days) Independent Rater Screening  2 to 14 days after IR Screening	Prior to enrolling: review all screening measures, medical history, discussion with outside providers and sponsor, and any clarification phone calls with participant. Visit is 1.5 hours to review eligibility and medical tapering plan. If enrolled, begin taper, (5 half-lives plus 1 week for stabilization). Adverse Event (AE) collection begins.

<b>Preparatory Period with Enrollment Confirmation</b>			
From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 4): ~6 weeks (+5/-4 weeks)			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Preparatory Period	Preparatory Session 1 (Visit 1)	1.5 hours/ Within 1 week (-7/+5 days) after Enrollment (V0)  0 to 12 days after Enrollment (V0)	90-minute 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.
	Preparatory Session 2 (Visit 2)	1.5 hours/ At least 2 days after Preparatory Session 1 (V1); within 3 weeks of Preparatory Session 1 (V1)  2 to 21 days after Preparatory Session 1 (V1)	90-minute 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.
	Phone Call End Taper	1 hour/ Within 1 week of planned taper end & stabilization off medications; before Baseline CAPS T1 (V3); within 8 weeks of V0  0 to 56 days after Enrollment (V0); within 7 days of the end of tapering and stabilization; prior to baseline CAPS T1 (V3)	If needed, confirm medication taper and stabilization is complete and participant is eligible for Baseline CAPS-5. Schedule V3 and V4.
Baseline & Enrollment Confirmation	Baseline CAPS-5 T1 (Visit 3)	1.5 hours/ Post Preparatory Session 2 (V2) & confirmation of Medication Taper and stabilization; before V4  At least 7 days after Preparatory Session 2 (V2)	CAPS-5, SDS, and DSP-I completed by an IR via tele-assessment after taper is complete. CAPS-5 scores sent ASAP to the therapy team/Principal Investigator.



	<p>Preparatory Session 3 &amp; Enrollment Confirmation (Visit 4)</p>	<p>3 hours: (90 minutes of measures, 90-minute therapy) Within 6 days of Baseline CAPS T1 (V3); within 4 days prior to Experimental Session 1 (V5) but not on the same day</p> <p>3 to 6 days after Baseline CAPS T1 (V3); 1 to 4 days before Experimental Session 1 (V5). Both Baseline CAPS T1 (V3) and Preparatory Session 3 and Enrollment Confirmation (V4) must take place within 7 days prior to Experimental Session 1 (V5).</p>	<p>Prior to visit, ensure CAPS-5 confirms PTSD diagnosis and Total Severity Score of <math>\geq 35</math> and confirm enrollment by reassessing specified eligibility criteria. Complete Baseline self-report measures. Complete 3-hour Preparatory Session (~90-minute measures, 90-minute therapy) and schedule V5. If enrollment is not confirmed do not perform visit, complete termination.</p>
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<b>Treatment Period</b> From Experimental Session 1 (Visit 5) to Integrative Session 2.3(Visit 13): 8 weeks (-3/+4)			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Treatment 1	Experimental Session 1 (Visit 5)	<p>8 hours + overnight/ Within 1 week of Baseline CAPS-5 T1 (V3) and Preparatory Session 3 and Enrollment Confirmation (V4)</p> <p>4 to 7 days after Baseline CAPS-5 T1 (V3); 1 to 4 days after Preparatory Session 3 and Enrollment Confirmation (V4). Experimental Session 1 (V5) must occur within 7 days of the Baseline CAPS-5 T1 (V3) and after Preparatory Session 3 and Enrollment Confirmation (V4)</p> <p>At least 14 days after Preparatory Session 2 (V2); after Therapist Supervision Meeting</p>	First Experimental Session is within 1 week of the Baseline CAPS-5 (V3) and 2 weeks after Preparatory Session 2 (V2); it lasts 8 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless tolerability issues emerge with the first dose or the participant declines. Negative pregnancy test and drug test must be confirmed prior to dosing.
	Integrative Session 1.1 (Visit 6)	<p>1.5 hours/ Morning after Experimental Session 1 (V5)</p> <p>1 day after Experimental Session 1 (V5)</p>	V6 is a 90-minute Integrative Session the morning after V5. Followed by 4 phone check-ins over the 7 days post V5.
	Integrative Session 1.2 (Visit 7)	<p>1.5 hours/ At least 3 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.1 (V6); within 2 weeks after Experimental Session 1 (V5)</p> <p>3 to 14 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.1 (V6)</p>	Approximately 2 weeks after V5, a 90-minute Integrative Session (V7) is completed.

	CAPS-5 T2 (Visit 8)	1 hour/ 3 weeks (-3/+9 days) after Experimental Session 1 (V5); after Integrative Session 1.2 (V7) and before Integrative Session 1.3 (V9)  18 to 30 days after Experimental Session 1 (V5); between Integrative Sessions 1.2 and 1.3 (V7 & V9) but may be same day as either.	Between V7 and V9, CAPS-5, SDS, and DSP-I assessment completed by an IR via tele-assessment.
	Integrative Session 1.3 (Visit 9)	1.5 hours/ 3 to 5 weeks after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.2 (V7); may be the same day as CAPS-5 T2 (V8); 1 to 7 days before Experimental Session 2 (V10)  20 to 34 days after Experimental Session 1 (V5); at least 2 days after Integrative Session 1.2 (V7); 1 to 7 days before Experimental Session 2 (V10)	90-minute Integrative Session post V8 and in preparation for V10. Can occur 1 to 7 days before V10. Measures include LEC-5, PCL-5, and Since Last Visit C-SSRS.

Study Visit/ Visit #		Visit Duration/ Visit Timing/ (Scheduling Window)	Brief Description of Events
Treatment 2	Experimental Session 2 (Visit 10)	8 hours + overnight/ 3 to 5 weeks after Experimental Session 1 (V5); at least 2 weeks after Integrative Session 1.3 (V9)  21 to 35 days after Experimental Session 1 (V5)  At least 14 days after Integrative Session 1.2 (V7); after Therapist Supervision Meeting	3 to 5 weeks after V5, and 2 weeks after Integrative Session 1.1 (V6). The second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose (80 mg + supplemental 40 mg -OR- 120 mg + supplemental 60 mg) unless tolerability issues emerge with the first dose or the participant declines. Negative pregnancy test and drug test must be confirmed prior to dosing.

	Integrative Session 2.1 (Visit 11)	1.5 hours/ Morning after Experimental Session 2 (V10)  1 day after Experimental Session 2 (V10)	V11 is a 90-minute Integrative Session the morning after V10. Followed by 4 phone check-ins over 7 days post V10.
	Integrative Session 2.2 (Visit 12)	1.5 hours/ At least 3 days after Experimental Session 2 (V10); at least 2 days after Integrative Session 2.1 (V11); within 2 weeks after Experimental Session 2 (V10)  3 to 14 days after Experimental session 2 (V10); at least 2 days after Integrative Session 2.1 (V11)	Approximately 2 weeks after V10, a 90-minute Integrative Session (V12) is completed.
	Integrative Session 2.3 (Visit 13)	1.5 hours/ 3 to 5 weeks after Experimental Session 2 (V10)  20 to 34 days after Experimental Session 2 (V10); at least 2 days after Integrative Session 2.2 (V12)	90-minute Integrative Session post V12. Measures include LEC-5, PCL-5 and Since Last Visit C-SSRS.
<b>Follow-up Period and Study Termination</b> From Integrative Session 2.3 (Visit 13) until Study Termination (Visit 15): 4 weeks (+/-2). After Integrative Session 2.3 (Visit 13), ~4 weeks with no scheduled study visits until the Primary Outcome is completed.			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Primary Outcome	Primary Outcome CAPS-5 T3 (Visit 14)	1 hour/ ~13 (+/-3) weeks after Baseline CAPS-5 T1 (V3) & 8 weeks (+/-2) after Experimental Session 2 (V10)  67 to 112 days post Baseline CAPS-5 T1 (V3); 42 to 70 days after Experimental Session 2 (V10)	Primary Outcome CAPS-5, SDS, and DSP-I assessment completed by an IR via tele-assessment. Although there are allowable windows for all visits throughout the protocol, this visit must be completed within the overall window. Other visits should be scheduled to ensure the timing of the Primary Outcome CAPS-5 T3 assessment is appropriate.

Study Termination (Visit 15)	<p>2 hours ~13 (-3/+4) weeks after Baseline CAPS-5 T1 (V3) &amp; 2 days (-1/+7 days) after Primary Outcome CAPS-5 T3 (V14)</p> <p>68 to 121 days after Baseline CAPS-5 T1 (V3); 1 to 9 days after Primary Outcome CAPS-5 T3 (V14)</p>	Complete self-reported and safety measures; create an exit plan for participant.
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Qualified IRs selected based on availability from the IR Pool will perform the CAPS-5 assessments as described Table 2.

**Table 2: Primary Outcome (CAPS-5) Data Collection by Visit**

CAPS Administration	Visit	Description/Timing	Target Timing Post Baseline (V3)
Baseline CAPS-5 T1	V3	Baseline; between V2 and confirmation of end of tapering and stabilization of medications	0 days
CAPS-5 T2	V8	Post Experimental Session 1 (3 weeks -3/+9 days); between Integrative Sessions 1.2 and 1.3 (V7 & V9)	~6 weeks
Primary Outcome CAPS-5 T3	V14	Post Experimental Session 2 (8 weeks +/-2) after Experimental Session 2 (V10); after Integrative Session 2.3 (V13) (4 weeks +/-2).	~13 weeks

## 4.2 Planned Duration of Study

Full screening may take 2 to 6 weeks after completion of phone screening, where performed. The Preparatory Period begins at enrollment and can be as brief as 2 weeks. Depending on medication tapering could be as long as 11 weeks to ensure an appropriate medication washout of at least five half-lives of pre-study psychiatric medications and active metabolites, and at least one additional week for stabilization.

Enrollment Confirmation takes place at the completion of the Preparatory Period, at which time the Treatment period will commence. The approximate 8-week Treatment Period will consist of two Experimental Sessions 3 to 5 weeks apart with associated non-drug Integrative Sessions and CAPS-5 assessment.

After the final Integrative Session 2.3 (Visit 13), participants will enter follow-up with no study visits for approximately 4 weeks, after which the Primary Outcome CAPS-5 T3 assessment will take place (Visit 14). Although there are allowable windows for all visits throughout the protocol, the overall timelines should comply with the target timing of the Primary Outcome CAPS-5 T3 assessment, which must be completed 13 weeks (+/-3 weeks) post Baseline, even if the maximum possible visit windows were used between visits. Other visits should be scheduled to ensure the timing of the Primary Outcome CAPS-5 T3 assessment is appropriate. The Study Termination visit follows 1 to 9 days after the final CAPS-5 assessment.

The minimum time that a participant who completes all study visits from Screening to Study Termination will be in the clinical trial is 14 weeks and the maximum is 27 weeks. The average participant is expected to complete the study in 17 weeks. Any delays between visits outside of the protocol-defined windows may result in a corresponding extension of study duration and should be documented as a deviation as appropriate.

### **4.3 Discontinuation and Completion Criteria**

#### **4.3.1 Complete or Evaluable Participants**

A participant is considered ‘Evaluable’ and eligible for the *mITT* analysis if they have completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline.

A participant is considered ‘Evaluable and Completed Per Protocol’ if they have completed all Experimental Sessions and CAPS-5 assessments as planned. These participants will be included in the *mITT* analysis set and the Per Protocol analysis set.

A participant is considered ‘Evaluable and Early Termination’ if they have completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline but terminated early. These participants will be included in the *mITT* analysis.

A participant is considered to be in good standing with the clinical site if, in the opinion of the investigator and/or therapy team, the participant was compliant with protocol requirements, even if they were unable to complete all study visits.

#### **4.3.2 Screen Failures**

‘Screen Failures’ are defined as participants 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 participants who begin Screening will be tracked on a Screening Log, and reasons for Screen Failure will be recorded. Screen Failures are not considered evaluable.

Screen Failures may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. Medical assessments may be repeated for confirmation. At any time during Screening, if a potential participant is deemed to be ineligible, classify as a Screen Failure, notify the potential participant that they are not eligible for the study, and do not schedule additional Screening assessments.

Participants 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 an IR assessment will be entered into the Electronic Data Capture (EDC) system.

#### **4.3.3 Pre-Dosing Early Terminations**

‘Pre-Dosing Early Terminations’ are defined as participants 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 participants may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to Enrollment Confirmation or the site may withdraw the participant for reasons described in Section 5.3.4 Early Termination from the Study). Participants who fail Enrollment Confirmation may not be re-

enrolled into this study at a later date. All enrolled participants, even those failing Enrollment Confirmation, 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 participant. At any time during the Preparatory Period, if a potential participant is deemed to be ineligible, classify as a Pre-Dosing Early Termination, notify the potential participant that they are not eligible for the study, and do not schedule additional assessments. Do not perform the next visit. Pre-Dosing Early Terminations will be provided an Exit Plan as described in Section 7.4.4 Exit Plan.

#### **4.3.4 Early Termination from the Study**

Participants who are removed from the study after they are enrolled and receive IP but do not complete the study may fall into one of these categories: Post-Dosing Early Termination or Dropout. If the participant has received IP in at least one Experimental Session and completed one CAPS-5 assessment beyond Baseline, they will be considered evaluable. All participants who receive IP in at least one Experimental Session will be included in all safety analyses.

Participants can withdraw from treatment or withdraw consent at any time for any reason without judgment. The site team can withdraw a participant if, in their clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the site team makes the decision to terminate the participant from treatment or the study, they will explain the reason for withdrawal and document in the participant's source records and eCRF. If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Site, affects the safety of the participant, including psychiatric diagnosis, pregnancy, or requiring use of prohibited medications, the participant will discontinue treatment in Experimental Sessions but remain in the study for the associated Integrative Sessions. Any time a participant terminates from the study early, the site team will attempt to obtain information about AE outcomes if appropriate, as determined by the site physician and Medical Monitor. The site team will provide the participant with an Exit Plan as described in Section 7.4.4 Exit Plan.

- **Post-Dosing Early Termination:** Participants who discontinue study treatment but continue to participate in study evaluations and outcome assessments. Data collection by Irs will continue on the same schedule as planned through Study Termination visit procedures.
- **Dropout:** If a participant decides to withdraw consent, they will terminate without further follow-up. If the participant agrees, they will complete a final CAPS-5 assessment at that time and complete Study Termination visit procedures. These participants are defined as dropouts who withdraw consent due to any reason after receiving at least one dose of IP and no longer participate in the study, *i.e.* no further contact with investigators or site staff. Data collected on study participants 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.
- Participants who dropped out or are lost to follow up may be replaced depending on timing of the discontinuation and whether sufficient video was gathered to provide clinical supervision.

#### **4.3.5 Lost to Follow-up**

A participant will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the site staff. If the participant has completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline, they will be considered evaluable. All participants with at least one Experimental Session will be included in the safety analysis.

If a participant does not attend a scheduled visit, the site must attempt to contact the participant to reschedule the visit as soon as possible and emphasize the importance of complying with the protocol specified visit schedule. The staff should determine if the participant is willing to comply with future visits.

If a participant does not respond to this initial contact, the site staff must make an effort to contact the study participant and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 1 week, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. In addition, site shall reach out to the contact person (relative, spouse, close friend or other support person) provided by the participant. Lastly, a certified letter (or equivalent) should be sent to their last known mailing address. If the participant fails to respond to all of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up.

#### **4.4 End of Study Definition and Premature Discontinuation**

The end of the trial is defined as the date of the last patient last visit (LPLV) for the last participant globally. LPLV for this study is scheduled at Visit 15 (study termination) as shown in Table 7: Time and Events – Study Measures.

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

In addition, the study may be halted or terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population is unacceptable.

#### **4.5 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 [ $d_{IGPP}$ ]=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 (75 to 125 mg) participants receiving two Experimental Sessions (N=72). 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 divided-dose of 80 mg to 180 mg MDMA administered in two Experimental Sessions. Initial doses per Experimental Session range from 80 mg to 120 mg MDMA, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg). 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 there is a reason to withhold. Total amounts of MDMA to be administered per Experimental Session range from 80 mg to 180 mg (Table 3).

**Table 3: Dose Regimen of MDMA**

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120* mg	40 or 60 mg	80 mg to 180 mg
<b>Total Cumulative Dose</b>			160 mg to 300 mg

\* Unless tolerability issues emerge with the initial dose or the participant declines

In the first Experimental Session, the initial dose will be 80 mg MDMA. In the second Experimental Session, the initial dose may be increased to 120 mg MDMA unless tolerability issues emerge with the initial dose or the participant declines. The choice of whether to keep the dose the same or increase it from the first Experimental Session will be made by the site team based on observed response, tolerability to the previously administered dose, and discussion with the participant. If a participant experiences a severe adverse event, soon after administration of MDMA during an experimental session, or they experience clinical signs and symptoms that may suggest end organ effects, the dose may not be escalated, or a supplemental dose may not be administered. Examples of these symptoms include chest pain, shortness of breath, neurological deficit or confusion, or other potential indicators of end organ effects that will prompt additional vital sign measurements, and intervention if appropriate. Please refer to the section 9.2 for additional details. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental half-dose unless tolerability issues emerge or the participant declines. Examples of tolerability issues include: if a patient experiences a severe adverse event after administration of MDMA during an experimental session, or they experience clinical signs and symptoms that may suggest end organ effects as specified in the protocol, the dose may not be escalated or a supplemental dose may not be administered. Examples of these symptoms include chest pain, shortness of breath, neurological deficit or confusion, or other potential indicators of end organ effects that will prompt additional vital sign measurements, and intervention if appropriate.

## 5.0 Psychotherapy

### 5.1 Description of Therapeutic Method

The largely non-directive therapeutic method of MDMA-assisted psychotherapy is described in detail in the Treatment Manual. All therapy teams will be extensively trained in a training program prior to the study to ensure all participants are treated in a similar manner. The non-directive approach pertains to inviting inquiry and providing suggestion rather than directing the participant in the therapeutic approach. This requires active or engaged listening and responding, as well as facilitation of therapeutic action by providing support for approaching difficult material in a manner that does not interfere with the participant's spontaneous experience.

## **5.2 Therapy Team Qualifications**

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

- One person licensed to manage and administer controlled substances for each site
- A physician to assess participant safety at Screening
- One or more male/female therapy teams
- One person per therapy team is required to be licensed to provide psychotherapy according to national requirements
- If one person on the therapy team is unlicensed, they must work under the direct supervision of the licensed team member

## **5.3 Training**

### **5.3.1 Therapy Training Program**

The MDMA Therapy Training Program is designed to teach competency in applying the essential elements of this method of 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 online training modules, and participating in an in-person training that includes watching and discussing videos of Experimental Sessions recorded in previous clinical trials. The required elements of the therapy are defined in the Treatment Manual, and teams will be trained on visit-specific sets of adherence criteria. The final part of training includes supervision provided by the sponsor at three dedicated time points during treatment of each therapy team member's first subject, and additionally as needed in subsequent cases. In addition to this specific training, it is required that participating therapy team members have the proper background, education, and experience.

## **5.4 Adherence to Therapeutic Method**

Psychotherapy sessions, including Experimental Sessions, will be videorecorded. Adherence rating and commentary will be conducted by qualified, trained, and reliable adherence raters who will analyze video data from select Preparatory Sessions, Experimental Sessions, and Integrative Sessions. The elements included in adherence criteria are specific to each type of session and are defined in the Treatment Manual. These ratings will be collected, at minimum, for each therapy team in the study. Ratings will be used to provide feedback to therapy teams through each team's supervisors.

## **6.0 Measures and Reliability**

The following eligibility, outcome, exploratory, and safety measures will be used in the study, in accordance with Protocol Objectives and Assessment Tools (Table 4) and Time and Events Study Measures (Table 7).

**Table 4: Protocol Objectives and Assessment Tools**

Objectives	Measure	Measure Type	Administration
<b>Eligibility</b>			
Assess Axis 1 psychiatric disorders	MINI	Eligibility	Tele-assessment (IR)/
Assess personality disorders	CIPD	Eligibility	Tele-assessment (IR) and Self-report measure at Site
Confirm PTSD diagnosis and severity	PCL-5 with LEC-5	Eligibility	Site
Identify Dissociative Identity Disorder	DDIS	Eligibility	Site
<b>Primary</b>			
Assess changes in PTSD symptom severity from Visit 3 to Visit 14	CAPS-5	Outcome	Tele-assessment (IR)
<b>Secondary</b>			
Assess changes in clinician-rated functional impairment from Visit 3 to Visit 14	SDS	Outcome	Tele-assessment (IR)
<b>Safety</b>			
Assess incidence of positive or serious ideation and suicidal behavior	C-SSRS	Safety	Tele-assessment (IR screening) and Site
<b>Exploratory</b>			
Characterization of CAPS-5 Total Severity score at weeks 3, 8, and 14 to explore onset of treatment efficacy with a descriptive time course plot	CAPS-5	Outcome	Tele-assessment
Explore changes in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, sleep and hyperarousal as measured by changes in CAPS-5 subscale scores	CAPS-5 subscale scores	Outcome	Tele-assessment
Assess overall changes in clinician-rated functional impairment through item scores from Visit 3 to Visit 14	SDS item scores	Outcome	Tele-assessment
Assess changes in severity of dissociative symptoms associated with PTSD from Visit 3 to Visit 14	DSP-I	Outcome	Tele-assessment
Explore correlation of dissociative symptoms associated with PTSD with the CAPS-5 Total Severity analyses	DSP-I CAPS-5	Outcome	Tele-assessment
Explore the effect of presence of secondary traumatic stressors during the assessment period as a covariate on the CAPS-5 Total Severity analyses	LEC-5 CAPS-5	Outcome	Site and Tele-assessment
Explore the effect of adverse childhood experiences on PTSD treatment outcomes as a covariate on the CAPS-5 Total Severity analyses	ACE CAPS-5	Outcome	Site and Tele-assessment
Explore changes in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal as measured by changes in CAPS-5 subscale scores	CAPS-5	Outcome	Tele-assessment

Objectives	Measure	Measure Type	Administration
Assess changes in depression symptoms from Visit 4 to Visit 15	BDI-II	Outcome	Site
Assess changes in chronic pain from Visit 4 to Visit 15	CPGS	Outcome	Site
Assess changes in quality of life from Visit 4 to Visit 15	EQ-5D-5L	Outcome	Site
Assess changes in self-compassion from Visit 4 to Visit 15	SCS	Outcome	Site
Assess changes in subjective effects from prior to drug intake, peak and at the end of the experimental session	SE	Subjective effects	Self-report measure at Site
Assess changes in alcohol use from Screening to Visit 15	AUDIT	Healthcare cost	Site
Assess changes in drug use from Screening to Visit 15	DUDIT	Healthcare cost	Site
Assess changes in nicotine use from Visit 4 to Visit 15	SRNU	Healthcare cost	Site
Assess changes in disordered eating from Visit 4 to Visit 15	EAT-26	Healthcare cost	Site
Assess facility-based healthcare utilization and economic productivity at Screening	UFEC	Healthcare cost	Site

## 6.1

### Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The last month CAPS-5 is a semi-structured interview that assesses index history of DSM-5-defined traumatic event exposure [72], including the most distressing event, time since exposure, to produce a diagnostic score (presence vs. absence) and a PTSD Total Severity score [72]. The CAPS-5 rates intrusion symptoms (intrusive thoughts or memories), avoidance, cognitive and mood symptoms, arousal and reactivity symptoms, duration and degree of distress and dissociation. The CAPS-5 will be administered by a blinded IR via tele-assessment. Interviews will be conducted by the centralized remote IR pool to enhance quality control by reducing site-level variation in interview fidelity and quality. The IRs will be trained and supervised by senior independent raters (SIRs) fluent in the local language. Per the CAPS-5 Training Manual for the IR Pool, IRs will ensure that every single item-level score is collected in every CAPS-5 interview. The CAPS-5 is administered by the IR in a neutral, non-leading manner to minimize the chance for bias. Avoiding a biased administration can be achieved by adhering to administration guidelines verbatim and only deviating from the script to clarify, re-direct, or query further if behavioral examples are needed to determine the appropriate symptom intensity rating. Avoiding building therapeutic/clinical rapport beyond the basic level of rapport needed to conduct the interview in the research setting also minimizes the chance for bias. Remote assessment assures that the rater who is collecting the Primary Outcome will not witness Experimental Sessions and the acute effects of IP. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy. After the initial screening visit, the IRs will be blinded to visit number, number of treatments received, and any study data for the participant. IR visits will be assigned based on availability.

## 6.2 Secondary Outcome Measure

### Sheehan Disability Scale (SDS)

The SDS is a clinician-rated assessment of functional impairment [73]. 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). For participants who are not able to work for reasons related to PTSD, the functional impairment item will be scored as a 10. The SDS takes 1 to 2 minutes to complete [73, 74].

## 6.3 Safety Measures

### Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [75]. 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. Participants who are discontinuing medications to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS Intensity scale 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 [76].

## 6.4 Screening Measures and Reliability

### Mini-International Neuropsychiatric Interview (MINI)

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 [77], is now compatible with DSM-5 and will be administered by a member of the Independent Rater Pool to screen for all psychiatric conditions other than personality disorders. 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 [78]. The MINI takes between 1-1.5 hours to perform and addresses major psychiatric disorders. MINI items were highly reliable (interrater 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 [78, 79]. Testing on non-psychiatric samples did not create false positives [77].

### Clinical Interview for Personality Disorders (CIPD)

A clinical interview for personality disorders (CIPD) will be conducted using either the Structured Clinical Interview for Personality Disorders DSM-5 (SCID-5-PD) or DSM-4 (SCID-4-PD) [80] or any other diagnostic measure approved by the sponsor and the responsible Ethics Committee and Competent Authority, as applicable per country.

Prior to the CIPD participants will complete a brief self-report (SR) questionnaire SCID-5-PD or SCID-4-PD or any other SR measure as applicable per country as a self-screening tool for personality disorders. Potential personality disorders that satisfy diagnostic thresholds will be

further assessed via clinical interview by a blinded IR via tele-assessment. IRs will receive training on administering these measures from a trainer. Interviews may be recorded as necessary to establish reliability of a random selection of interviews for accuracy.

### **Life Events Checklist for DSM-5 (LEC-5)**

The LEC-5 is a 17-item self-report instrument designed to determine the presence of traumatic life events in the assessment and diagnosis of PTSD. It is a companion measure to the PCL-5 and will be used to assess PTSD. The participant indicates whether each event listed has occurred during their lifetime, permitting the possibility of marking multiple events [81].

### **PTSD Checklist for DSM-5 (PCL-5)**

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the symptoms of PTSD per DSM-5 [82]. 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). A total PCL-5 score of 46 or greater at Screening will be required for initial enrollment.

### **Dissociative Disorders Interview Schedule for DSM-5 (DDIS)**

Questions on the DDIS specifically addressing dissociative disorder symptoms (items 117 to 132) will be asked by an IR during Screening. These questions are part of an intensive interview that includes questions concerning somatic and psychiatric symptoms. The interview is intended to assess and potentially distinguish between dissociative disorders and other disorders and between Dissociative Identity Disorder (DID) and a dissociative disorder not otherwise specified [83]. Owing to overlap with items found between the DDIS and other screening measures, only questions specifically addressing DID will be assessed.

## **6.5 Exploratory Measures**

### **The Dissociative Subtype of PTSD Interview (DSP-I)**

The DSP-I is a clinician-administered interview designed by an international team of PTSD researchers to detect and assess severity of the dissociative type of PTSD and recommended for use as an additional or complementary measure (“add-on”) to the CAPS-5 [84-87]. Assessments of military veterans and civilians support the existence of a dissociative subtype of PTSD that is associated with PTSD severity and derealization and depersonalization. The DSP-I takes approximately 5 to 15 minutes to complete. It consists of two parts, only Part 1 will be administered. Part 1 contains five items addressing depersonalization, four items addressing derealization, and a section that is administered if dissociative episodes are endorsed that assesses duration and perceived cause of episodes (seven items) and observer items (three items) addressing interviewee demeanor, including evidence of dissociation, such as forgetfulness or giving a statement that is bizarre within the context of the interview. If two or more items within this section are endorsed, this indicates the presence of other dissociative symptoms beyond depersonalization and derealization. The DSP-I was first developed in 2016 and revised in 2017.

### **Adverse Childhood Experience Questionnaire (ACE)**

The ACE is a 10-item checklist measure assessing number and types of adverse childhood experiences, including neglect and emotional, physical, and sexual abuse. Respondents are asked if an experience happened “often” and if so, to write “1”. The total score reflects the number of adverse childhood experiences. The measure was first used in the context of a study investigating the relationship between childhood adverse experiences and health outcomes in adulthood [88]. 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 [89-92]. The scoring method has been used in archival research, finding an association between increased scores and health problems in several generations [91].

In addition, developmental trauma events (DTE) during childhood and adolescence, including description and frequency of the events will be evaluated at screening and throughout the trial.

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

The BDI-II is a revision of the BDI, a 21-item self-report measure [93, 94] that will serve as a measure of depression symptom severity [95]. 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 [95]. 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 [95, 96]. Higher scores indicate more severe depressive symptoms.

### **Chronic Pain Grade Scale (CPGS)**

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 [97]. 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 [98].

### **EuroQol Five Dimensions – Five Levels Questionnaire (EQ-5D-5L)**

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 statements 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”) [99, 100]. In the second part of the EQ-5D-5L, current degree of health (“your health today”) is indicated by marking a 100 mm line, 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 (Visual Analogue Scale) is the location of the mark. 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 [101]. 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 [102]. The EQ-5D-5L takes about 3 minutes to complete.

### **Self-Compassion Scale (SCS)**

The SCS is a 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience [103]. Respondents complete the SCS by indicating how typical they feel on each item on a five-point Likert scale (1=Almost never and 5=Almost always). It is estimated to take between 4 to 8 minutes to complete. The scale has six sub-scales: Self-Kindness, Self-Judgment, Common Humanity, Isolation, Mindfulness, and Over-Identified. The mean of subscale scores serves as a total score. Analysis of SCS response indicated that subscales are all related to a higher order factor of self-compassion, and the measure has high test-test reliability at a level of 0.93. Neff *et al.* reported an inverse relationship between SCS total scores and scores on measures of depression and anxiety. Self-compassion and global self-esteem are both related to positive mood and optimism, but self-compassion may be more strongly associated with stable mood and less associated with self-rumination and anger [104].

### **Alcohol Use Disorders Identification Test (AUDIT)**

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) [105]. 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 [106].

### **Drug Use Disorders Identification Test (DUDIT)**

The DUDIT is an 11-item measure designed to assess presence of substance use disorders [107]. 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% [107]. The English translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.

### **Self-reported Nicotine Use (SRNU)**

The SRNU is a sponsor-developed measure that will assess participant'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.

### **Eating Attitudes Test (EAT-26)**

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 27<sup>th</sup> 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 [\[108\]](#).

### **Utilization of Facility-based and Emergent Care (UFEC) and Economic Productivity**

The UFEC is a sponsor-developed measure assessing participant 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.

In addition, participants employment/disability status and income level will be collected in order to assess economic productivity.

### **Subjective Effects (SE)**

Subjective effects on 15 items (negative mood, body perception changes, confusion, difficulty concentrating, compassion for self, compassion for others, euphoria, positive mood, intellectual efficiency, social, calmness, talkative, open to new experiences, meaningful experience, emotional distress) will be collected using the VAS at three time points: initial dose of MDMA, prior to supplemental dose of MDMA and at the end of the experimental session (see Table 8). VAS items are rated on a series of 100 mm long lines, marked from 'not at all' on the left to 'extremely' on the right. The subjective effects chosen for the scales are based on literature reviews of subjective effects of MDMA among healthy volunteers in controlled studies [\[109\]](#), [\[110\]](#).

## **7.0 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 (Table 5 and 6) and Medical Monitor consulted if necessary. If there are delays of more than a week between visits or contact, the site should assess the need for additional telephone contact with the participant to ensure safety.

**Table 5: Time and Events – Screening and Preparatory Study Procedures**

	Screening Period (2 to 6 weeks)			Preparatory Period w/ Enrollment Confirmation (2 to 11 weeks)				
	Screening		Enrollment	Preparatory		Baseline CAPS-5 T1	Baseline & Enrollment Confirmation	
Visit	Phone Screening	Screening	IR Screening	V0	V1	V2	V3	V4
Visit Description	Phone Calls	In-person Visits & Labs	Tele- assessment	Enrollment	Prep. 1	Prep. 2	Tele- assessment	Prep. 3 & Enrollment Confirmation
Visit Timing	Prior to Initial Screening	Over 3 weeks (-2 /+1 weeks)	2 days after initial eligibility met (+7 days)	2 days post IR Screening (+12 days)	Within 1 week of V0 (0 to 12 days)	2 to 21 days of V1	Post V2 & Taper	3 to 6 days after V3; 1 to 4 days before V5
Initial Phone Screen	✓ <sup>A</sup>							
Informed Consent	Send Copy	✓						
Follow-up Phone Screen	✓							
Assess Eligibility	✓	✓		✓	✓	✓		✓
Medical/Psychiatric History	✓ <sup>B</sup>	✓			✓	✓		✓
Past/Current Medication & Adherence	✓	✓			✓	✓		✓
Weight, Blood Pressure, Pulse, Temperature		✓						
Physical Exam		✓						
ECG <sup>C</sup> & Rhythm Strip		✓						
Clinical Lab Tests		✓						
Drug Test <sup>D</sup>		✓						✓
Pregnancy Test <sup>E</sup>		✓						✓
Digital Recording of Visit			✓		✓	✓	✓	✓
Medication Taper				✓	✓	✓		
Study Enrollment				✓				✓ Confirmed
AE Assessment <sup>F</sup>				✓	✓	✓		✓
90-min Preparatory Session					✓	✓		✓
Phone Call Follow-up <sup>G</sup>						✓		

<sup>A</sup> In Germany phone screening is not permitted

<sup>B</sup> At Screening, collect data on previous hospitalizations, healthcare utilization and economic productivity. Request participants to obtain medical/psychiatric records to bring to the next in-person screening visit.

<sup>C</sup> ECG to be conducted at any time if clinically indicated.

<sup>D</sup> In the UK, also includes testing for alcohol.

<sup>E</sup> PABP Only. Urine or serum (UK: serum only).

<sup>F</sup> Adverse Events (Aes) Assessment includes collecting Serious Adverse Events, Aes of Special Interest, Aes of Psychiatric Status, Aes requiring medical advice or attention, Aes that indicate withdrawal of a participant, and all other Aes

<sup>G</sup> If needed, call participant to confirm medication tapering and stabilization is complete prior to Visit 3

**Table 6: Time and Events – Treatment and Follow-up Period**

	Treatment Period ~8 weeks (+/-3 weeks)									Follow-up Period & Study Termination (~4 weeks) 13 weeks (+/-3 weeks) post baseline	
	Treatment 1					Treatment 2				Primary Outcome	Study Termination
Visit	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Visit Description	Exp. 1	Int. 1.1	Int. 1.2	CAPS-5 T2: Tele-assessment	Int. 1.3	Exp. 2	Int. 2.1	Int. 2.2	Int. 2.3	CAPS-5 T3 Outcome: Tele-assessment <sup>A</sup>	Study Termination
Visit Timing	Within 1 week of V3	Morning after V5	3 to 14 days after V5	18 to 30 days after V5	20 to 34 days after V5	21 to 35 days after V5	Morning after V10	3 to 14 days after V10	20 to 34 days after V10	13 weeks post V5 (+/-3 weeks)	2 days post V14 (-1/+7 days)
Concomitant medication review	✓	✓	✓		✓	✓	✓	✓	✓		✓
Symptom-directed Physical Exam	✓					✓					✓ <sup>B</sup>
Drug Test <sup>C</sup>	✓					✓					
Pregnancy Test <sup>D</sup>	✓					✓			✓		
Digital Recording of Visit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
AE Assessment <sup>E</sup>	✓	✓	✓		✓	✓	✓	✓	✓		✓
Administer IP	✓					✓					
8-hour Exp. Session	✓					✓					
Blood Pressure, Pulse, Temperature <sup>F</sup>	✓					✓					✓
Overnight Stay	✓					✓					
90-min Integrative Session		✓	✓		✓		✓	✓	✓		
Phone Call Follow-up <sup>G</sup>		✓					✓				

<sup>A</sup> All visits must be scheduled to ensure that the Primary Outcome CAPS-5 T3 assessment is within the overall window provided: 13 weeks (+/-3 weeks) post V5

<sup>B</sup> At Study Termination, includes weight. A symptom-directed physical exam to be conducted only if clinically indicated.

<sup>C</sup> In the UK, also includes testing for alcohol. Must be completed prior to IMP dosing.

<sup>D</sup> PABP only. At Visit 5 and Visit 10, a negative urine pregnancy test must be confirmed prior to IMP dosing.

<sup>E</sup> Adverse Events (Aes) Assessment includes collecting Serious Adverse Events, Aes of Special Interest, Aes of Psychiatric Status, Aes requiring medical advice or attention, Aes that indicate withdrawal of a participant, and all other Aes.

<sup>F</sup> During Experimental Sessions, vitals are measured before Investigational Product administration, immediately before the supplemental dose is administered (or would be, if supplemental dose not given), approximately 8 hours after initial dose, and as needed.

<sup>G</sup> 4 days of phone call follow-up: Day 2 and 7 after the Experimental Session, with two additional calls in between.

**Table 7: Time and Events – Study Measures**

	Visit #	Screening		Baseline & Enrollment Confirmation		Treatment 1				Treatment 2			Follow-up & Study Termination	
		Site <sup>A</sup>	IR Screening	IR V3	V4	V5	V6&7	IR V8	V9	V10	V11&12	V13	IR V14	V15
Visit Description	~Time to Complete Measure (minutes)	Site Visit	Tele-assessment	Tele-assessment	Site Visit	Exp. Session 1	Int. Sessions 1.1 & 1.2	CAPS-5 T2: Tele-assessment	Int. Session 1.3	Exp. Session 2	Int. Sessions 2.1 & 2.2	Int. Session 2.3	CAPS-5 T3: Outcome: Tele-assessment	Study Termination
CAPS-5	90 (Baseline) 60 (all others)			✓				✓					✓	
SDS	2			✓				✓					✓	
DSP-I	15			✓				✓					✓	
C-SSRS <sup>B</sup>	10	✓	✓		✓	✓ <sup>C</sup>	✓		✓	✓ <sup>C</sup>	✓	✓		✓
MINI	90		✓											
CIPD-SR	20	✓												
CIPD	60		✓											
LEC-5	5	✓			✓				✓			✓		✓
PCL-5	8	✓			✓				✓			✓		✓
DDIS <sup>D</sup>	5		✓											
ACE	4				✓									
BDI-II	10 (Baseline) 5 (all others)				✓									✓
CPGS	5				✓									✓
EQ-5D-5L	3				✓									✓
SCS	6				✓									✓
AUDIT	3	✓												✓
DUDIT	3	✓												✓
SRNU	3				✓									✓
EAT-26	6				✓									✓
UFEC	3				✓									
SE	2					✓				✓				
~Total Time of Completing Measures (minutes)		49	165	107	50	12	10	77	23	12	10	23	77	57

<sup>A</sup> Ensure that LEC-5 and CIPD-SR results are sent to the Independent Rater

<sup>B</sup> First C-SSRS is a Lifetime assessment, other assessments are Since Last Visit

<sup>C</sup> Conducted pre- and post-IP administration, and at phone calls on Days 2 and 7 after Experimental Session

<sup>D</sup> The relevant questions (117 to 132) from the DDIS will be asked by the Independent Rater during the IR Screening visit. The entire measure will never be administered.

## 7.1 Screening Period

### 7.1.1 Screening

Prospective participants will be pre-screened by telephone (*except in Germany*) according to an EC/HA-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 participants 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 participant is deemed ineligible, they will be classified as a Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments.

Site staff (preferably one of the therapists who would be treating this potential participant) will explain and obtain written informed consent using the EC/HA-approved informed consent form (ICF). If deemed eligible, the potential participant will receive a copy of the ICF for review and will be invited to the site for in-person discussion and screening. The ICF will always be thoroughly explained and signed during the in-person visit at site.

Written consent must be obtained prior to performing any tests or evaluations for the study.

Medical and psychiatric records are required for the site physician to obtain a well-characterized medical history and assess eligibility. The physician may need to contact the prescribing physician to discuss the tapering of medications (see Section 11.0 Concomitant Medications). If a participant 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 tele-assessment, 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 site staff will schedule the IR assessment and send IR the results of initial measures.

The sponsor recommends the following order of assessments:

#### *Initial Eligibility*

Qualified site staff will:

- Review medical and psychiatric history with the participant via interview and review of provided records. If no records were provided or those provided are not sufficient, request additional records. Collect data on previous hospitalizations, healthcare utilization and economic productivity.
- Assess depersonalization (out of body experiences) and derealization (unreal experiences) history.

- Support the participant during completion of the LEC-5 with PCL-5 to confirm PTSD diagnosis and 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.
- Review past and current medications and adherence to prescriptions.
- Assess ability to become pregnant and discuss requirement for commitment to adequate birth control for the duration of the study. Collect sample for pregnancy test from PABP (serum in UK; serum or urine for all other countries).
- Perform a urine drug test.
- Perform alcohol test (UK only).
- Direct participant to complete self-reported Screening measures:
  - CIPD-SR
  - AUDIT
  - DUDIT
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, potential participant 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, except in Germany where all assessments will be conducted within study site facilities.

### *Medical Assessments*

The physical exam must be performed by a qualified physician and laboratory assessments must be completed at a designated laboratory. 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)
- TBI assessment with residual neurological signs or symptoms on the neurological part of the physical exam
- ECG and 1-minute rhythm strip
- Clinical laboratory assessments, per Section 12.0 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 participant'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 participant will not be eligible for enrollment and will be advised to see their personal physician for further evaluation. If HCV serology is positive and the potential participant has not already been evaluated for possible treatment of HCV, they will be referred to a physician with expertise in evaluating and treating liver disease. After this evaluation and after completion of any recommended treatment, if the HCV is judged by this physician to be relatively stable and of mild severity, the participant may be enrolled, if there are no other contraindications.

- If the potential participant has well-controlled hypertension and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG, and if the investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for stress test with either echocardiography or nuclear imaging, and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the person may be enrolled if there are no other contraindications. Additional cardiovascular testing to confirm eligibility may be performed in consultation with Medical Monitor. Participants taking one or more antihypertensives may be enrolled in the study. The investigators will record and review medications used to control hypertension prior to enrollment.

Additional visits or repeat assessments (in person, at home, by telephone, or via tele-assessment) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential participant. For instance, at home blood pressure measurements may be required to corroborate or rule out undiagnosed hypertension or to determine if an ongoing diagnosis of hypertension is controlled per the ESC guidelines, and as required per the eligibility criteria of this protocol.

Once all results are obtained, the site team will review all medical assessments, notes from interviews and discussions, medical records, and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the site physician will request additional tests, assessments, or measures as indicated. The site physician may also contact outside providers with participant permission as needed. If deemed initially eligible, the site staff will schedule the IR screening and send results of LEC-5 and CIPD-SR to the IR. Although the IR visit is by tele-assessment, the participant will be provided a location to complete the tele-assessment visits at the study site if needed. For the first IR assessment, the site can provide technical support before the assessment and therapeutic support after, if needed. The site staff will instruct the participant on how to access the tele-assessment visits going forward. For all IR visits discuss with the participants that they should have adequate internet access and be in a private and quiet space where they are comfortable talking about personal matters.

### **7.1.2 Remote Visits**

Some of the non-drug psychotherapy sessions and online evaluations may be permitted remotely, via tele-assessment (online video meetings), rather than at the study site. Remote visits if deemed appropriate may be permitted based on prior experience or in the context of local regulation due to a pandemic. There may be benefits to remote visits, such as convenience and reduced risk of COVID-19 transmission. There may be risks, including potential breach of security and technological difficulties or interruptions.

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

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

- Integrative Sessions may be conducted by tele-medicine

- Delaying the start of medication tapering after enrollment and the subsequent Treatment Period per Section 11.1 Tapering Instructions
- Delaying Experimental Sessions and associated Integrative Sessions
- Delaying Independent Rater assessments for participants who cannot complete them remotely off-site
- Use of prohibited medications and/or cannabis or initiation of new therapy for participants with significant study delays, which will be reviewed by the study team before each Experimental Session and re-tapered prior to resuming treatment per Section 11.0 Concomitant Medications.

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

### **7.1.4 Independent Rater Screening**

If participants meet initial eligibility during Screening, an IR will continue the eligibility assessment via tele-assessment after reviewing the results of the LEC-5 and CIPD-SR. The IR interview will be recorded to assess reliability of ratings. If possible, the potential participant should be present at the study site during this assessment, in case the therapy team is needed for support. If a participant reports suicidal ideation during this assessment, the IR will contact the therapy team after the call and present any concerns. The therapy team will follow-up with the participant to ensure safety, provide support, recommend treatment, or schedule a visit to the study site.

- Using the results of the CIPD-SR to guide the interview, the IR will perform the CIPD to assess personality disorders. Only appropriate modules will be completed.
- The IR will also ask relevant questions from the DDIS to identify dissociative disorders and administer the Since Last Visit C-SSRS to determine suicidal risk.
- The IR will complete MINI interview to assess Axis I psychiatric disorders.

The results from the MINI, CIPD, DDIS, and C-SSRS will be provided to the therapy team at the site to review along with all other Screening information to determine eligibility. Items assessed by the IR at this visit will be confirmed in the Preparatory Period by clinical observation, but the measures will not be repeated. If site staff deem the participant eligible, schedule Enrollment (Visit 0).

If the results of the any measure or interview indicate a diagnosis is present, the investigator is not permitted to use their clinical judgment to question the diagnosis. However, if a diagnosis is not present or uncertain according to any measure or interview, but the investigator believes the participant presents with a particular disorder, they may diagnose and deem the participant ineligible for the trial.

### **7.1.5 Enrollment**

In advance of Visit 0, the site team will review all notes from Screening visits, medical assessments, IR assessments, notes, discussions, medical records, and measures against eligibility criteria. If the participant 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 participants. For all details on concomitant



medications, tapering, allowed, and prohibited medications refer to Section 11.0 Concomitant Medications.

At study onset at each site, if a potential participant is eligible, the study team will contact the Medical Monitor to discuss the medical history and screening data available for review to confirm the potential participant is eligible for enrollment.

If a participant is confirmed as eligible for enrollment, the participant will be notified of enrollment at Visit 0 in-person, via tele-assessment, or by telephone.

Medical history and medication information will be reviewed for completeness. A medication tapering plan will be discussed with the participant, if applicable. If agreeable, the participant will be enrolled in the study. Once enrolled, AE collection requirements begin (refer to Section 10.0 Safety). V0 should take place 2 days (+12 days) after Independent Rater Screening is completed. Visit 0 and Visit 1 may take place on the same day.

## **7.2 Preparatory Period with Enrollment Confirmation**

Participants will undergo three Preparatory Sessions (Visits 1, 2, and 4) lasting approximately 90 minutes with the therapy team prior to the first Experimental Session. The Preparatory Period will be initiated within 12 days of Visit 0 and last 2-11 weeks, depending on duration of medication tapering. There must be at least 48 hours between Preparatory Sessions. The minimum time to complete the Preparatory Period is 2 weeks. The Preparatory Period will also include the Baseline CAPS-5 assessment (Visit 3), which will be assessed by an IR.

Adherence criteria for Preparatory Sessions should be followed per the Treatment Manual. In these visits, the therapy team will work with the participant 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.

### **7.2.1 Preparatory Session 1 and Preparatory Session 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 participant 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 1 week (0 to 12 days) 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 at least 2 days after Visit 1. The visit timing should take into account appropriate times for monitoring medication tapering. Visit 2 must take place at least 2 days after and within 3 weeks of Preparatory Session 1 (Visit 1)

- If tapering is ongoing at Preparatory Session 2 (Visit 2), the site team will schedule a telephone call after tapering and stabilization are complete to confirm that the participant is eligible for the Baseline CAPS-5 assessment. If tapering is complete or not needed, the site team will confirm eligibility and schedule Baseline CAPS-5 T1 (Visit 3) and Preparatory Session 3 (Visit 4) as soon as possible.

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

- Record the therapy session.
- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record AEs as described in Section 10.0 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 [\[111\]](#).

If a participant would like a companion present during or after the Experimental Session, a meeting between the therapy team and that individual will be scheduled prior to the first Experimental Session. There must be mutual agreement between the participant and therapy team concerning the presence of the companion and companion should receive study information to read and to sign informed consent form before joining therapy or experimental sessions.

During one of the Preparatory Sessions, if possible, the therapy team will introduce the participant to the attendant who will remain with the participant during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress. The site will make all attempts to have the same attendant for each Experimental Session for a given participant, but it is not guaranteed.

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

### **7.2.2 Baseline: CAPS-5 by Independent Rater**

At Visit 3, an IR will measure the Baseline CAPS-5 (referred to as Baseline CAPS-5 T1) via tele-assessment as soon as possible after medication tapering, stabilization, and two Preparatory Sessions are complete. This visit will be recorded to video to establish inter-rater reliability. The scores will be sent as soon as possible to the site staff. A CAPS-5 Total Severity Score of at least 35 is required to meet Enrollment Confirmation criteria. The IR will also administer the DSP-I and SDS.

### **7.2.3 Baseline: Preparatory Session 3 and Enrollment Confirmation**

Prior to Visit 4, the site team will review the results of the IR visit to ensure that the CAPS-5 Total Severity Score is at least 35. Visit 4 should be scheduled within 6 days of the Baseline CAPS-5 assessment but ideally will take place as close to Experimental Session 1 (Visit 5) as possible, but not on the same day.

At Visit 4, the site team will confirm eligibility by reassessing specified eligibility criteria and ensuring that the participant continues to agree to all lifestyle modifications. If the participant continues to be eligible for the study, enrollment will be confirmed (after approval from the Medical Monitor for the initial participants until confidence is established). If any requirements are not met before or during Visit 4, the participant will be considered a Pre-Dosing Early Termination.

For eligible participants at Visit 4, qualified site staff will ensure at least 3 hours are scheduled for the visit and:

- Collect urine sample for pregnancy test from PABP.
- Perform urine drug test.
- Perform alcohol test (UK only).
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- Actively support participant in the completion of Baseline self-reported measures:
  - PCL-5- ensure assessment is in relation to index trauma
  - ACE
  - BDI-II
  - CPGS
  - EQ-5D-5L
  - SCS
  - SRNU
  - EAT-26
  - UFEC and economic productivity

Completion of the measures does not need to be recorded.

- Complete the third 90-minute Preparatory Session (as described in Section 7.2.1 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 participants of lifestyle modifications, including fasting and refraining from using psychoactive or non-approved medications, pertinent prior to the Experimental Session per Section 3.3 Lifestyle Modifications.
- Schedule Visit 5.

### **7.3 Treatment Period**

During the Treatment Period, which occurs over a duration of 5 to 12 weeks (Visits 5 to 13), participants will complete two treatments. Each treatment consists of an Experimental Session, followed the morning after by an Integrative Session, phone follow-ups over the next week, a second Integrative Session within 2 weeks, and a third Integrative Session within 3 to 5 weeks. The Experimental Sessions will be scheduled 3 to 5 weeks apart. The CAPS-5 will be assessed at one time point during the Treatment Period: CAPS-5 T2 after Integrative Session 1.2 (Visit 7). The Primary Outcome CAPS-5 T3 will be assessed after the last Experimental Session during the Follow-up Period.

## 7.3.1 Experimental Sessions

### 7.3.1.1 Psychotherapy Session

There will be two open-label Experimental Sessions (Visits 5 and 10). Procedures for MDMA-assisted psychotherapy will remain the same across all sessions and all procedures regardless of dose received (Table 7). Experimental Sessions must be at least 8 hours long, measured from 30 minutes prior to IP administration.

- Experimental Session 1 (Visit 5) will occur within 1 week of the Baseline CAPS-5 (Visit 3) assessment. If the Baseline CAPS-5 assessment is completed outside of the allowed window, the investigator should consult the CRA and Medical Monitor to determine if the assessment should be repeated. The first Experimental Session will include 80 mg of IP followed by a supplemental half-dose 1.5 to 2 hours after the initial dose unless tolerability issues emerge with the first dose or the participant declines.
- Experimental Session 2 (Visit 10) will occur within 3 to 5 weeks of Experimental Session 1 (Visit 5) and after Integrative Session 1.3 (Visit 9). 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 tolerability issues emerge with the first dose or the participant declines.

**Table 8: Schedule of Procedures for Experimental Sessions**

Approximate Time	Procedure or Action
9:30	Urine drug screen, alcohol test (UK only), pregnancy test, Symptom-directed Physical Exam, concomitant medication information collected, participant acclimated to environment, C-SSRS
9:55	Baseline BP, body temperature, pulse, SE
10:00	<b>IP Administration</b> , Begin video recording
11:30	BP, body temperature pulse, SE <b>Supplemental Dose Administration</b> , unless tolerability issues emerge with the first dose or the participant declines
17:30	C-SSRS, BP, body temperature, pulse, SE

#### *Pre-IP administration*

- On the day of the Experimental Session, the participant will arrive approximately 30 to 60 minutes prior to IP administration.
- The site team will ensure the participant has not used caffeine or nicotine 2 hours prior and fasted for 10 hours prior to IP administration and complied with all other requirements per Section 3.3 Lifestyle Modifications.
- The site team will inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements and record AEs as described in Section 10.0 Safety.
- The site team will instruct the participant that they will not be able to use caffeine or nicotine at least 6 hours after the IP administration.
- The site team will complete symptom-directed physical exam, 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 IP administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study, based on Medical Monitor review.

- b. A positive pregnancy screen is cause for withdrawal from the protocol.
- The therapy team will administer Since Last Visit C-SSRS.
  - The therapy team will review procedures for the Experimental Session with the participant and discuss the participant'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 therapy team in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the participant.
  - If the participant 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. Participant subjective effects (SE) self-rated VAS measures on 15 items (negative mood, body perception changes, confusion, difficulty concentrating, compassion for self, compassion for others, euphoria, positive mood, intellectual efficiency, social, calmness, talkative, open to new experiences, meaningful experience, emotional distress) will be collected at three time points: prior to initial dose of MDMA, prior to supplemental dose of MDMA and at the end of the experimental session (see Table 8). A symptom-directed physical examination will be conducted at any time if clinically indicated.

#### *During the Experimental Session*

- After video recording has begun, at approximately 10:00 in the morning, a qualified staff member will administer the initial dose of IP with water. The participant will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided for the participant if they wish to use them. Whenever they wish, participants may speak to the therapy team, who will provide guidance and support, as needed.
- After the first hour, if the participant has not spoken spontaneously, the therapy team will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the therapy team will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.
- Fluids will be provided throughout the session but not to exceed three liters overall.
- Blood pressure, body temperature, pulse and SE will be measured approximately 1.5 to 2 hours after the initial dose, before the supplemental dose is administered.
- The site physician (if not part of the therapy team) 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 with a glass of water approximately 1.5 to 2 hours after the initial dose, unless the participant experiences tolerability issues.
- 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 remain in the waiting room until a member of the therapy team brings them to the session room. Alternatively, the companion may arrive after the session has ended.

#### *End of Experimental Session*

- The therapy team will administer Since Last Visit C-SSRS.
- The therapy team will record AEs and concomitant medications.

- Blood pressure, body temperature, pulse and SE will be measured including a symptom-directed physical exam if clinically indicated.
- The session may be ended if all medical and psychiatric parameters are acceptable, elevations in vital signs have resolved to pre-IP levels, the participant is alert, ambulatory, and emotionally stable, and the night attendant has arrived.
- The therapy team or site physician shall remain available to participants via 24-hour cellular phone for integration, as needed.

#### *Overnight Stay*

- Participants will remain overnight in an appropriately furnished room at or near the study site until after the Integrative Session the morning after each Experimental Session. If in line with country specific regulations and site standard operation procedures, with prior approval of the therapy team, a companion may accompany the participant during the overnight stay.
- An attendant will check in periodically on the participant during the overnight stay, even if a companion is present. The attendant will monitor participant condition and will help participants relax during the overnight stay. The attendant will be an individual with previous training in managing psychological distress and will be supportive but not intrusive. If there is an emergency or the participant needs additional support, the attendant can contact the therapy team.
- The participant and a companion (if applicable) will receive information that will allow them to contact the therapy team during the overnight stay in the case of an emergency or to request for additional support.
- Participants 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.
- The participant will be driven home after the integration session by either a driver arranged by the participant, by site personnel or taxi.

### **7.3.2 Telephone Contact After Experimental Sessions**

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

At each telephone contact, the therapy team will:

- Inquire about any possible changes in health, assess the participant's mental health and the status of any previously recorded AEs, and record AEs as described in Section 10.0 Safety
- Inquire about concomitant medication use and compliance
- Offer support in accordance with the Treatment Manual
- On the second and seventh contact day after an Experimental Session the therapy team will administer the Since Last Visit C-SSRS.

### 7.3.3 Integrative Sessions

After each Experimental Session, three Integrative Sessions will take place. Each session will consist of 90 minutes of psychotherapy.

#### *Treatment 1*

- Integrative Session 1.1 (Visit 6): morning after Experimental Session 1 (Visit 5)
- Integrative Session 1.2 (Visit 7): 3 to 14 days after Experimental Session 1 (Visit 5) and at least 2 days after Integrative Session 1.1 (Visit 6)
- Integrative Session 1.3 (Visit 9): within 3 to 5 weeks after Experimental Session 1 (Visit 5) and 1 to 7 days in advance of Experimental Session 2 (Visit 10). At least two days after Integrative Session 1.2 (Visit 7). This visit serves two purposes: to continue integration and to prepare for the next Experimental Session. The participant will complete the LEC-5 and PCL-5 self-report measures.

#### *Treatment 2*

- Integrative Session 2.1 (Visit 11): morning after Experimental Session 2 (Visit 10)
- Integrative Session 2.2 (Visit 12): approximately 2 weeks after Experimental Session 2 (Visit 10)
- Integrative Session 2.3 (Visit 13): within 3 to 5 weeks of Experimental Session 2 (Visit 10). This visit serves to continue integration. The participant will complete the LEC-5 and PCL-5 self-report measures. For PABP, a final urine pregnancy test will be conducted at this visit, Visit 14 or Visit 15 (representing the end of the relevant systemic exposure, 5 half-lives after the last IMP dose, and at least 2 weeks after the last MDMA experimental session).

During Integrative Sessions, the therapy team will:

- Record the session.
- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 10.0 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 participant during the Experimental Session, including thoughts, feelings, and memories. If necessary, the therapy team will help the participant to reduce any residual psychological distress they are experiencing. The therapy teams will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in Experimental Sessions to emotionally threatening everyday situations. The therapy teams will be supportive, validate the experience, and facilitate understanding and emotional clearing.
- Be accessible for additional support via telephone or tele-assessment if needed.
- At each third Integrative Session, direct the participants to complete the LEC-5.
- At each third Integrative Session, direct the participants to complete the PCL-5.

### **7.3.4 Independent Rater Assessments**

Participants will have one CAPS-5 assessment during the first treatment period of the study (Visits 8). An IR from the IR Pool will conduct the assessments via tele-assessment. These assessments may be recorded to establish inter-rater reliability. The results may be shared with site staff, but the IR Coordinator will enter the data. The IR will also administer the DSP-I and SDS at these time-points:

- Baseline CAPS-5 T1 (Visit 3): At least 7 days after Preparatory Session 2 (Visit 2) and confirmation of end of tapering and stabilization off medications and eligibility is confirmed.
- CAPS-5 T2 (Visit 8): 3 weeks (-3/+9 days) after Experimental Session 1 (Visit 5) or 18 to 30 days after Experimental Session 1 (Visit 5), between Integrative Session 1.2 (Visit 7) and Integrative Session 1.3 (Visit 9)
- CAPS-5 T3 (Visit 14): 8 weeks (+/-2 weeks) after Experimental Session 2 (Visit 10), after last Integrative Session 2.3 (Visit 13)

### **7.4 Follow-up Period and Study Termination**

#### **7.4.1 Follow-up Period**

After the last Integrative Session 2.3 (Visit 13), participants will enter follow-up for approximately 4 weeks (+/- 2 weeks) with no protocol required visits until the final CAPS-5 assessment (Visit 14) followed by a Study Termination (Visit 15). Participants will have access to therapy teams for support if needed, and additional visits via telephone, tele-assessment, or in person can be scheduled if requested. Participants will continue to comply with protocol requirements for concomitant medications until after Study Termination.

#### **7.4.2 Final Independent Rater Assessment**

Participants will have a final CAPS-5 assessment at the completion of the follow-up period (Visit 14). An IR from the IR Pool will conduct the assessments via tele-assessment. These assessments may be recorded to establish inter-rater reliability. The IR Coordinator will enter the data in stand-alone database. The results may be shared with site staff during supervision by the therapy training team. Although there are allowable windows for all visits throughout the protocol, the Primary Outcome CAPS-5 T3 assessment must be completed 13 weeks (+/- 3 weeks) after the Baseline CAPS-5 assessment and within 8 weeks (+/-2 weeks) of Experimental Session 2 (Visit 10). Participants who have withdrawn from treatment will also complete a final CAPS-5 assessment immediately upon withdrawal. The IR will also administer the DSP-I and SDS.

#### **7.4.3 Study Termination**

Study Termination (Visit 15) will take place 2 (-1/+7) days after the final CAPS-5 assessment (Visit 14). Participants who have withdrawn from treatment but have continued for follow-up will also complete this assessment immediately upon withdrawal.

The site team will:



- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS.
- Conduct symptom-directed physical examination if clinically indicated.
- Conduct pregnancy test (at Visit 13, 14 or 15, or earlier if early withdrawal).
- Measure weight (used to calculate BMI).
- Measure blood pressure.
- Provide and discuss a study exit plan.
- Actively support participant in completion of Study Termination self-reported measures:
  - LEC-5
  - PCL-5, ensure assessment is in relation to index trauma
  - BDI-II
  - CPGS
  - EQ-5D-5L
  - SCS
  - AUDIT
  - DUDIT
  - SRNU
  - EAT-26

Completion of the measures do not need to be recorded.

After all Study Termination measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life. The study team will provide an Exit Plan, which may include a referral for additional medical or therapeutic care, as described in Section 7.4.4 Exit Plan. Eligible participants will be asked whether they are interested in participating in the LTFU extension study.

#### **7.4.4 Exit Plan**

At Study Termination, participants 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. Participants may request a referral for further therapeutic or medical care if appropriate. Enrolled participants who terminate the study early will be provided an Exit Plan at their last contact. Screen Failures will be provided a referral if requested.

### **8.0 Investigational Medicinal Product**

#### **8.1 Description of Active Compounds**

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

### **8.1.1 Doses**

This study will compare the effects of two 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 mannitol and magnesium stearate, 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 (Table 3). All drug is encapsulated with HPMC capsules.

### **8.1.2 Dose Modifications**

In the first Experimental Session, the initial dose will be 80 mg MDMA. In the second Experimental Sessions, the initial dose may be increased to 120 mg MDMA unless tolerability issues emerge with the first dose or the participant declines. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the therapy team in consultation with the site physician based on observed response, tolerability of the previously administered dose, and discussion with the participant. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental half-dose unless tolerability issues emerge with the first dose or the participant declines. Tolerability issues include: if a patient experiences a severe adverse event after administration of MDMA during an experimental session, or they experience clinical signs and symptoms that may suggest end organ effects as specified in the protocol, the dose may not be escalated or a supplemental dose may not be administered. Examples of these symptoms include chest pain, shortness of breath, neurological deficit or confusion, or other potential indicators of end organ effects that will prompt additional vital sign measurements, and intervention if appropriate.

### **8.1.3 Stability**

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

## **8.2 Handling**

### **8.2.1 Encapsulation, Packaging, and Labelling**

The IMP is packaged in 40 mg and 60 mg containers. All container labels will comply with country and EMA regulations. Each container will be labelled with a unique container number, protocol number, IMP name, lot number, sponsor name and contact information, investigator, dosage form, route and directions for administration, storage conditions, retest date, and strength/potency and a statement that the IMP is restricted to clinical trial use only.

### **8.2.2 Accountability**

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

Each container label will contain a unique container number for the IMP assigned to a single Experimental Session. The container numbers will be used to track IMP administration in the Source Record and the IMP administration log.

### **8.2.3 Storage**

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

### **8.2.4 Administration**

IMP will only be removed from storage for a single Experimental Session at a time and will be administered orally at the study site. All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each Experimental Session. Supplemental doses should be administered unless tolerability issues emerge with the first dose or the participant declines. Each dose (initial and supplemental) will be administered with a glass of water.

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

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant local country regulations.

### **8.2.5 Treatment Compliance**

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

## **8.3 Participant Numbering**

Every potential participant who is prescreened by telephone according to the IRB/EC-approved script will be assigned a seven-character alphanumeric Screening Number and recorded on the Screening Log. This number will begin with 'S8' to identify that it is a Screening Number. The next two digits represent the site number (e.g., '17'), followed by a three-digit screening identifier starting with '801'. The screening identifier will be assigned to each prescreened participant at a site sequentially. For example, the first Screening Number at Site 17 will be S817801 and first Screening Number at Site 18 will be S818801.

Each participant who passes Screening and is enrolled in the trial at Visit 0 will be assigned a seven-digit Participant Number. The first digits will be '18'. The next two digits represent the site number (e.g., '17'), followed by a three-digit participant identifier starting with '001'. The participant identifier will be assigned to each enrolled participant at a site sequentially. For example, the first Participant Number at Site 17 will be 1817001.

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

## **8.4 Bias Minimization**

Before a participant is deemed eligible and enrolled into the study, participant's medical history and screening assessments will be reviewed by the Principal Investigator and therapy team. If needed, Medical Monitor will be consulted.

Two different processes exist to ensure bias minimization: the primary and secondary outcome assessments performed by the IR team will be recorded and then reviewed by a senior (local) IR, and all psychotherapy study visits (including the experimental sessions) will be reviewed by adherence raters to ensure adherence to the Treatment Manual, and consistency among therapy pairs and sites. The paragraphs below describe these processes in more detail.

To minimize bias in measuring effect, the sponsor will use an observer-blind, centralized, reliable IR pool to administer the Primary Outcome measure via live video interviews. The IR Pool will have no knowledge of participant's study data or AEs and will only evaluate participants at Baseline and at the assessments scheduled after each Experimental Session. The IR Pool is blinded to study design, visit number, number of treatments, and any data from the treating therapy team after Baseline. IRs will be assigned to participants based on availability. Data will be entered into a dedicated IR Database by the IR Coordinator who is not part of the study assessments or procedures. Timing of CAPS-5 assessments are provided in Table 2.

To ensure that all participants are treated in a similar manner, the sites will be required to follow the protocol and Treatment Manual delineating minimum length of time per visit type and describing delivery of treatment. All Experimental Sessions are required to be at least 8 hours long. Adherence to the Treatment Manual will be checked by review of video by adherence raters. The sponsor will monitor data in real-time to ensure complete data collection for all participants, including those who discontinue treatment. Sites will be required to make and document a specific number of attempts to obtain follow-up data per protocol. All participants who receive at least one dose of IP and complete at least one follow-up assessment will be included in the final *mITT* analysis.

## **9.0 Risks**

### **9.1 Non-drug Related Risks**

#### **9.1.1 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. See Section 7.1.1 for the list of medical assessments to be performed within the screening visit in order to confirm participant's eligibility.

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.

### 9.1.2 PTSD, Suicide Risk, and Psychotherapy

During Screening, throughout MDMA-assisted psychotherapy, and during assessment of study measures, participants 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. Therapy teams will provide emotional support to participants during any psychological distress.

The therapy team will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts will not be excluded unless significant risk of suicidal behavior is present at the time of Screening. Participants will be enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician, therapy team, and Medical Monitor.

A qualified individual will administer the C-SSRS according to Table 7: Time and Events – Study Measures, and as needed depending on clinical presentation of the participants, to monitor for development and intensity of suicidal ideation and/or behavior. The therapy team will implement the following plan to assess elevated or imminent suicide risk.

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

1. If the participant 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 participant is evaluated by the investigator and/or site physician to determine an appropriate course of action. Findings will be discussed with the participant and their personal therapist, if applicable.
  - b. Regular check-ins via phone or in-person will be continued until the participant has stabilized or a new course of action is taken based on changes in C-SSRS score and/or ongoing clinical assessment.
  - c. Increases in suicidality will be captured as an AE.
  - 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 participant will enter follow-up.
2. If the participant 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 five 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. Participants are evaluated by the investigator or site physician to determine an appropriate course of action, and the therapy team will contact their personal

- therapist, who will be invited to come to the study site to assist, depending on their location.
- b. If it is determined that the participant is at imminent risk of suicide, the therapy team will do one of the following:
    - i. Escort the participant to the ED;
    - ii. Escort the participant to an appropriate mental health services facility (e.g., hospital psychiatric unit); or
    - iii. Call EMS and ensure that the participant is transferred to the responding medical personnel.
  - c. If the participant will not comply and wishes to leave without consultation, call EMS. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
  - d. Notify appropriate members of the study team and sponsor representatives.
  - e. The event will be collected as an AE and the seriousness will be evaluated. SAEs will be reported per local 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 participant will enter follow-up.

### **9.1.3 Recorded Content**

All psychotherapy sessions and IR assessments will be video recorded . There is a risk that participants may feel uncomfortable with having their sessions recorded. The recordings are necessary for participant safety, for assessing adherence to the Treatment Manual, as well as providing clinical supervision to therapy teams that will be trained as a part of this study. Both types of videos will be deleted after the appropriate reviews are performed.

The sponsor uses encrypted, secure technology to store recordings. In the case of a confidentiality breach, the participant will be notified and all efforts will be made to minimize the dissemination of recorded content. The sponsor is committed to taking preventative measures to avoid such an event.

## **9.2 Risks of Receiving MDMA**

Study procedures and eligibility criteria have been developed based on Phase 2 and Phase 3 PTSD trials which exclude potential participants with pre-existing exclusionary medical conditions that would exacerbate risk. The therapy teams and site physicians are available via telephone throughout the study if any problem occurs when a participant is not at the site. In the event of a medical emergency or any other medical problem during an Experimental Session, the site physician should be immediately available by telephone, and based on assessment of the situation, they should make the decision to either evaluate the participant themselves at the site or arrange for transfer of the participant to the Emergency Department.

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

### 9.2.1 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 of MDMA have been identified based on the RACT assessment.

### 9.2.2 Medium Level Risks

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

#### 9.2.2.1 Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. Participants with PTSD in MAPS-sponsored Phase 2 and Phase 3 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 and Phase 3 studies of MDMA-assisted psychotherapy detected a dose-dependent increase in SBP and to a lesser extent DBP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure are 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 drug administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy team should attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction (AMI) during Experimental Sessions. Any symptoms such as chest pain, shortness of breath, neurological deficit or confusion other potential indicators of end organ effects of hypertension should prompt additional vital sign measurements and intervene if appropriate. Therapy teams should notify the site physician if this occurs for evaluation. If any participant has neurological deficits, as assessed by the site physician, whether or not they are associated with hypertensive crisis, they should be monitored as described above and transported to the hospital if medically indicated. If evaluation at the hospital reveals an acute ischemic stroke, there should be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the 2019 American Heart Association/American Stroke Association (AHA/ASA) guidelines [\[112\]](#) ,.

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, the study physician should be contacted immediately, and the participant should be taken to an emergency room by ambulance as expeditiously as possible to assess the patient and act in accordance with the assessment of the expert on site supported by local and/or European Society of Cardiology (ESC) Guidelines [\[113\]](#). Pending transport to the hospital the site team may take any measures ordered by the site physician including administering medication such as aspirin or nitroglycerin or providing supplemental oxygen per local standards. If further evaluation at the hospital reveals that the participant has had an AMI, they should be well within the time frame required for definitive therapy. Any participant who experiences such medical complications during an Experimental Session should not be given another Experimental Session.

QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event. If at any time a participant develops a QT/QTcF interval >450 ms or of >30 ms over baseline during ECG evaluation, the participant should be discontinued from treatment.

### 9.2.2.2 Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [58, 114]. Psychological distress from MDMA could arise from the first indications of MDMA effects until the last effects have dissipated or even later. Anxiety or distress during the session may last for as little as 5 minutes or for as long as 5 hours or more. In addition, psychological distress could arise following an Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In clinical studies, these symptoms have been self-limiting and have responded well to reassurance from the therapy team, with occasional use of benzodiazepines for anxiety. In this study, participants 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 participants 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 (such as people diagnosed with bipolar affective disorder type 1 or with psychotic disorders)
- Preparatory Sessions of non-drug psychotherapy before the Experimental Session
- Creating an atmosphere of trust during the Experimental Session
- Close monitoring
- Phone contact with participants during the week after the Experimental Session
- Integrative Sessions
- Overnight stays at the study site for the night of each Experimental Session. Qualified personnel will be available during the overnight stay to respond to the needs of the participant. Attendants will be instructed to contact the therapy team upon request or at the appearance of signs of a potential SAE.

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

If the participant is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a psychotherapy session, at least one member of the therapy team will remain with the participant for at least 2 more hours. During this time, the therapy team will employ affect management techniques, will talk with the participant to help them gain cognitive perspective of their experiences, and will help the participant implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the participant remains severely anxious, agitated, in danger of self-harm



or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and therapy team will decide between the following options:

1. If severe distress occurs at the end of an Experimental Session, a nurse, therapeutic assistant, physician, or therapy team member should stay with the participant until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The therapy team should then meet with the participant daily until the period of destabilization has passed.
2. If the participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, 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 participant will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the therapy team.
3. If a participant should become psychotic, arrangements should be made to stabilize them or transfer them to the Emergency Department if hospitalization is necessary. Any participant who is hospitalized after a severe psychological reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator and/or site physician will carefully evaluate the participant's emotional status.

For those participants engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapist(s) should be involved in the management of any psychiatric complications. For those participants engaged in an ongoing psychotherapeutic relationship with the investigator or member of the therapy team, the management of any psychiatric complications should be undertaken by them in their capacity as the participant's therapist.

### **9.2.3 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.

#### **9.2.3.1 Thermoregulatory Risks and Mitigation**

MDMA administered in a controlled setting produces only a slight increase in body temperature [114]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 and Phase 3 studies, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1 degree Celsius (°C) above baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1°C above baseline.

Ambient temperature should be kept at a comfortable level during Experimental Sessions. If a participant's temperature rises more than 1° C or the participant states that they feel hot, attempts should be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, the site physician should be consulted for further evaluation and treatment.

### 9.2.3.2 Osmoregulatory Risk and Mitigation

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

### 9.2.3.3 Genotoxicity Risk and Mitigation

The standard genotoxicity battery for MDMA has demonstrated that MDMA is negative for in vitro and in vivo genotoxicity, both with and without metabolic activation.

### 9.2.3.4 Reproductive and Developmental Risks and Mitigation

There are no data from the use of MDMA in pregnant women. In the absence of these data, epidemiological studies of Ecstasy are the only source of human data. One of two studies of Ecstasy users suggest that use of Ecstasy and polydrug use during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [115, 116].

Studies in rats and rabbits have not shown direct or indirect harmful effects with respect to reproductive toxicity. Repeated dose toxicity studies of adequate duration, fertility, early embryonic development, and embryofetal development studies of MDMA with toxicokinetics have been completed. These studies established the NOAEL dose to be the highest dose level evaluated at  $\leq 10$  mg/kg/day (supratherapeutic dose) in both sexes of the rat for fertility, reproductive performance, and for maternal and developmental toxicity in the rabbit. The NOAEL dose was the highest dose level evaluated at  $\leq 15$  mg/kg/day (supratherapeutic dose) for maternal and developmental toxicity in the rat. Due to the short half-life and single-dose dosing regimen of MDMA, pre- and post-natal development studies are not considered necessary for assessment of risk to the unborn. Assessment of embryofetal risk based on all available non-clinical and clinical data supports unlikely human teratogenicity/fetotoxicity in early pregnancy. On the basis of male fertility studies, the embryofetal risk posed from treatment of male participants with MDMA is also unlikely.

PABP are included in the studies in this program, defined as those who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. As a precautionary measure in clinical trials, participants who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session, which are conducted at approximately monthly intervals, and must agree to use adequate contraception at least during the Treatment Period which is one month post last dose of MDMA. The end of relevant systemic exposure to MDMA is approximately 48 hours [117].

### 9.2.4 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.

#### **9.2.4.1 Common Expected AEs**

Common expected AEs were typically observed during Experimental Sessions but were transient and typically diminished as MDMA was metabolized and excreted over the next 72 hours after dosing. In the Phase 3 study MAPP1, the most common adverse events reported more frequently in the MDMA group were muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, restlessness, mydriasis, dizziness (postural), bruxism, nystagmus, increased blood pressure, feeling jittery, chest pain (non-cardiac), dry mouth, vision blurred, pollakiuria, intrusive thoughts, vomiting, stress, and musculoskeletal chest pain. AEs were typically self-limiting.

#### **9.2.4.2 Neurotoxicity Risk**

It does not appear that MDMA-assisted psychotherapy negatively impacts cognitive function based on data from Phase 2 studies sponsored by MAPS. The sponsor has carefully considered the risks of neurotoxicity and concludes that they are minimal in the intended clinical dosing regimen. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of CNS toxicity reported in nonclinical MDMA studies.

#### **9.2.4.3 Abuse Potential**

Despite its classification as a Schedule I drug, an examination of 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. There have been no AESIs reported in Phase 2 and Phase 3 studies that could be suggestive of abuse potential among research study participants treated with MDMA. Diversion is not an issue for sponsor-supported studies because MDMA is only administered under the supervision of the clinical investigator and no take-home doses are permitted. MDMA administration and handling follows all regulations pertaining to the use of controlled substances within research studies.

Studies assessing prevalence of problematic Ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic Ecstasy use or dependence. An observational long-term follow-up assessment conducted at least 12 months after participation in a MAPS-sponsored early Phase 2 PTSD study of MDMA-assisted psychotherapy found that 8.7% (8 of 92) participants reported using Ecstasy subsequent to study participation, with 6 of these 8 participants having used Ecstasy prior to study enrollment. Several participants volunteered that they would not seek out MDMA outside of a psychotherapeutic setting.

### **10.0 Safety**

#### **10.1 Adverse Events**

An Adverse Event (AE) is defined as any medical occurrence in a participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant’s involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

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

An unexpected AE is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event.

The site physician will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapy teams will collect AEs during study visits from Enrollment (Visit 0) through Study Termination (Visit 15). All SAEs will be collected from the time of informed consent signed through Study Termination (Visit 15). Participants will be asked directly how they are feeling during each contact, and AEs may be captured spontaneously during psychotherapy sessions, telephone calls, or other correspondence. Completed measures may create suspicion that an AE occurred; in this case, the site staff should follow-up with the participant.

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

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

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

The seriousness and relationship of study treatment to an AE will be determined by the Investigator based on the following definitions:

1. “Not Related”: The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, *i.e.*, there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.
2. “Related”: The administration of the investigational product and AE are considered reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE or is the most likely cause of the AE.

### **10.1.1 Adverse Events of Special Interest**

The sponsor will pay special attention to a subset of AEs involving psychological distress, including Low Mood (occurring up to 5 days after Experimental Sessions), suicidal ideation and suicidal behavior, as well as 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, syncope (non-postural), and seizures. 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 IP in the intended patient population:

- AESIs involving the terms of Behavioral addiction, Drug abuser, Substance abuser, Dependence, Intentional product misuse (including facilitation of product use outside of research setting), Overdose (accidental, intentional, or prescribed), or Drug diversion will be collected and coded as AESIs in the eCRF if noted in relation to MDMA or Ecstasy.
- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs.
- Qualitative urine drug test data will be collected prior to each 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 SAE, it should be reported via the eCRF within 24 hours of the site's awareness of the event.

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

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe Adverse Event need not be serious in nature and that a SAE need not, by definition, be severe. In addition, SAE's will be evaluated by the Sponsor or designee for "expectedness." An unexpected SAE 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.

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

All SAEs will be collected from the time of informed consent through Study Termination. All SAEs which occur during the course of the trial, whether considered to be associated with IP or not, must be reported to the sponsor within 24 hours of the site staff's awareness of occurrence. Reporting procedures will be provided to the site. All SAEs will be assessed for relationship, expectedness and any required actions to address safety at the time of reporting of the event. SAEs will be evaluated by the site physician and Medical Monitor to determine if it is appropriate for the participant to continue treatment or enter follow-up. Any participant who experiences a SAE considered related to the IMP administration will be permanently discontinued from future IMP treatments. All SAE's must be reported by the investigator to his/her corresponding EC or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

### **10.1.3 Suspected unexpected serious adverse reaction**

A suspected unexpected serious adverse reactions (SUSAR) is defined as any untoward and unintended response to a study drug, which is not expected, and meets one of the following serious criteria:

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

All SUSARs will be collected from enrollment through Study Termination. All SUSARs must be reported to the sponsor immediately, within 24 hours of the site staff's awareness of occurrence. MAPS or its designee will comply with Directive 2001/20/EC or with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse reactions (SUSARs) to the regulatory authority(ies) and the EC.

If a SUSAR or other safety signal relating to use of the IP is reported to MAPS or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

### **10.2 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 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.

## 10.3 Pregnancy

### 10.3.1 Definition of People Able to Become Pregnant

A participant is considered able to become pregnant if they were assigned female at birth and are post-menarche. A participant is considered not able to become pregnant if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male at birth.

### 10.3.2 Contraception Guidelines

Adequate and only highly effective birth control methods are required for participants who are able to become pregnant (PABP), *i.e.* fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Acceptable birth control methods include:

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal
- Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide)
- Vasectomized partner, if partner is the sole sexual partner of the PABP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Abstinence from penile-vaginal intercourse, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.
  - The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle and will be evaluated in relation to the duration of the clinical trial.
- Note: Hormonal contraception must be associated with inhibition of ovulation.

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

### 10.3.3 Follow-up Requirements

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

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

The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported in the 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.

## **11.0 Concomitant Medications**

### **11.1 Tapering Instructions**

The site physician will record concomitant medications during Screening. If the prospective participant is being treated with psychiatric medications at enrollment, the prospective participant will be encouraged to discuss medication tapering with their outside treating physician, if any, and will be required to give the site physician permission to do so as well. 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, participants 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 participants, as they must refrain from taking psychiatric medications throughout the study, with some exceptions (see Section 11.2 Allowable Concomitant Medications). The prescribing physician's opinion about medication discontinuation will be documented either in writing from the prescribing physician, or in writing by the site physician documenting phone contact with the prescribing physician. Tapering will follow a time course appropriate for the medication based on its half-life, with the first Experimental Session scheduled to occur after complete washout (five half-lives plus at least 1 week for stabilization). If the health of the participant worsens after tapering, the participant will be withdrawn from the study and will be treated according to standard clinical practice. This will be recorded in the eCRF.

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

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

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

### **11.2 Allowed Concomitant Medications**

The site physician may prescribe necessary and appropriate medications in accordance with local country 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 11.3 Prohibited Medications.

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 study drug, participants 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. 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 IP administration at the Experimental Session to 24 hours after. If a participant 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 participant 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 research team. Failure to comply with protocol requirements for concomitant medications may result in withdrawal from treatment, depending on the investigator and Medical Monitor judgment.

### **11.3 Prohibited Medications**

To be enrolled in the study participants must:

- Refrain from the use of any psychoactive medication not approved by the research 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 research team).
  - Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) unless with prior approval of the research team.
  - Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the research team).

The research team should only approve medications that clearly would not be expected to have any interactions with MDMA, including, but not limited to, any drugs with sympathomimetic

activity or activity on the serotonin or other monoamine systems, and any other drugs that would be contraindicated with or have any interaction with monoamine oxidase inhibitors (MAOIs).

The following medications are prohibited as they would present potential confounds for interpretation of the data collected from this study as they have notable serotonergic effects or are under potential or available treatments for PTSD:

Use of Marijuana, St. John's Wort, and other herbs and medicines with notable serotonergic effects are prohibited from Baseline to Study Termination. Any investigational treatments under study for PTSD treatment are prohibited from use concurrent with this study.

Diphenhydramine is excluded from this study unless prior approval is granted by the site physician.

If an SSRI, SNRI, or other antidepressant is used between Experimental Session 1 (Visit 4) and Study Termination (Visit 15), the participant will be withdrawn from treatment and continue in follow-up.

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

## 12.0 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 participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values after consultation with the Medical Monitor.

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

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

- Hemoglobin
  - Mean corpuscular volume (MCV)
  - Mean corpuscular hemoglobin (MCH)
  - Mean corpuscular hemoglobin concentration (MCHC)
  - Red cell distribution width (RDW)
  - Percentage and absolute differential counts
  - Red blood cell (RBC) count
  - White blood cell (WBC) count
- Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Occult blood
  - Leukocyte esterase
  - Nitrite
  - Bilirubin
  - Urobilinogen
- Thyroid function
  - Thyroid-stimulating hormone (TSH) high sensitivity (if abnormal, free T3 and T4 will also be tested)
- HCV antibody *if indicated*, with reflexive RNA test
- %Carbohydrate deficient transferrin (%CDT) to detect heavy alcohol use
- Pregnancy test
  - A highly sensitive pregnancy test for PABP will be performed at the site or by the central lab at screening, and at the site before each experimental session.
  - A serum or urine sample may be used.
    - In the UK, screening pregnancy test must use serum only.
  - A final urine pregnancy test should be completed at Visit 13 (or at Visit 14 or 15, if Visit 13 is done remotely) for PABP.
- Qualitative drugs test
  - To be performed at the site during screening and before each experimental session.
    - In the UK, also includes alcohol.

Laboratory assessments, with the exception of urine pregnancy and drug tests, will be performed by a central laboratory in Europe. Certificates and normal ranges will be stored in the site's Investigator Site File (ISF).

Additional laboratory assessments may be ordered by the Principal Investigator if indicated, in consultation with the Medical Monitor.

### 13.0 Statistical Considerations

Key personnel, MAPS, and the biostatistician will agree on a Statistical Analysis Plan at the beginning of the study, which will provide more detail about analyses than provided in this

protocol. An overview of the statistical analyses that will be performed is provided in the following sections.

### 13.1 Statistical Analyses

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

The following analysis sets are defined for this study:

- All Enrolled: all participants who sign informed consent and are initially enrolled
- *mITT*: all participants who receive investigational product in at least one Experimental Session and have at least one follow-up CAPS-5 assessment
- Per Protocol (PP): all participants who receive investigational product in two Experimental Sessions and have three CAPS-5 assessments
- Not Per Protocol (NPP): all participants who are included in the *mITT* Set but not the PP Set
- Safety: all participants who receive the IP

#### 13.1.1 Effectiveness Analyses

##### 13.1.1.1 Primary Outcome Analyses

The primary analysis will be conducted after all participants complete Study Termination (Visit 14) and the study database has been locked. All outcome analyses will be based on the *mITT* analysis set. The *de jure* estimand of treatment effectiveness is of the most relevance to measure the effect of two experimental sessions, given actual adherence to treatment of MDMA-assisted psychotherapy in a controlled clinic setting on PTSD symptom severity in the intended population of patients with PTSD from any cause. The primary estimator of effectiveness will be the mean change in CAPS-5 Total Severity Scores from Baseline to 14 weeks after start of dosing (Visit 14). Least squares means from a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be used to estimate the change in CAPS-5 from baseline to each visit. Ninety-five percent confidence intervals will be calculated for the estimated mean change from baseline CAPS-5 scores at each visit. Missing data will not be imputed and will be considered missing at random.

##### 13.1.1.2 Secondary Outcome Analyses

Sheehan Disability Scale (SDS), the secondary outcome measure, will be analyzed in the same manner as the Primary Outcome. The secondary estimator of effectiveness will be the mean change in SDS Mean Item Scores from Baseline to 14 weeks after start of dosing (Visit 14). Least squares means from a REML-based MMRM will be used to estimate the change from Baseline to each visit. SDS data collected after treatment discontinuation will not be included in the *de jure* estimand.

##### 13.1.1.3 Exploratory Analyses

One-group pretest-posttest Cohen's *d* effect size will be estimated. Exploratory sub-group analyses may be conducted when possible to evaluate effects and by individual demographic

characteristics (*e.g.*, age, gender, ethnicity, index trauma, ACE score, presence of secondary traumatic stressors during the assessment period with LEC-5, medication tapering, diagnosis of comorbid depression, diagnosis of comorbid diagnosis, and number of experimental sessions completed). Post-hoc exploratory analyses not described in the protocol or Statistical Analysis Plan may be performed to further examine the study data. These analyses will be clearly identified as such in the final clinical study report.

### **13.1.2 Safety Analyses**

Safety data will be summarized by exposure to IP, unsolicited AEs, concomitant medications, suicidal ideation and behavior, and vital signs overall. If a participant has more than one AE mapped to the same PT, that AE will be reported once using the highest severity. AEs that occur on Day 0 (Experimental Session), Day 1, Day 2 after IP administration will be presented separately. Report incidence of AEs during Experimental Sessions such as clinical signs and symptoms, such as chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that may be indicative of a medical complication of the IP.

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

## **14.0 Study Governance**

MAPS Europe B.V. is a small/medium-sized enterprise that is a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit research and educational organization based in the United States. The sponsor, MAPS Europe B.V., is developing MDMA for treatment of PTSD in Europe and is responsible for trial organization, including designing, initiating, managing, coordinating, continuing, and concluding the clinical trials within the Clinical Development Program. Funding for the trials is provided by MAPS. The sponsor is tasked with maintaining the quality of study conduct through ongoing monitoring of data. The sponsor has delegated the design, systems infrastructure, and retention of Essential Documents to the MAPS Public Benefit Corporation (MPBC). The sponsor contracts with independent entities who represent clinical sites to accomplish these goals.

### **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 European Directive 2001/20/EC, US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki [\[118, 119\]](#).

The protocol, the ICF and other study documents must be reviewed and approved by a properly constituted institutional review board (IRB) or ethics committee (EC) and country regulatory

agency 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 her or his 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**

"Informed consent" is the voluntary agreement of an individual to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

The investigator and therapy team are responsible for obtaining informed consent in adherence to protocol, GCP and according to applicable local regulations prior to entering the participant into the trial. Potential participants may be sent the Informed Consent Form (ICF) to review after the initial phone screen. Preferably, informed consent will be obtained by the one of the therapists that will treat the participant. Information about the study must be given orally and in an understandable written ICF. The informed consent discussion must be conducted by a person who is qualified according to local country regulations. The participant should have the opportunity to inquire about details of the study and should be given sufficient time to read and consider participation. Potential participants will be given approximately two weeks to read the information and decide whether they are interested in participating in the study.

Discussion about the study and informed consent may take place either at site or via tele-assessment/video call. However, the informed consent form (ICF) should be signed in the presence of the investigator or delegate at the first in-person visit at the site. The study staff will counter sign the ICF, copy the ICF for the participant and file the original at the site in the ISF.

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 site staff to request and view the participant'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 participants may only be included in the study after signing the IRB/EC approved ICF. Informed consent must be obtained before conducting any study-specific procedures (*i.e.*, all of the procedures described in the protocol beyond phone screening). The process of obtaining informed consent should be documented in the participant's source records.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the

participant's consent. Any revised ICF and written information should receive approval from an IRB/EC before use. The participant should be informed in a timely manner if new information becomes available that may affect the decision to take part or continue in the study. The communication of this information should be documented. Participants can withdraw consent at any time without prejudice.

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

CAPS-5 results may be shared with site staff. The IR Coordinator will be responsible for review and data entry of the CAPS-5 source records into CAPS-5 eCRFs.

Videos from selected sessions will be reviewed for adherence to the Treatment Manual as described in Section 6.4. Findings from video reviews may be discussed between the therapy team and their supervisor as needed to ensure continued adherence to the protocol.

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.

### **14.2.1 Source Records**

Prior to start of the study the site staff participating in the study conduct will be trained on what documents will be required for review as source documentation. The kind of documentation that will serve as source documents will be specified on the Source Document Agreement and this agreement will be finalized before the first participant's first visit at each site.

Source records contain all primary evidence of existence of the participant and document all study procedures. Source records include but are not limited to medical records, measures, checklists, notes, emails, MRI scans (if applicable) and laboratory reports. The participant must also allow access to their medical records if available. Each participant must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All data reported in the eCRF are transcribed from primary source documents and must be consistent. These documents are to be maintained at the study site securely. Source records of CAPS-5 assessments will be stored in dedicated limited access files during the study.

### **14.3 Confidentiality and Data Protection**

Every effort will be made to strictly safeguard the confidentiality of participants. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data. Except for the Screening Log, the Informed Consent, previous medical records, emails with the participant, and a Contact Information Sheet that will be stored separately from other study documents, all source data will be identified only by the participant number and the participant's identifier code. All source documents 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 with access to data, other than the investigators who are directly involved in the protocol, will not be provided with any information that would identify participants by name or by other means, such as social security number.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Data will be securely transferred to remote and secure servers. Clinical trial data other than video data will be hosted on an EDC system compliant with Title 21 Part 11 policies of the Code of Federal Regulations in the US and with applicable EU Directives. The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy. All data entered into this system will be de-identified. Participants will only be referred to by numbers and a secondary identifier code. Source Records and identifying information will be retained at clinical sites per GCP. The sponsor will train the study staff on EDC procedures.

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

The sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations. With regards to any personal data processed in the context of this study, the sponsor and MAPS PBC serve as joint data controllers according to the General Data Protection Regulation (GDPR). The sponsor is responsible for exercising the rights of data subjects. The legal basis for data transfer between the sponsor and MAPS PBC, including responsibilities related to cross-border data transfers, is described in a controller-to-controller agreement with Standard Contractual Clauses.

### **14.4 Costs to Participants**

There will be no costs to the study participants for participation. The sponsor will cover all direct costs of study procedures required for participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of a participant's condition that are unrelated to the research study or any unrelated procedures will not be covered by the Sponsor. Patients who previously received therapy from a therapy team member prior to the study, and who will continue to receive ongoing treatment outside of the study from that therapist, are responsible for those non-study related costs. Participants may be



reimbursed for reasonable expenses incurred for study participation, such as local travel expenses. This is specified in each site's informed consent.

Participants will not receive monetary compensation for taking part in the study.

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

#### **14.6 Record Retention**

Investigators must retain all study records required by the sponsor and applicable ICH-GCP and local country regulations in a secure and safe facility. The Investigator must consult a representative of the sponsor before disposal of any study records and must notify the sponsor of any change in the location, disposition, or custody of the study files. "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.

Essential documents should be retained in the sponsor Trial Master File until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor (ICH E6 (R2))[\[120\]](#). 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 participants enrolled in a study and therefore, encourage publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences. For multi-center studies, it is intended that the first publication of the study's primary clinical data be co-authored by designated participating centers and the sponsor or designated representatives. Inclusion of PIs 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 Principal Investigators that the information generated in this study will be used by the sponsor in connection with the development of the IP 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 PIs 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 Master Service Agreement and Clinical Trial Agreements.

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## Appendix A: Imaging Sub-Study

This sub-study to the MP18 protocol “An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder” allows participants to participate in pre and post treatment imaging (Visits 4.1 and 14.1) and will be performed at pre-selected study sites.

Study site and participants will follow all protocol procedures described in the main protocol, with the addition of imaging visits as described below.

### 1.0 Neurocircuitry of PTSD

Neuroimaging of individuals with PTSD has demonstrated structural and functional abnormalities in brain regions such as the amygdala, insula, medial prefrontal cortex (mPFC), and hippocampus [121]. These regions are associated with fear conditioning, fear extinction and the regulation of emotions [122]. Some brain abnormalities may predispose to the development of PTSD, whilst others are a sequela of PTSD [123]. For instance, non-trauma exposed twins of sufferers may show smaller hippocampal volumes [124] and increased resting metabolic activity in the anterior cingulate cortex [122], whilst PTSD sufferers acquire further secondary loss of hippocampal volumes [125] and lower grey matter density of the pregenual ACC [126].

A common functional brain imaging task involves script driven imagery, whereby individuals are prompted to relive their trauma [127]. This task closely replicates reactions that would be seen during imaginal exposure in TFPT, and would therefore be a useful tool in exploring the therapeutic mechanism of a new drug that could augment therapy. Another task involves presenting individuals with non-trauma related emotional stimuli which may replicate hypervigilance within the therapeutic relationship [128].

The amygdala is a medial temporal lobe structure that plays an important role in fear conditioning and threat detection [129]. PTSD is characterized by hyperactivity in the amygdala, which may account for the failure of fear extinction and exaggerated startle response observed [130]. Increases in amygdala activation have been reported in several task based functional imaging studies of PTSD, where symptoms are provoked using traumatic memory cues such as combat images, sounds and smells [121].

The neurocircuitry model of PTSD hypothesizes that the amygdala, medial prefrontal cortex (mPFC) and hippocampus are dysfunctional [131]. Specifically, the amygdala is hyperactive in response to threat-related stimuli [127], and this accords with both an exaggerated fear response and overgeneralized fear conditioning [131]. Additionally, compared to traumatized controls, people with PTSD show a relative failure to activate the mPFC (hypoactivation) when engaged in trauma imagery [127] and the mPFC fails to exert top-down control over the amygdala [131], leading to both emotional dysregulation and impaired fear extinction. Lastly, impaired hippocampal activity may underlie deficits in recognizing present contexts as safe during fear extinction [131].

Combat veterans with PTSD show more physiological reactivity, including increased heart rate and blood pressure in response to combat related stimuli than combat veterans without PTSD [132]. Neuroimaging studies have demonstrated that the amygdala is hyperactive when personalized trauma scripts are used [133, 134]. Increased amygdala activation also extends to emotional, non-trauma related stimuli. Exposure to emotional faces has been an especially effective probe of amygdala function [135]. There is increased amygdala activity in individuals with PTSD in response to fearful versus happy faces [125, 130, 136, 137] and this increased amygdala activation has been positively correlated with PTSD symptom severity [121, 138]. Successful exposure therapy has been associated with decreased amygdala activation during fear conditioning [139].

The insula is structurally interconnected with the amygdala and specifically sensitive to salient environmental stimuli, marking such stimuli for further processing [140]. Several studies have reported hyperactivity of the insula in PTSD using trauma script symptom provocation [141, 142] as well as increased activity when processing fearful versus happy facial expressions [143]). A positive correlation has been reported between insula activation and PTSD severity [121] as well as in other anxiety disorders [135, 144, 145].

PTSD sufferers describe persistent re-experiencing symptoms and difficulty suppressing thoughts related to their trauma when performing unrelated cognitive tasks. The anterior cingulate cortex is involved in recruiting cognitive control over emotional processes [146], by decreasing the significance of affective information [147]. The rostral subdivision plays an important role in regulating amygdala activity, with impairment of rACC leading to hyperactivity of the amygdala [148, 149]. The medial prefrontal cortex, including the rACC and vmPFC, acts in functional opposition to the amygdala, by extinguishing fear conditioning and retaining extinction [150].

Individuals with PTSD show reduced activation or greater deactivation in regions of the medial prefrontal cortex in response to traumatic-script driven imagery [127, 132, 151]. Diminished rACC and mPFC activation was also seen in response to fearful versus happy facial expressions, with rACC activation being negatively correlated with PTSD severity [136]. Likewise, there is diminished rACC activity in response to trauma-related and unrelated emotional interference [152] with a negative correlation between rACC activation and PTSD symptom severity. Poor response to cognitive behavioural therapy has been predicted by deficient pre-treatment rACC activation [137], whilst successful exposure therapy has been associated with increased rACC activation and decreased amygdala activation during fear processing [139]. Taken together, this suggests that the amygdala and mPFC are part of an emotional regulation circuit, and that mPFC inhibition of the amygdala-mediated fear response is required for fear extinction.

PTSD sufferers experience disturbances in memory with symptoms such as intrusive recollections, dissociative flashbacks and psychogenic amnesia [138]. The hippocampus is involved in consolidating the memories of emotionally arousing experiences and modulating memories according to context during fear conditioning [153, 154]. There have been conflicting reports as to whether the hippocampus is hyperactive or hypoactive in PTSD but a meta-analysis suggested that overall there is reduced activity in PTSD [144]. In particular, individuals with PTSD have demonstrated reduced hippocampal activation in response to traumatic script provocation [132]. Reduced hippocampal activation in a virtual Morris water task (designed to test learning, memory and spatial navigation) predicted symptom severity in participants with PTSD [155]. Successful treatment with psychotherapy in patients with subthreshold PTSD has found increased hippocampal activation in response to traumatic scripts [156].

The findings described above illustrate functional changes in task-based conditions. Similar changes have also been demonstrated in spontaneous, resting brain activity and functional connectivity [157]. A functional MRI study of non-provocation, resting state activity in veterans with PTSD found increased magnitudes of spontaneous brain activity in the left amygdala, as well as the right anterior insula, ventral anterior cingulate and orbital frontal cortex. Veterans also showed decreased spontaneous activity in the precuneus, dorsal lateral prefrontal cortex and thalamus [158], with a negative correlation between resting thalamic activity and severity of re-experiencing symptoms [152, 158]. Interestingly, a case study has described a veteran who developed PTSD symptoms following a thalamic infarct [159].

Certain brain regions, including the mPFC, posterior cingulate cortex (PCC), precuneus and lateral parietal cortices, are more active and temporally synchronised with each other when an individual is in a state of wakeful rest. This has been termed the default mode network [160]. The default mode network may reflect a brain state that is involved in processing self-referential thought and is temporarily suspended during goal

directed activity [161]. Alterations in the resting state functional connectivity (RSFC) of the default mode network have been discovered for individuals with PTSD and may be associated with disturbances in self-referential processing and dissociative symptoms [157]. Individuals with PTSD have been found to have increased positive RSFC between the amygdala and insula [162] and reduced positive connectivity between the amygdala and hippocampus. Additionally, there are negative correlations between the amygdala and the mPFC, rACC and dorsal ACC, supporting the hypothesis of an inhibitory role of the mPFC in relation to the amygdala.

In the first resting state fMRI investigation of MDMA in healthy participants, the intensity of the euphoric effect correlated with reductions of cerebral blood flow (CBF) in the amygdala and hippocampus. Amygdalar response to angry faces was reduced in people given MDMA [163]. Moreover, a decreased RSFC was found between the hippocampus and vmPFC, whilst an increased RSFC was seen between the hippocampus and amygdala. The magnitude of the former correlated with the intensity and euphoria of the MDMA experience, suggesting that MDMA may exert some of its therapeutic effect by decreasing the coupling between the mPFC and hippocampus [54].

MDMA administration in healthy participants has been shown to produce changes in regional blood flow, including increases in ventromedial frontal and occipital cortex, inferior temporal lobe and cerebellum; and decreases in the motor and somatosensory cortex, temporal lobe including left amygdala, cingulate cortex, insula and thalamus [42]. This has the potential to reverse some of those abnormalities seen in participants with PTSD.

A recent study showed that participants given MDMA are more likely to use words relating to friendship, support and intimacy, in comparison to the drug methamphetamine, which by contrast reduced participants' discussions about compassion [163]. MDMA appears to enhance the quality of social interactions and thereby improve relationships, recently tested using a simulated experimental paradigm of social exclusion by Frye et al, 2014, showing how participants taking MDMA exhibited reduced social exclusion phenomena [164]. Another recent study showed similarly that MDMA enhances levels of shared empathy and pro-social behavior compared with placebo [165]. Furthermore, Wardle showed how MDMA can facilitate a faster detection of happy faces, and reduces the detection of negative facial expressions, which leads participants to view their social interaction partner as more caring [166]. Additionally, a recent study by comparing MDMA against intranasal oxytocin demonstrated the former produced the greater improvements in pro-social communication [167]. And the positive effects of MDMA appear consistent across different environments, with participants examined in San Francisco, Chicago and Basel demonstrating broadly similar pro-social outcomes [167].

Emotional numbing is a characteristic feature of PTSD, where sufferers find it difficult to benefit from the positive effects of social contact (DSM-5). There is a strong link between the strength of the therapeutic alliance and positive outcome in PTSD therapy [168]. MDMA induces the release of oxytocin and produces robust pro-social feelings, the strength of which is strongly correlated to the level of oxytocin released [169].

Oxytocin has been found to markedly dampen fear related amygdala activity, causing a decreased stress response, decreased social anxiety [170-172] and alters negative evaluations of aversive conditioned stimuli such as fearful faces [173]. The amygdala is required for accurate social judgements of others based on their facial expression [174]. Healthy volunteers given MDMA were better able to detect positive facial expressions than negative ones [165]. As described above, the vmPFC plays an inhibitory role opposing the amygdala and is essential for fear extinction learning. MDMA causes increased vmPFC activation and decreased amygdala activation when given to healthy controls [42] and in response to observing angry faces [163].



Possible biological correlates of response to treatment in PTSD will be assessed by MRI. We aim to investigate pre-post effects of MDMA-assisted psychotherapy on brain function and connectivity as measured by functional magnetic resonance imaging (fMRI), including response to trauma-unrelated emotional stimuli (emotional faces), response to trauma symptom provocation (personal trauma narrative).

This sub-study will measure changes in brain activity at rest, and in response to stressful or threatening stimuli in the form of an emotional eliciting task and personalized trauma script. Conclusions concerning the efficacy of MDMA-assisted therapy may be further supported if changes in PTSD symptoms are accompanied by changes in brain activity and alterations in brain metabolites.

## 2.0 Implementation of Sub-Study

All eligibility criteria from the main study protocol will apply, except for the following inclusion criteria:

- Absence of Traumatic Brain Injury
- Absence of metal implants or metal fragments in the body
- Absence of claustrophobia
- Absence of tattoos in the head/neck or permanent eye makeup

## 3.0 Sub-Study Design Overview

The sub-study visits are presented below in relation to preceding visits from the main study.

<b>Preparatory Period with Enrollment Confirmation</b>			
From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 4): ~6 weeks (+5/-4 weeks)			
<b>Study Visit/ Visit #</b>		<b>Visit Duration/ Visit Timing/ (Scheduling Window)</b>	<b>Brief Description of Events</b>
Baseline & Enrollment Confirmation & MRI	Baseline CAPS-5 T1 (Visit 3)	1.5 hours/ Post Preparatory Session 2 (V2) & confirmation of Medication Taper and stabilization; before V4	CAPS-5, SDS, and DSP-I completed by an IR via tele-assessment after taper is complete. CAPS-5 scores sent ASAP to the therapy team/PI.

	Preparatory Session 3 & Enrollment Confirmation (Visit 4)	3h30min: (~30 min trauma script paradigm preparation, 90 minutes of measures, 90-minute therapy) within 6 days of Baseline CAPS-5 T1 (V3); within 4 days prior to Experimental Session 1 (V5) but not same day  3 to 6 days after Baseline CAPS T1 (V3); 1 to 4 days before Experimental Session 1 (V5). Both Baseline CAPS T1 (V3) and Preparatory Session 3 and Enrollment Confirmation (V4) must take place within 7 days prior to Experimental Session 1 (V5)	Prior to visit, ensure CAPS-5 confirms PTSD diagnosis and Total Severity Score of $\geq 35$ and confirm enrollment by reassessing specified eligibility criteria. Complete Baseline self-report measures. Complete Preparatory Session 3 (~30 min trauma script paradigm preparation, 90-minute measures, 90-minute therapy) and schedule V5. If enrollment is not confirmed, do not perform visit; complete termination.
	Baseline MRI session (Visit 4.1)	~1.5 hours/After Preparatory Session 3 & Enrollment Confirmation (V4) and within 6 days of Experimental Session 1 (V5)	30 min MRI preparatory session; ~63 min MRI scanning session including three paradigms: response to non-trauma-related stimuli, trauma-script provocation.

#### Follow-up Period and Study Termination

From Integrative Session 2.3 (Visit 13) until Study Termination (Visit 15): 4 weeks (+/-2).  
After Integrative Session 2.3 (Visit 13), ~4 weeks with no scheduled study visits until the Primary Outcome is completed.

Study Visit/ Visit #		Visit Duration/ Visit Timing/ (Scheduling Window)	Brief Description of Events
Primary Outcome	Primary Outcome CAPS-5 T3 (Visit 14)	1 hour/ ~13 (+/-3) weeks post Baseline CAPS-5 T1 (Visit 3) & 8 weeks (+/-2) after Experimental Session 2 (V10)	Primary Outcome CAPS-5, SDS, and DSP-I assessment completed by an IR via tele-assessment. Although there are allowable windows for all visits throughout the protocol, this visit must be completed within the overall window. Other visits should be scheduled to ensure the timing of the Primary Outcome CAPS-5 T3 assessment is appropriate.
MRI post-therapy	MRI-2 (Visit 14.1)	~63 min/ ~13 (+/-3) weeks post Baseline & 8 (+/-2) weeks post V10. After CAPS-5 T3	~63 min MRI scanning session including three paradigms: response to non-trauma-related stimuli, trauma-script provocation.

## 4.0 Sub-Study Methods



## 4.1 MRI Experimental Session

**Table 1: Schedule of Procedures for MRI Session**

Approximate Time (minutes)	Cumulated time	Procedure or Action
8		<b>Set up (fieldmap; localizer; anatomical scan)</b>
12	20'	<b>Resting state scan</b>
	21'	SUDS-1
12	33'	<b>Emotional faces task</b>
	34'	SUDS-2
8	40'	<b>Neutral Audio Script</b>
	41'	SUDS-3 neutral script
6	49'	<b>Traumatic Audio Script</b>
	50'	SUDS-4 traumatic script

### *Pre-Scan Session*

- On the day of the scan sessions, participants will arrive at the scan facilities 30 minutes prior to the scan session.
- The participant will be asked to fill out any documents required for the session and will ensure that they are MR compatible (*i.e.*, have removed all free metals including piercings, are wearing suitable clothing).
- The participant will be informed of all activities during the scan session and will have time to ask questions.
- If available, the participant will have the option to briefly lay down in a mock scanner in order to become more familiarized with the real scanner environment. If unavailable, a detailed description of the scanner environment will be verbally explained.

### *Scan Session – Set Up*

- The participant will be invited to lay down in the scanner, and will be given necessary equipment (ear plugs; padding; alarm button; MR compatible glasses if necessary)
- During the first 8 minutes, preliminary scans will be taken (fieldmap; localizer; anatomical scan). During this time the participant will be instructed to relax and remain still. A neutral image (*e.g.*, nature picture) will be displayed on the screen for participants to focus on.

### *Scan Session – Resting State*

- During the resting state scan, participants will be asked to relax with eyes closed. During this time, participants will be instructed to empty their mind.

### *Scan Session – Emotional Faces Task*

- Participants will be presented with stimuli consisting of either picture of faces in various emotional states (angry, fearful, sad, happy and neutral) or scrambled faces (control). In the emotion condition, participants have to indicate the gender of the face. In the control condition, participants have to press the corresponding button as indicated on the screen, *i.e.*, an arrow pointing left or right.

#### *Scan Session – Traumatic Audio Script Cue Paradigm*

- This task will closely replicate the imaginal exposure technique, which is a characteristic feature of trauma-focused psychotherapy. A neutral and a traumatic event will be collected during preparatory session and condensed into audio recording of approximately 30 seconds. During the scanning session, each participant will be instructed to lie still, breathe through his/her nose, and allow himself/herself to begin focusing on the neutral script as soon as the script is played. As soon as the participant has heard the script, he/she is encouraged to remember all sensations that are associated with the event for 60 seconds. The neutral script will be followed by the traumatic condition. The procedure will be as follows:

60 sec Rest

30 sec Neutral script > 60 sec time to remember all sensations > 120 sec break

30 sec Neutral script > 60 sec time to remember all sensations > 120 sec break

60 sec SUDS-neutral script

30 sec Traumatic script > 60 sec time to remember all sensations > 120 sec break

30 sec Traumatic script > 60 sec remember all sensations

60 sec SUDS-traumatic script

#### *Scan Session – Subjective Units of Distress Scale (SUDS)*

- Participants will be asked to rate how distressed they feel after preparation of neutral and traumatic script at preparatory session 3.
- Participants will be asked to rate how distressed they feel at set times throughout the scan session as explained in Table 1 above: Schedule of Procedures for MRI Session.

## **5.0 Sub-Study Objectives and Evaluation**

The primary objective of this sub-study will be to explore possible biological correlates of treatment outcomes obtained from MDMA-assisted psychotherapy among participants with PTSD.

- To investigate pre-post effects of MDMA-assisted psychotherapy on brain function and connectivity as measured by functional magnetic resonance imaging (fMRI), including response to trauma-unrelated emotional stimuli (emotional faces), response to trauma symptom provocation (personal trauma narrative). The outcome variables will be compared between timepoints (Baseline scan V 4.1 and post-treatment scan V 14.1).
- To examine the relationship between fMRI outcome variables and the primary outcome variable, namely change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

## **6.0 Methods, Data Analysis, and Hypothesis**

All measures will be performed on a 3-Tesla MRI machine (Siemens or Philips, depending on site) equipped with a standard head coil. The measurements will remain the same for both scan 1 (pretreatment) and scan 2 (posttreatment). The impact of MDMA-assisted psychotherapy (scan 2) on the outcome measures will be compared with those at baseline (scan 1).

fMRI sub-study data may be analyzed at the later stage and presented in an addendum to the clinical study report.

## 7.0 Resting State

During resting state, participants will be instructed to relax with eyes closed. During this time, they will be instructed to empty their mind.

## 8.0 Data analysis: Resting State

Resting state images will be analyzed via functional connectivity. Functional connectivity data will be produced with the MATLAB toolbox DPARSF. Sphere regions of interest (ROI) will be created that are located in key areas of the fear circuitry system. Average time courses will be obtained for each sphere ROI and correlational analysis will be performed voxel wise to generate FC maps for each sphere ROI. Finally, the correlation coefficient map will be converted into z-maps by Fisher's r-to-z transform to improve normality.

## 9.0 Hypothesis: Resting State

We hypothesize that upon completion of the treatment (post-treatment scan vs. baseline scan), there will be decreased BOLD activity in the amygdala and hippocampus. Additionally, there will be decreased coupling between the vmPFC and hippocampus and increased coupling between the amygdala and hippocampus, and that these changes will positively correlate with subjective effects ratings of the MDMA experience.

## 10.0 Emotional Faces Task

The experimental paradigm during functional MRI scanning consists of a blocked design, including an emotion condition with angry, fearful, sad, happy and neutral face stimuli known to reliably activate the anterior medial temporal lobe including the amygdala [128], and a control condition with scrambled faces. Twenty-four stimuli were selected for each of five facial expressions, comprising 12 female and 12 male faces. Each face will not be presented more than four times. The control condition (scrambled faces) will be presented 80 times. To reduce anticipatory effects, an event-related design was used that involved a pseudo-random presentation of a total of 200 stimuli against a black background. Each photograph will be shown on the screen for 2.5 s, with an interstimulus (black screen) interval varying between 0.5 and 1.5 s. Participants have to indicate each face's gender by pressing one of two buttons with the index finger of the left or right hand on two magnet-compatible button boxes. During the presentation of scrambled faces, participants have to press left or right buttons in conformity with the instruction presented on the screen (*i.e.*, an arrow pointing to the left or to the right). The reaction time will be recorded.

## 11.0 Data Analysis: Emotional Face-Matching Task

Image analysis will be performed with SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). The first five EPI-volumes will be discarded, and the remaining images will be realigned to the first volume. Images will be then co-registered to the anatomical scan, corrected for differences in slice acquisition time, spatially normalized to the MNI T1 template, resampled into  $2 \times 2 \times 2 \text{ mm}^3$  voxels, and spatially smoothed (8 mm FWHM). Statistical analysis will be performed within the framework of the general linear model. To assess the influence of MDMA-assisted psychotherapy on neural responsivity, the two experimental conditions (posttreatment scan; baseline scan) will be modeled as box-car regressors convolved with the canonical hemodynamic response function of SPM12. In addition, the realignment parameters will be included to

model potential movement artifacts, as well as a constant. Furthermore, a high-pass filter (cut-off 1/128 Hz) will be included, and temporal autocorrelation will be modeled with an AR (1) process. Contrast images subtracting the visuo-motor control condition from the emotion condition will be obtained and analyzed in subsequent random effects models.

## **12.0 Hypothesis: Emotional Face-Matching Task**

We hypothesize that upon completion of the treatment (post-treatment scan vs. baseline scan) participants will display a reduced amygdala response to fearful vs. angry faces.

## **13.0 Traumatic Audio Script Paradigm**

The script-driven imagery procedure is based on previously published fMRI methods [127]. A neutral and a traumatic event will be collected during preparatory session 3 and condensed into an audio recording of 30 seconds. Patient will be asked to rate how distressed they feel (SUDS) after collection of the neutral event and after the collection of the traumatic event. During the paradigm, participants will be instructed to lie still, breathe through his/her nose, and allow themselves to begin focusing on the script, as soon as the audio recording is played. As soon as the participant has heard the script, they will be encouraged to remember all sensations that were associated with the event for approximately 60 seconds. Both the neutral and the traumatic script will be played two times. The total task time is of approximately 14 minutes. The heart rate will be measured during the entire Traumatic Audio Script Paradigm period.

## **14.0 Data Analysis: Traumatic Audio Script Paradigm**

Brain activation during the recall of the neutral event will be calculated by using the average activation patterns during the final 30 seconds of each period of recollection of the neutral event. Brain activation during the recall of the traumatic event will be calculated on the basis of the average activation patterns during the final 30 seconds of each period of recollection of the traumatic event. The difference in brain activation between these two conditions will be compared between baseline scan and post-treatment scan.

Functional maps of the activated pixels will be constructed by pixel-by-pixel comparisons of the signal intensity in the baseline and task-related images. Statistical parametric mapping methods (SPM12 software) will be used. Basis functions representing epochs of interest will be entered into SPM12. Variability in scans attributed to each basis function relative to SPM12's implicit baseline will be revealed by using contrasts. Fixed-effects analyses will be performed by modeling each group's evoked blood-oxygen-level-dependent (BOLD) response with hemodynamically convolved boxcar basis functions. The regions of interest will be defined on the basis of T1-weighted images and Talairach coordinates.

## **15.0 Hypothesis: Traumatic Audio Script Paradigm**

We hypothesize that upon completion of the treatment (post-treatment scan vs. baseline scan), participants will rate their traumatic script as less emotionally overwhelming and more tolerable to imagine. This will correlate with decreased activation of the amygdala and insula, and increased activation of the mPFC and hippocampus and the strength will correlate with reductions in Subjective Units of Distress (SUDS) ratings.