MPLONG Protocol and Synopsis
IND #063384

Long-Term Safety and Persistence of Effectiveness of Manualized MDMA-Assisted Therapy for the Treatment of Posttraumatic Stress Disorder

AMENDMENT AND DATE	Amendment 3, Version 1, 25 October 2022
BRIEF TITLE	Long-Term Safety and Effectiveness of Manualized MDMA-Assisted Therapy for the Treatment of Posttraumatic Stress Disorder
STUDY NUMBER	MPLONG
SPONSOR NAME	Multidisciplinary Association for Psychedelic Studies (MAPS)
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Disclaimer: This protocol version is for public viewing. Some information has been removed to maintain the integrity of this ongoing study.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 Version 1	29 June 2021
Amendment 1 Version 1	07 April 2021
Original Protocol Version 2	27 June 2019
Original Protocol Version 1	07 May 2019

Amendment 3 Version 1: 25 October 2022

This amendment is considered to be non-substantial because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment is adding C-SSRS assessments according to FDA Guidance for Industry on Suicidal Ideation and Behavior.

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List of Abbreviations

ACE	Adverse Childhood Experiences Questionnaire
AE	Adverse Event
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory-II
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CPGS	Chronic Pain Grade Scale
CRA	Clinical Research Associate
C-SSRS	Columbia-Suicide Severity Rating Scale
DID	Dissociative Identity Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
ED	Emergency Department
EDC	Electronic Data Capture
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ePRO	Electronic Participant Reported Outcome
EQ-5D-5L	EuroQol Five Dimensions – Five Levels Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability
HPA	Hypothalamic-pituitary-adrenal
HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IR	Independent Rater
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
kg	Kilogram
LEC-5	Life Events Checklist
LTFU	Long-term Follow-up
LTFUQ	Long-term Follow-up Questionnaire
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	3,4-methylenedioxymethamphetamine
mg	Milligram
*m*ITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measure
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
PCL-5	PTSD Checklist for DSM-5
PHI	Protected Health Information
PTSD	Posttraumatic Stress Disorder
SAE	Serious Adverse Event
SCS	Self-compassion Scale
SDS	Sheehan Disability Scale

SRNU	Self-reported Nicotine Use
SSR	Sample size re-estimation
SSRI	Selective serotonin reuptake inhibitor
TAS-20	Toronto Alexithymia Scale
UFEC	Utilization of Facility-based and Emergent Care
U.S.	United States
VA	U.S. Department of Veterans Affairs
VAS	Visual Analog Scale
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced™

1.0 Public MPLONG Protocol Synopsis

1.1 Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and education organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy for treatment of posttraumatic stress disorder (PTSD). Data from a series of Phase 2 and 3 studies of MDMA-assisted therapy conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, is treatable with up to three sessions of MDMA-assisted therapy. This non-interventional study will serve as the long-term follow-up (LTFU) protocol for MDMA-assisted therapy clinical trials and will measure persistence of effectiveness using the CAPS-5.

Additionally, this study will gather data to support health economics and cost effectiveness analyses of this treatment. Participants who have received at least one dose of Investigational Medicinal Product (IMP) in the main study will be eligible to participate in this study.

1.2 Study Design

Data to be collected will include effectiveness data collected with the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) and the Posttraumatic Symptom Checklist for DSM-5 (PCL- 5), exploratory data supporting effectiveness, as well as health economics and safety data. No IMP or therapy will be administered in this study. The study will consist of two visits which can be completed over 7 to 60 days. Participants will meet with a study therapy team member to provide information about changes in health and medications either in person or via teleassessment, followed by a teleassessment visit with an Independent Rater (IR) who will administer the CAPS-5, Sheehan Disability Scale (SDS), and C-SSRS. Subsequently the participant will complete several self-report measures.

1.3 Protocol Objective

The overall objective of this study is to use standard clinical measures to determine the long-term safety and effectiveness of flexible dose, manualized MDMA-assisted therapy, at least six months after the last Experimental Session in the main study.

1.3.1 Primary Objective

The primary objective of this study is to evaluate the long-term effectiveness of MDMA-assisted therapy for treatment of PTSD as measured by the change in CAPS-5 Total Severity Score (actual or imputed) from the main study Baseline and Study Termination to LTFU IR Assessments.

1.3.2 Key Secondary Objective

The key secondary objective of this study is to evaluate the long-term effectiveness of MDMA-assisted therapy for treatment of functional impairment associated with PTSD as measured by the change in Sheehan Disability Scale (SDS) item scores from the main study Baseline and Study Termination to LTFU IR Assessments.

1.3.3 Safety Objectives

This protocol will include the following safety objectives to evaluate the long-term safety of MDMA-assisted therapy:

1. Assess interim medical history in the LTFU period after main study completion for any effects of MDMA-assisted therapy on long-term safety
2. Assess incidence of concomitant medication use in the LTFU period after main study completion
3. Assess incidence of Ecstasy use during the LTFU period after main study completion
4. Assess incidence of therapy in the LTFU period after main study completion
5. Assess incidence of serious suicidal ideation and positive suicidal behavior with the C-SSRS, during the LTFU period after main study completion

1.4 Exploratory Objectives

These objectives may be explored to characterize the long-term effects of participants receiving MDMA-assisted therapy. These exploratory objectives will be compared to baseline values as well as the last reported outcome values from the main study. This protocol will include the following self-reported exploratory objectives to evaluate healthcare utilization or cost effectiveness of MDMA-assisted therapy:

1. Assess changes in facility-based healthcare utilization with the UFEC since main study
2. Assess changes in alcohol use with the AUDIT since main study
3. Assess changes in drug use with the DUDIT since main study
4. Assess changes in depression with the BDI-II since main study
5. Assess changes in chronic pain with the CPGS since main study
6. Assess changes in quality of life with the EQ-5D-5L since main study
7. Assess changes in health and work performance with the HPQSF since main study
8. Assess changes in disordered eating with the EAT-26 since main study
9. Assess changes in nicotine use with the SRNU since main study
10. Assess changes in economic factors and occupation since main study

This protocol will include the following exploratory objectives to evaluate potential long-term changes associated with MDMA-assisted therapy since the main study:

11. Assess changes in alexithymia with the TAS-20 since main study
12. Assess changes in self compassion with the SCS since main study
13. Assess changes in depression symptom severity with the BDI-II since main study
14. Explore the effect of presence of stressors during the follow-up period with the LEC-5 as a covariate on the CAPS-5 Total Severity analyses
15. 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 during the follow-up period
16. Assess incidence of relapse, treatment response, loss of diagnosis, and remission during the follow-up period per CAPS-5
17. Explore the effect of adverse childhood experiences, as captured in the Adverse Childhood Experiences Questionnaire (ACE) in the main study, on the CAPS-5 Total Severity analyses during the follow-up period
18. Assess the participant's experiences in daily life after participating in the main study through the LTFUQ

1.5 Statistical Analysis

Descriptive statistics will be computed for study measures, including minimum, maximum, mean, median, and standard deviation for continuous measures and counts and percentages for categorical measures.

The following analysis sets are defined for this study:

- All Enrolled Set: All participants who received any IMP in the primary study where they were initially enrolled.

An MMRM model will be used to characterize the mean change in CAPS-5 from Baseline to Study Termination from the main study and to the LTFU Visit.

Missing data will not be imputed. The least squares means from the MMRM model will be reported by visit with 95% confidence intervals. Additional baseline covariates (such as age, gender, race, ethnicity, index trauma, complexity and severity of trauma, medication tapering and duration thereof, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences), time since enrollment in parent study, may be assessed for inclusion in the model at a $p<0.05$.

Sheehan Disability Scale (SDS), the secondary outcome, will be analyzed in the same manner as the Primary Outcome.

Cohen's *d* one-group pretest-posttest will be used to estimate the effect size from Baseline in the main study to the LTFU Visit for the CAPS-5 and SDS.

2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and education organization working as a clinical trial sponsor to obtain marketing approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy in patients with posttraumatic stress disorder (PTSD). Controlled Phase 1 studies, nonclinical studies, Phase 2 and Phase 3 studies, and investigator-initiated studies formed the basis for starting the Clinical Development Program of MDMA under Investigational New Drug (IND) #063384. MDMA is a Breakthrough Designated treatment for PTSD on the basis of substantial potential improvement over available medications. MAPS-sponsored studies are implemented through MAPS' wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (MPBC).

MAPS-sponsored Phase 2 and Phase 3 studies are intended to gather data on the safety and effectiveness of manualized MDMA-assisted therapy as a treatment for PTSD. The Primary Outcome measure is the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), which evaluates the changes in PTSD symptom severity and is assessed by a centralized Independent Rater (IR) pool for participant who completed this assessment in the main study. For participants who did not complete the CAPS-5 in the main study, the PCL-5 data from the primary study will be used to impute the CAPS-5 data. This long-term follow-up (LTFU) extension protocol will investigate the persistence of effectiveness of MDMA-assisted therapy after the main study. Data to be collected will include effectiveness data collected with the CAPS-5, data supporting effectiveness, and safety data. No Investigational Medicinal Product (IMP) or therapy will be administered in this LTFU study. Eligible participants who have completed at least one Experimental Session in the main study protocol will be asked to enroll in this LTFU extension study.

2.1 Rationale

Data from a series of Phase 2 and 3 studies of MDMA-assisted therapy conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, is treatable with up to three sessions of MDMA-assisted therapy. This non-interventional study will serve as the long-term follow-up (LTFU) protocol for MDMA-assisted therapy clinical trials and will measure persistence of effectiveness using the CAPS-5. Additionally, this study will gather data to support health economics and cost effectiveness analyses of this treatment. Participants who have received at least one dose of Investigational Medicinal Product (IMP) in the main study will be eligible to participate in this study.

2.2 Background

2.2.1 PTSD

PTSD is a serious debilitating disorder associated with increased mortality and cardio-metabolic morbidity. PTSD is a stress-related psychiatric condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, and accidents. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares. PTSD negatively impacts a person's daily life, resulting in fractured relationships, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization, and increased depression and suicide risk. People who suffer from PTSD often relive the experience through nightmares and flashbacks, have poor sleep quality, and feel detached or estranged. Confronting overwhelming internal distress and frightening external environments can also lead to high levels of depersonalization and derealization, which led clinicians to identify a dissociative subtype of PTSD in the DSM-5. Adaptations in normal brain function have been observed in imaging studies of patients with PTSD that underlie alterations in emotional processing and regulation, cognition, and many aspects of behavior, though clinical symptoms and changes in brain activity are not homogenous across patients [1]. The dissociative subtype occurs in 12 to 30% of people with PTSD and is characterized by detachment and emotional numbing and visualized in the brain as overmodulation of affect mediated by midline prefrontal inhibition of limbic regions, while the non-dissociative subtype presents symptoms of hyperarousal and re-experiencing, an emotional under-modulation mediated by the failure of prefrontal inhibition of the same limbic regions [2, 3]. Patients suffering from the dissociative subtype of PTSD typically have early childhood trauma and appear to be particularly difficult to treat, with mixed response to existing evidence-based treatments.

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 [4-6]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are 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 therapy as routine first-line treatment by the VA's National Center for PTSD in the U.S., as well as by the World Health Organization (WHO). An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but have only small effect sizes in reducing PTSD symptoms. PTSD brings a high public burden, both economically and socially, by increased use of health and social services, lost wages, and

disability payments [7, 8]. Given the chronicity of PTSD, low compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients suffer from unmet medical need.

One treatment approach is to develop medications and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [9, 10], although some patients may need more than one type of treatment to reduce or resolve those symptoms. A meta-analysis concluded that all "bona fide" psychotherapies, including those listed above, are similarly effective with PTSD [11]. In the past decade, there has been a growing amount of research into medications and other methods that may augment the effectiveness of therapy for PTSD (see [12] for a review). Examples of this are virtual reality-assisted exposure therapy [13, 14] and D-cycloserine-assisted psychotherapy [15]. MDMA-assisted therapy is another such approach.

2.2.2 MDMA-Assisted Therapy for PTSD

Many psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in therapy with an appropriate level of emotional engagement [10]. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion [16]. This has been referred to as working within the "optimal arousal zone" or "window of tolerance" [17-19].

The combined neurobiological effects of MDMA increase compassion, reduce defenses and fear of emotional injury, and enhance communication and introspection. MDMA produces anxiolytic and prosocial effects, which counteract avoidance and hyperarousal in the context of therapy. PTSD increases amygdala activity, causing heightened encoding of fearful memories and decreasing blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [20], and there is some indication that MDMA may increase activity in the prefrontal cortex [21]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [20]. This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [22-24]. The reduction in stress- induced activation of the amygdala may be supported and enhanced by interacting with the therapy team during and after the MDMA experience. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process. MDMA is capable of inducing unique psychopharmacological effects typically leading to decreased fear and increased wellbeing, sociability, interpersonal trust, acceptance of self and others, and ability to address psychological issues without extreme disorientation or ego loss, while maintaining an alert state of consciousness and enhanced recall. These factors taken together can provide the opportunity for a corrective emotional experience.

A combined treatment of MDMA and therapy may be especially useful for treating PTSD because MDMA can attenuate the fear response to a perceived threat to one's emotional integrity and can decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [25-28]. Attenuation of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [29]. Participants are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal awareness that even painful feelings that arise during therapy are an important part of the therapeutic process. In addition to facilitating the processing of traumatic memories and painful emotions, MDMA can engender feelings of empathy, love,

and deep appreciation, 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 therapy may enable participants to restructure their intra-psychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

In MAPS-sponsored Phase 2 studies, participants completed long-term follow-up 12 months or more after their last experimental session. In one study (MP1), long-term follow-up occurred after an average of 3.8 years. Results for each study indicate that for the majority of participants PTSD symptom levels at LTFU were comparable to those at the end of treatment. In some cases, there was continued improvement at LTFU with participants in one study (MP2) exhibiting a delayed response by achieving statistically significant CAPS improvement only at LTFU. Pooled results show marked and sustained improvements for the majority of participants. A within-subject comparison of CAPS-4 scores from the end of treatment to LTFU failed to reach significance for any group, indicating that the beneficial effects of MDMA therapy in mitigating PTSD symptoms at the end of treatment were long-lasting for most subjects. Primary and secondary CAPS-4 data observations are further supported by within-subject comparisons that found no significant difference in secondary outcome measures when comparing LTFU and end of treatment for any group. This demonstrated effects of MDMA-assisted therapy on reducing depression measured with the Beck Depression Inventory (BDI-II), improving psychological functioning with the Global Assessment of Functioning (GAF), and posttraumatic growth with the Posttraumatic Growth Inventory (PTGI), were also sustained over time. Results from long-term follow-ups after treatment with MDMA-assisted therapy demonstrate durable improvements in PTSD symptoms that will be further explored in this study.

3.0 Protocol Objective

The overall objective of this study is to use standard clinical measures to determine the long-term safety and effectiveness of flexible dose, manualized MDMA-assisted therapy, at least six months after the last Experimental Session in the main study.

3.1 Primary Objective

The primary objective of this study is to evaluate the long-term effectiveness of MDMA-assisted therapy for treatment of PTSD as measured by the change in CAPS-5 Total Severity Score from the main study Baseline and Study Termination to LTFU IR Assessments.

3.2 Key Secondary Objective

The key secondary objective of this study is to evaluate the long-term effectiveness of MDMA-assisted therapy for treatment of functional impairment associated with PTSD as measured by the change in Sheehan Disability Scale (SDS) item scores from the main study Baseline and Study Termination to LTFU IR Assessments.

3.3 Safety Objectives

This protocol will include the following safety objectives to evaluate the long-term safety of MDMA-assisted therapy:

1. Assess interim medical history in the LTFU period after main study completion for any effects of MDMA-assisted therapy on long-term safety
2. Assess incidence of concomitant medication use in the LTFU period after main study completion

3. Assess incidence of Ecstasy use during the LTFU period after main study completion
4. Assess incidence of therapy in the LTFU period after main study completion
5. Assess incidence of serious suicidal ideation and positive suicidal behavior with the C-SSRS during the LTFU period after main study completion.

3.4 Exploratory Objectives

These objectives may be explored to characterize the long-term effects of participants receiving MDMA-assisted therapy. These exploratory objectives will be compared to baseline values as well as the last reported outcome values from the main study. This protocol will include the following self-reported exploratory objectives to evaluate healthcare utilization or cost effectiveness of MDMA-assisted therapy:

6. Assess changes in facility-based healthcare utilization with the UFEC since main study
7. Assess changes in alcohol use with the AUDIT since main study
8. Assess changes in drug use with the DUDIT since main study
9. Assess changes in depression with the BDI-II since main study
10. Assess changes in chronic pain with the CPGS since main study
11. Assess changes in quality of life with the EQ-5D-5L since main study
12. Assess changes in health and work performance with the HPQSF since main study
13. Assess changes in disordered eating with the EAT-26 since main study
14. Assess changes in nicotine use with the SRNU since main study
15. Assess changes in economic factors and occupation since main study

This protocol will include the following exploratory objectives to evaluate potential long-term changes associated with MDMA-assisted therapy:

16. Assess changes in alexithymia with the TAS-20 since main study
17. Assess changes in self compassion with the SCS since main study
18. Assess changes in depression symptom severity with the BDI-II since main study
19. Explore the effect of presence of stressors during the follow-up period with the LEC-5 as a covariate on the CAPS-5 Total Severity analyses
20. 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 during the follow-up period
21. Assess incidence of relapse, treatment response, loss of diagnosis and remission during the follow-up period visit per CAPS-5
22. Explore the effect of adverse childhood experiences, as captured in the Adverse Childhood Experiences Questionnaire (ACE) in main study, on the CAPS-5 Total Severity analyses during the follow-up period
23. Assess the participant's experiences in daily life after participating in the main study through the LTFUQ

4.0 Eligibility Criteria

4.1 Inclusion Criteria

Participants eligible for participation in this extension study are individuals who:

1. Enrolled in a MAPS-sponsored study of MDMA-assisted therapy for the treatment of PTSD
2. Have received IMP in at least one Experimental Session in the main study
3. Agree to be contacted by study team approximately six months after the last Experimental Session in the main study to schedule and participate in LTFU visits

4.2 Exclusion Criteria

Participants cannot take part in this extension study if they:

1. Are not able to give adequate informed consent
2. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation

5.0 Protocol Design

This multi-site non-interventional study will assess the long-term safety and effectiveness of MDMA-assisted therapy in participants diagnosed with PTSD when enrolled in a MAPS-sponsored study and completed at least one Experimental Session. The IR will assess PTSD symptoms with the CAPS-5 and participants will complete self-report measures. Safety data and changes in medications and therapy since the termination of main study will be collected and reported.

For each participant, study participation will consist of:

- **Informed Consent**: Prior to collection of data for IR Assessments
- **Enrollment**: Eligibility assessment and enrollment of eligible participants
- **Long-term Follow-up Visits**: At least six months after last Experimental Session in the main study, administration of CAPS-5 and self-report measures, and collection of safety data
- **Termination**: Contact from study site informing participant that study procedures are complete

Table 1: Study Design Overview

Study Visit		**Visit Duration/ Visit Timing/ (Scheduling Window) ***	**Brief Description of Events**
Screening and enrollment	Consent and Eligibility Determination	~70 minutes/ Prior to Enrollment (does not need to be completed on same day)	Informed Consent and assessment of eligibility via teleassessment or in-person visit. Informed Consent Form to be sent to participant and returned to the site for confirmation of consent. A member of the study team will collect C-SSRS, medication and therapy changes since main study, and interim medical history. If eligible, participant will enroll in LTFU study.
LTFU Visits	IR Assessments	2 hours/ At least 6 months after final Experimental Session	CAPS-5, SDS, and C-SSRS completed by an IR via teleassessment. IR visit not required for participants who enrolled in the MAPPUSX main study
	Measures	2 hours/ Within 30 days after IR Assessments	Participant will meet with study staff via teleassessment or in person to be guided in the completion of appropriate self-report measures, which may include the following: PCL-5, LEC-5, BDI-II, SDS, UFEC, AUDIT, DUDIT, CPGS, EQ-5D-5L, SCS, TAS-20, SRNU, EAT-26, HPQSF, C-SSRS, and Long-term Follow-up Questionnaire (LTFUQ).

Termination	Termination Phone Call	5 minutes/ After Measures and Medical History Collection	Study Coordinator or other site staff will inform participant that study participation is complete via a phone call.

* Visit windows are provided as a guide and all available data will be analyzed regardless of visits being completed within protocol windows.

5.1 Planned Duration of Study

This long-term follow-up study is expected to last approximately 3 years from enrollment of the first participant.

5.1.1 Early Termination from the Study

Participants can withdraw consent at any time for any reason without repercussions. 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, they will explain the reason for withdrawal and document in the participant's source records and electronic Case Report Form (eCRF).

5.1.2 Lost to Follow-up

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 multiple efforts to contact the study participant and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 1 week, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. The emergency contact the participant provided should be contacted, along with any support persons previously known to the study team. Lastly, a certified letter (or equivalent) should be sent to their last known mailing address. If the participant fails to respond to any of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up.

5.2 End of Study Definition and Premature Discontinuation

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in Table 2: Time and Events for the last participant in the trial.

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 follow-up and an Exit Plan. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and state regulations.

6.0 Measures

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

The last month CAPS-5 is a semi-structured interview that assesses index history of DSM-5- defined traumatic event exposure including the most distressing event, time since exposure, to produce a diagnostic score (presence vs. absence) and a PTSD Total Severity score [30]. 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 telemedicine. 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 a research reliable trainer and will be supervised by qualified personnel. 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. Additionally, the IRs are trained to carefully assess trauma-relatedness of each symptom according to standard CAPS-5 procedures. Doing so ensures that all symptoms contributing to the CAPS-5 PTSD diagnostic status and total severity score are either temporally or functionally related to the index trauma rather than attributable to non-trauma current life stressors or current world events such as the COVID-19 pandemic. 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. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy.

6.2 SDS (Sheehan Disability Scale)

The SDS is a self-report assessment of functional impairment [31]. The reporting period for the SDS is the past week. 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). Per FDA request, 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. [32].

6.3 C-SSRS (Columbia Suicide Severity Rating Scale)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [33]. This extension study will use the Since Last Visit version to assess suicidal ideation, ideation intensity, and behavior, which for this study measures from the last visit of the main study and for the previous 2 weeks. During screening, the Since Last Visit C-SSRS and the Past 2 Weeks C-SSRS will be administered. The Since Last Visit C-SSRS will be administered during the IR Assessments to assess suicidal ideation, ideation intensity, and behavior since the C-SSRS administered at Screening. The Since Last Visit C-SSRS will also be administered at subsequent visits to assess suicidal ideation, ideation intensity, and behavior since the initial visit. The C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The C-SSRS Intensity scale obtained a Cronbach's alpha of 0.94 for the Since Last Visit form [34].

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

The LEC-5 is a 17-item self-report instrument designed to determine the presence of traumatic life events in the assessment and diagnosis of PTSD, from the last administration in the main study to present. 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 since the Primary Endpoint of the main study, permitting the possibility of marking multiple events [35].

6.5 PCL-5 (PTSD Checklist)

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the symptoms of PTSD per DSM-5 [36] over the last month. 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).

6.6 BDI-II (Beck Depression Inventory II)

The BDI-II is a revision of the BDI, a 21-item self-report measure [37, 38] that will serve as a measure of depression symptom severity [39]. The reporting periods of this measure is the past two weeks. 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 [39]. 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 [39, 40]. Higher scores indicate more severe depressive symptoms.

6.7 CPGS (Chronic Pain Grade Scale)

The CPGS is a seven-item measure of pain. Responses to six of the seven items are made on a 10- point Likert scale, and a response on the other item is the number of days in the past 6 months when pain prevented the respondent from carrying out everyday activities [41]. 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 [42].

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

The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions - mobility, self-care, usual activities, pain-discomfort and anxiety-depression; and one visual analog scale (VAS). Responses are made on each dimension by checking one of five statement that best reflects their health on the day of measure completion, from the healthiest or fewest problems (e.g., "I have no trouble walking about") to the most trouble (e.g., "I am unable to walk about") [43, 44]. In the second part of the EQ-5D-5L, current degree of health ("your health today") is indicated by marking a 20 cm line marked from one to 100, with 100 considered "the best health you can imagine" and one "the worst health you can imagine." The EQ-5D-5L does not sum responses but treats each response on a dimension as a scale score, and the VAS is the location of the mark in centimeters. For items that do not specify "today", the reporting period of this measure is the time since participation in the main study was terminated. 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 [45]. The instrument has been validated in populations from eight countries. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation [46]. The EQ-5D-5L takes about 3 minutes to complete.

6.9 SCS (Self-Compassion Scale)

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 [47]. The reporting period of the SCS is the time since termination in the main study. 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 [48].

6.10 TAS-20 (Toronto Alexithymia Scale)

The TAS-20 is a 20-item measure of self-reported difficulties with recognizing and verbalizing emotions [49, 50] since termination of main study participation. Responses are made on a 5-point Likert scale (1=Strongly disagree to 5=Strongly agree). Estimated time of measurement is 5 to 8 minutes. The scale is comprised of three subscales: Difficulty Describing Feelings, Difficulty Identifying Feelings, and Externally-Oriented Thinking, with all scales summed to create a total score reflecting presence and degree of alexithymia. The TAS-20 is an established measure and can be used diagnostically with a score of 61 or higher indicative of alexithymia. The TAS-20 is reliable and has good test-retest reliability (Cronbach's alpha of 0.81, test-retest of 0.77).

6.11 AUDIT (Alcohol Use Disorders Identification Test)

The AUDIT is a ten-item self-report test. Respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) [51]. 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). For items that do not indicate a time period, the reporting period is since termination of participation in the main study. The measure can readily detect alcohol abuse disorders in a wide array of individuals [52].

6.12 DUDIT (Drug Use Disorders Identification Test)

The DUDIT is an 11-item measure designed to assess presence of substance use disorders [53]. 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. For items that do not indicate a time period, the reporting period is since termination of participation in the main study. 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% [53]. The English

translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.

6.13 SRNU (Self-reported Nicotine Use)

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.

6.14 EAT-26 (Eating Attitudes Test)

The EAT-26 is a 26-item self-report measure that assesses attitudes about eating and food and is used to assess presence of eating disorders. The time period of the measure is since termination of participation in the main study. Responses are made on a six-point scale (1=Always to 6=Never), and gathers information on gender, age, height, and weight. The EAT-26 produces a total score and can be used to generate a "referral score." The 27th item addresses the occurrence and frequency of specific eating behaviors, such as binge eating. Estimated time to complete is 4 to 8 minutes. Items on the EAT-26 have high reliability coefficients (Cronbach alpha of 0.83 to 0.90) and has concurrent validity [54].

6.15 HPQSF (Health and Work Performance Absenteeism and Presenteeism Short Form)

The HPQSF is a short form of a larger measure of health and work performance that has selected items referring to absenteeism and work performance [55]. The larger measure was created by the WHO as part of the Global Burden of Disease initiative. It consists of eight questions selected from the larger Health and Work Performance Questionnaire, with one question containing five additional items. Items include questions concerning hours worked during an average week, number of whole and partial days missed during a 4-week period, and items that rate average coworker and self-work performance on a ten-point Likert scale (1=Worst performance to 10=Top performance). Hours spent in work over a 4-week period and over the last 7 days can be used to estimate absenteeism, and the HPQSF can also score presenteeism, a measure of actual performance in relation to possible performance. Self-reports on measure appear to match employer records of presence or absence [56], and the HPQSF appears to be reliable between one time point and another (reliability of 0.52) and is sensitive to change [55].

6.16 UFEC (Utilization of Facility-based and Emergent Care)

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.

6.17 LTFU Questionnaire

The Long-term Follow-up Questionnaire has been developed by the sponsor to assess long-term reactions to MDMA-assisted therapy. The measure will be used to assess the participant's experiences in daily life after participating in the main study.

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 and Medical Monitor consulted if necessary.

7.1 Screening Period

7.1.1 Screening and Enrollment

Participants will be contacted by telephone or email approximately five months after their last Experimental Session in the main study to ascertain if they are interested in completing this LTFU study, and where applicable, obtain subject consent to share contact information with a LTFU site. If the participant is interested, the site staff will send a copy of the Informed Consent Form (ICF) to the participant for review. The site staff will conduct an ICF visit in person or over teleassessment, during which the participant and investigator will each sign their own copy of the ICF. Written consent must be obtained prior to performing any evaluations for the study. The signature may be obtained using an electronic 21 CFR Part 11 compliant system.

The site staff will confirm eligibility with the participant. If eligible, the participant will be considered enrolled into the LTFU study and the site staff will schedule IR Assessments. The participant will meet with study staff via teleassessment for administration of the C-SSRS, reviewing suicidality for the period of time since the main study ended and within the last 2 weeks. Demographic data will be reviewed for any changes as well.

Site staff will meet with the participant via teleassessment or in person to obtain the participant's interim medical history that occurred between Study Termination from the main study and the LTFU, capturing reported weight, any significant health changes, and changes in mental health. This information will be collected via self-report. Interim medical history and medications should be obtained after LTFU Enrollment and prior to termination from the LTFU study.

Participants will not be asked to request medical records that have been generated since the main study Termination unless the site team deems medical record collection necessary. At the discretion of the study team, the study team may collect existing medical records in order to minimize missing or incorrect data. If the study team needs to collect medical records from a provider and records cannot be obtained, the study team may ask for a health release to collect information over the phone.

7.1.2 IR Assessments

Participants will be scheduled for an IR visit via teleassessment for completion of CAPS-5 and SDS. The IR interview may be recorded to assess reliability of ratings. The IR will administer the Since Last Visit C-SSRS and contact the study team after the call and present any concerns. The study team will follow-up with the participant to ensure safety, provide support, recommend treatment if appropriate, and schedule the next visit.

The IR visit is not required for participants who enrolled in the MAPPUSX main study.

7.1.3 Measures

Participants will meet with study staff via teleassessment to be guided in the completion of self-report measures. Site staff will support the participant in completing the following self-report measures:

- Interim LEC-5
- PCL-5 (should be assessed in relation to index trauma reported in main study)
- BDI-II
- CPGS
- EQ-5D-5L
- SCS
- TAS-20
- AUDIT
- DUDIT
- SRNU
- EAT-26
- HPQSF
- UFEC
- C-SSRS
- LTFUQ

Measures do not need to be video-recorded. The study team will review self-report measures for completeness and follow-up on any discrepancies or missing data at the termination visit if needed. The study team will provide an Exit Plan, which may include a referral for additional medical or therapeutic care, if needed.

If a participant completed all MPLONG visits except for Study Termination (which is typically a 5-minute phone call), the study team will send the participant a letter instead of designating the participant as an Early Termination.

8.0 Participant Numbering

Every participant will be tracked using the same participant number used in the main study.

Some participants who previously enrolled in a blinded clinical trial may participate in this study twice. This may happen if a participant was randomized to placebo in their first main study and after unblinding, participate in a second main study (a crossover). Participants will use the same participant number and be able to enroll in this study a second time.

9.0 Risks of Study Participation

9.1 PTSD and Suicide Risk

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. 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 therapy sessions. Study teams may provide emotional support to participants during any psychological distress as needed.

To monitor for development and intensity of suicidal ideation and/or behavior, the C-SSRS will be administered by qualified site staff during Screening and a subsequent visit, and by an IR during IR Assessments . 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 kill themself (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 Interim Medical History.

2. If the participant has suicidal ideation, and a plan to kill themself (Suicidal Ideation Score=5) or positive Suicidal Behavior, the individual administering the C-SSRS will assess whether the risk is imminent. A Suicidal Ideation score of 5 does not necessarily indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and deterrents are strong. If there is no imminent risk, the individual will follow the procedure described above. If there is imminent risk of suicidal behavior, the individual will ensure:

    a. Participant is 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, if participant is on-site:
    i. Escort the participant to the Emergency Department (ED)
    ii. Escort the participant to an appropriate mental health services facility (e.g., hospital psychiatric unit)
    iii. Call Emergency Medical Services (EMS) and ensure that the participant is transferred to the responding medical personnel
c. If the participant is on-site 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 Interim Medical History.

9.2 Recorded Content

All IR assessments may be recorded for research and training purposes. Participants may feel uncomfortable with having their sessions recorded. The recordings are necessary for analyzing assessments. Any requests for use of audiovisual recordings outside of research and training requests will result in participants receiving information on the request. They will have control over any presentation of audiovisual recordings beyond viewing by authorized researchers, sponsor staff or regulatory agencies.

The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach (see Section 13.3). The sponsor is committed to taking preventative measures to avoid such an event. In the case of a security breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

10.0 Safety

10.1 Significant Events

Significant life events that may have occurred between Study Termination from the main study and participation in the LTFU study, including death of a loved one, loss of employment, or other hardship, may have an impact on outcome. The sponsor will capture these life events using the LEC-5 measure. Such events will be entered as Comments in the eCRF if additional information is required, and if appropriate, described in the Case Study Report for data outliers, if any.

10.2 Medical Monitor

The name for the Medical Monitor is: Sara Garcia Velazquez,

M.D.

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

11.0 Concomitant Medications

The medications list will be reviewed at the LTFU Consent and Enrollment Visit. Any medications used to treat interim medical history diagnoses will be recorded.

12.0 Statistical Considerations

An overview of the statistical analyses that will be performed is provided in the following sections. Interim analyses may be conducted prior to completion of the study for effectiveness or safety data. Data collected under this protocol may be used in future sub-studies to be developed by the sponsor.

12.1 Statistical Analyses

The following analysis sets are defined for this study:

- All Enrolled Set: All participants who received any IMP in the primary study where they were initially enrolled and completed a post treatment outcome measure, analyzed according to the treatment received

12.1.1 Effectiveness Analyses

12.1.1.1 Primary Outcome Analyses

Descriptive statistics will be computed for study data, including minimum, maximum, mean, median, and standard deviation for continuous measures and counts and percentages for categorical measures.

An MMRM model will be used to characterize the mean change in CAPS-5 from Baseline to Study Termination from the main study and to the LTFU IR Assessment. Missing data will not be imputed. Least squares means estimated from the MMRM model will be used to estimate the change in CAPS-5 from Baseline to Study Termination and LTFU. The least squares means from the MMRM model will be reported with 95% confidence intervals. Additional baseline covariates (such as age, gender, race, ethnicity, index trauma, complexity and severity of trauma, medication tapering and duration thereof, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences), length of time since the main study, may be assessed for inclusion in the model at a $p<0.05$. Details of primary, key secondary and safety analyses are described in the Statistical Analysis Plan.

Cohen's *d* one-group pretest-posttest will be used to estimate the effect size from Baseline in the main study to the LTFU Visit for the CAPS-5.

12.1.1.2 Key Secondary Outcome Analyses

SDS, the secondary outcome, will be analyzed in the same manner as the Primary.

12.1.1.3 Exploratory Analyses

Exploratory sub-group analyses may be conducted when possible to evaluate effects and by individual demographic characteristics (e.g., age, gender, race, ethnicity, index trauma, dissociative subtype of PTSD, presence of secondary traumatic stressors during the assessment period with LEC-5, medication tapering, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, and number of Experimental Sessions completed). Post-hoc exploratory analyses not described in the protocol may be performed to further examine the study data.

Exploratory Measures collected at Measures (listed in 7.1.3) will be analyzed with descriptive statistics and modelled as described in 12.1.1.1 when appropriate.

An exploratory responder analysis will further characterize persistence of effectiveness at the LTFU Visit based on the following categories. Participants can be included in more than one category.

- *Durable Treatment Response:* 10-point or greater reduction in CAPS-5 Total Severity Score at LTFU compared to Baseline in the main study.

- *Durable Loss of Diagnosis:* 10-point or greater reduction in CAPS-5 Total Severity Score at LTFU compared to Baseline in the main study and not meeting PTSD diagnostic criteria on CAPS-5 at Follow-up

- *Durable Remission:* CAPS-5 Total Severity Score of 11 or less and no longer meeting PTSD diagnostic criteria on CAPS-5 at LTFU.

- *Relapse after Treatment Response:* attained a 10-point or greater reduction in CAPS-5 Total Severity Score at Study Termination in the main study and had a 10-point or greater increase at LTFU compared to Study Termination.

- *Relapse after Loss of Diagnosis:* 10-point or greater reduction in CAPS-5 Total Severity Score and not meeting PTSD diagnostic criteria on CAPS-5 at Study Termination in the main study, and then had a 10-point or greater increase at LTFU compared to Study Termination and meets PTSD diagnostic criteria at LTFU.

- *Relapse of Remission:* CAPS-5 Total Severity Score of 11 or less and not meeting PTSD diagnostic criteria on CAPS-5 at Study Termination in the main study and has CAPS-5 Total Severity Score of 11 or greater at LTFU compared to Study Termination.

12.1.2 Safety Analyses

Safety data will be summarized with frequency tables of Interim Medical History, concomitant medication use, therapy utilization since main study, and suicidal ideation and behavior.

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by analysis set and category. Frequency and incidence of positive or serious suicidal ideation and positive suicidal behavior will be presented using descriptive statistics of C-SSRS scores in tabular format.

13.0 Study Governance

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

13.1 Ethics

This observational 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.

13.1.1 Informed Consent

The investigator and therapy team are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the participant into the trial. If the participant is interested in study participation, the site staff will send a copy of the ICF to the participant for review. The site staff will conduct an Informed Consent visit in person or over teleassessment, during which the participant and investigator will each sign their own copy of the ICF. The signature may be obtained using an electronic 21 CFR Part 11 compliant system.

Information about the study must be given orally and in an understandable written ICF. The ICF discussion must be conducted by a person who is qualified according to federal, state, or local regulations. The participant should have the opportunity to inquire about details of the study and to consider participation.

In addition to the explanation of study visits, the information should include that 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 if needed.

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

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised ICF and written information should receive approval from an Institutional Review Board (IRB) 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 withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the study team will have full access to any collected medical records, including information from the termination visit of this study. If a participant revokes only the HIPAA authorization, the study team will have full access to all medical records collected prior to the date and time of revocation.

13.2 Study Monitoring, Auditing, and Documentation

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

CAPS-5 results may be shared with site staff after the main Phase 3 studies are complete. The IR Coordinator will be responsible for review and data entry of the CAPS-5 source records into CAPS-5 eCRFs.

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

13.2.1 Source Records

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

13.3 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants. Despite this, privacy cannot be guaranteed. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data. Except for the Informed Consent, previous medical records, emails with the participant, and a Contact Information Sheet that will be stored separately from other documents, all source data will be identified only by the participant's initials. If past medical records are needed, participants will sign forms for the release of information upon consent. All assessment records will be kept in a locked file drawer or cabinet in a locked office or secure electronic storage, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators who are directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Audiovisual data will be securely transferred to remote servers. Clinical trial data other than audiovisual data will be hosted on an EDC system that is FDA-compliant. 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 other than video data will be retained at clinical sites per GCP. The sponsor will train the study staff on EDC procedures. Each study staff member with access to the data will be given an individual password.

The sponsor has developed a feature that will allow participants to create a password and enter their self-report questionnaire data directly into 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.

13.4 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 related procedures will not be covered by the sponsor.

Participants who previously received therapy from a therapy team member prior to the study, and who will continue to receive ongoing treatment outside of the study from that therapist, are responsible for those non-study related costs. Participants may be compensated for their participation in this study; this will be determined at the site level and will be specified in each site's consent.

13.5 Treatment and Compensation for Study Related Injury

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. 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.

13.6 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP guidance in a secure and safe facility. The Investigator must consult a representative of the sponsor before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the investigator or institution when these documents no longer need to be retained.

13.7 Publication Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to participants enrolled in a study and therefore, encourage publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences. For multi-center studies, it is intended that the first publication of the study's primary clinical data be co-authored by designated participating centers and the sponsor or designated representatives. Inclusion of Clinical Investigators in the authorship of any multi- center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the Study. All publications will follow ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, unless other guidelines are required by the journal. It is understood by the Clinical Investigators that the information generated in this study will be used by the sponsor in connection with the development of the IMP and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigators are obliged to provide the sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analyses are done on the official monitored sponsor database and that the Statistical Analysis Plan is agreed upon with the sponsor statistician.

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

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