MPVA6 Statistical Analysis Plan

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STUDY TITLE	A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Psychotherapy in U.S. Veterans with Chronic PTSD
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1.0 Introduction

This document contains a Statistical Analysis Plan (SAP) for MPVA6 "A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Therapy in U.S. Veterans with Chronic PTSD."

This open-label comparative effectiveness study was designed to explore the relative effectiveness of two vs. three randomly assigned active drug sessions in a sample of U.S. military veterans with at least moderate chronic PTSD. The Primary Outcome measure, the Clinician Administered PTSD Scale (CAPS-5), evaluates changes in PTSD symptom severity and is assessed by a blinded centralized Independent Rater (IR) pool.

Due to various administrative and non-safety related reasons, in May of 2023 MPBC decided to terminate this study with enrollment of approximately twenty participants. Since the new sample size will not support efficacy conclusions, the focus of the analyses described herein has shifted from safety and efficacy to safety only. Sections 2 through 6 state the study objectives, study measures, design, randomization, and sample size/power as described in the Protocol. Section 7, analysis, has been modified to reflect the changes resulting from early termination of the study.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy in treatment of PTSD, based on mean change in CAPS-5 Total Severity Score from T1 (Baseline) to T2 (Primary Outcome).

2.2 Secondary Objective

The key secondary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item score from Baseline to T2 (Primary Outcome).

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, and vital signs to support the package insert for MDMA-assisted therapy. The following safety objectives will evaluate the safety of MDMA-assisted therapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Medicinal Product (IMP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
2. Assess incidence of AEs by severity
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after IMP administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.

6. Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, 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 IMP administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of each Experimental Session.

2.4 Exploratory Objectives

Exploratory objectives include analyses of baseline predictors of treatment outcome (e.g., adverse childhood experiences, history of mild TBI), and post-treatment changes in self report measures of clinical state, including depression, PTSD, and moral injury as assessed by:

1. Explore changes between the two treatment groups 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 Baseline to Post-treatment and Follow-up.
2. Explore trajectories of change and onset of treatment effectiveness within and between groups using multiple assessments with PCL-5 self-reports.
3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses.
4. Explore differences between treatment groups using measures below regarding changes in clinical state associated with MDMA treatment, and regarding baseline predictors of outcome using the following measures:
    a. Acceptance and Action Questionnaire (AAQ-II)
    b. Dissociative Subtype of PTSD Interview (DSP-I)
    c. Columbia Suicide Severity Rating Scale (C-SSRS)
    d. Self Compassion Scale (SCS)
    e. Buss-Perry Aggression Questionnaire-Short Form (BPAQ-SF)
    f. Deployment Risk and Resilience Inventory 2 (DRRI-2)
    g. Life Events Checklist (LEC-5)
    h. PTSD Checklist for DSM-5 (PCL-5)
    i. Moral Injury (MIES)
    j. Depression (BDI-II)
    k. Posttraumatic Growth Inventory (PTGI)
    l. Chronic Pain Grade Scale (CPGS)
    m. World Health Organization Quality of Life-Brief Form (WHOQOL-BREF)
    n. Ohio State University Traumatic Brain Injury (OSU-TBI)
    o. The Utilization of Facility and Emergent Care (UFEC)
    p. Addictive behaviors including Alcohol Use Disorders Identification Test (AUDIT), Drug Use Disorders Identification Test (DUDIT)

3.0 Measures

3.1 Primary Measure

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

3.2 Secondary Outcome Measure

- Sheehan Disability Scale (SDS) for MPBC

3.3 Safety Measures

- Columbia Suicide Severity Rating Scale (C-SSRS)
- Adverse Events
- Treatment-emergent Adverse Events
- Serious Adverse Events
- Adverse Events of Special Interest
- Concomitant medication use
- Vitals signs during MDMA sessions

3.4 Exploratory Measures

- DSP-I (The Dissociative Subtype of PTSD Interview)
- ACE (Adverse Childhood Experience Questionnaire)
- BDI-II (Beck Depression Inventory II)
- CPGS (Chronic Pain Grade Scale)
- SCS (Self-Compassion Scale)
- AUDIT (Alcohol Use Disorders Identification Test)
- DUDIT (Drug Use Disorders Identification Test)
- MIES (Moral Injury Event Scale)
- PTGI (Posttraumatic Growth Inventory)
- BPAQ-SF (Buss Perry Aggression Questionnaire Short Form)
- AAQ-II (Acceptance and Action Questionnaire)
- WHOQOL-BREF (WHO Quality of Life-BREF)
- DRRI-II (Deployment Risk and Resilience Inventory-2)
- UFEC (Utilization of Facility-based and Emergent Care)
- OSU-TBI-ID (Ohio State University Traumatic Brain Injury Identification Method)

4.0 Study Design

This open-label, randomized Phase 2 study will assess the relative safety and effectiveness of two versus three Experimental Sessions of MDMA-assisted therapy in treatment-seeking veterans diagnosed with at least moderate PTSD.

The study was to be conducted in up to 60 participants, but the study was terminated early at approximately 20 participants. Randomization will occur in a 1:1 fashion. Randomization will be allocated to Group 1: 3 Experimental Sessions of MDMA-assisted therapy or Group 2: 2 Experimental Sessions of MDMA-assisted therapy.

For each participant, the study will consist of:

- **Screening Period**: Phone or in-person screen, informed consent, eligibility, and baseline assessments
- **Study Inclusion and Randomization:** Include eligible participants, randomize to group, complete baseline self-report measures,
- **Treatment Period:** 3 Preparatory Sessions, followed by 2 or 3 Experimental Sessions, depending on group. Each Experimental Session is followed by 3 Integrative Sessions.
- **Post treatment:** Clinical evaluation and self-report measures.
    - Note: the primary endpoint (T2) occurs approximately 1 month after the last experimental session. This means that the T2 occurs ~12 weeks after baseline for the 2-session group, and ~16 weeks after baseline for the 3-session group.
        - The 2-session group will have an additional clinical evaluation ~16 weeks post-baseline (T2.2).
- **Study Termination:** Clinical evaluation and self-report measures

A divided-dose of MDMA (120 mg initial dose, followed by a supplemental 40 mg dose), is administered during the Treatment Period with manualized therapy in two or three open-label monthly Experimental Sessions. This ~ 8-12-week Treatment Period includes three Preparatory Sessions prior to the first MDMA-assisted session. Each Experimental Session is followed by three Integrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay. The Primary Outcome measure, the change in CAPS-5 from Baseline, is assessed by a centralized IR pool at 7 weeks following the final treatment session (post treatment). The IR pool will be blinded to treatment arm assignment, visit number, and number of treatments received, and will not have access to data collected by the sites during the active Treatment Period. Self-reported PTSD symptoms will be assessed at the start of each treatment visit by the PCL-5.

Table 1: CAPS-5 Data Collection by Visit

CAPS Number	Visit	Description/Timing	Target Timing Post Baseline
Baseline CAPS-5 T1	Screening	Baseline 2-9 days after initial eligibility met	Not Applicable
CAPS-5 T2	V12 (2-session group) **or** V16 (3-session group)	Post Treatment Primary Outcome 28 to 35 days after last Experimental Session	~12 wk (±7 days) **or** ~16 wk (±7 days)
CAPS-5 T2.2	V13 *(2-session group only)*	Secondary outcome for 2-session group only 28 to 35 days weeks after T2	~16 wk (±7 days)

Dose Selection

This study will compare the effects of two versus three open-label manualized Experimental Sessions of therapy assisted by set doses of MDMA HCl (referred to as MDMA throughout) as described in the table below, along with associated non-drug preparatory and integrative therapy. Similar MDMA doses to those proposed in this study have been safelyused in previous Phase 2 and 3 studies sponsored by MAPS.

Table 2: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	120 mg	40 mg	120 mg to 160 mg
2	120 mg	40 mg	120 mg to 160 mg
3	120 mg	40 mg	120 mg to 160 mg
Total Cumulative Dose: 2 Session Group			240 mg to 320 mg
Total Cumulative Dose: 3 Session Group			360 mg to 480 mg

***** Unless initial dose is not tolerated or refused by participant

5.0 Randomization and Blinding

Participants will be randomized in 1:1 allocation to two versus three sessions of MDMA-assisted therapy.

To further minimize bias in measuring effectiveness, 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 AEs and will only evaluate participants at Baseline and at the assessments scheduled after each Experimental Session. The IR Pool is blinded to full study design, visit number, treatment assignment, number of treatments, and any data from the treating therapy pair after Baseline. IRs will be assigned to participants based on availability. Participants will be instructed to withhold study progress from IRs. Timing of CAPS-5 assessments are pre-specified in the study protocol within visit windows.

Sites will be required to make and document a specific number of attempts to obtain follow-up data per protocol. All randomized participants who receive at least one dose of IMP and complete at least one follow-up assessment will be included in the final *m*ITT set.

6.0 Sample Size and Power Considerations

Due to the early termination of this study, the initial power estimates are no longer valid, and the primary efficacy analysis will not be executed.

7.0 Analyses

7.1 Analysis Sets

The following analysis sets are defined for this study:

- All Enrolled: all participants who sign informed consent and are initially enrolled
- Safety: all participants who receive any IMP

7.2 Missing Data Handling

Missing outcome data will not be imputed.

7.2.1 Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

Start Dates:

1. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2. If the month is unknown, then:
    a. The month and day of the first dose date will be imputed if the year matches the first dose date year.
    b. Otherwise, 'January' will be assigned.
3. If the day is unknown, then:
    a. The day of the first dose date will be imputed if the month and year match the first dose date month and year.
    b. Otherwise, the first day of the month will be assigned.
4. In the event that an imputed start date is after a complete stop date, the start date will be set equal to the complete stop date.

Stop Dates:

1. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2. If the month is unknown, then 'December' will be assigned.
3. If the day is unknown, then the last day of the month will be assigned.

7.3 Protocol Deviations

Protocol deviations will be classified as major/minor by the MPBC protocol deviations review committee. The committee will determine the impact of the deviation on the study subjects' safety and rights, study compliance, data quality, and the proposed analyses. A subject level listing will report the description of the deviation and the impact.

A table of protocol deviations will summarize them by major/minor into the following categories:

- Informed Consent
- Inclusion/Exclusion
- Study Treatment
- Prohibited Concomitant Medication
- Trial Procedures
- Safety Reporting
- Discontinuation
- Miscellaneous

7.4 Baseline Values

Baseline values are from Baseline Visits for all measures, except C-SSRS, AUDIT, DUDIT, resting blood pressure (BP), Body Mass Index (BMI). For C-SSRS, the initial screening visit will be conducted with the 'Lifetime' version of the measure. The Independent Rater Screening assessment of 'Since Last Visit' suicidal ideation and behavior will be used as 'Baseline.' For the AUDIT and DUDIT measures and resting BP, BMI, results collected at Screening will be used as the Baseline value.

7.5 Participant Disposition and Dosing Summary

The All Enrolled Set will be used in the summary of participant disposition. The Safety Set will be included in the summary of accountability. The number and percent of participants who completed or discontinued the study will be displayed with reasons for early termination, where the percent is with respect to the total number of participants. The timepoint of doses and total MDMA (mg) administered will be summarized for the Safety Set.

7.6 Demographics and Baseline Characteristics

Participant demographic data and Baseline characteristics will be summarized descriptively for the Safety Set by treatment group and overall.

7.7 Efficacy Analyses

Due to the early termination of the study, the primary, secondary, and exploratory efficacy analyses specified in V1 of the SAP were removed. For all primary and secondary endpoints descriptive statistics (n, mean, standard deviation, median, interquartiles, range, or counts and percentages where appropriate) by timepoint will be provided for the overall sample and by treatment received.

7.7.1 Primary Effectiveness Analysis

Because of early termination at 1/3 of the planned sample size, the primary effectiveness analysis is no longer valid and will not be executed. Ninety-five percent confidence intervals will be calculated for the CAPS-5 raw means and change from baseline at T2 and T2.2 (for the 2 session group).

7.7.2 Secondary Effectiveness Analysis

The SDS will be presented in a similar manner to the CAPS-5 with descriptive statistics (n, mean, standard deviation, median, interquartile range, or counts and percentages where appropriate) by timepoint for the overall sample and by treatment received. Ninety-five percent confidence intervals will be calculated for the SDS raw means and change from baseline at T2 and T2.2 (for the 2 session group).

7.7.3 Exploratory Analyses

Data collected of the exploratory measures will be presented in by participant listings.

7.8 Safety Analyses

Safety analyses will confirm safety data with summary tables listing exposure to IMP, unsolicited AEs, concomitant medications, suicidal ideation and behavior, and vital signs overall and by treatment received. 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 IMP administration will be presented separately. Comparisons will be presented of relative incidence of AEs during experimental Sessions.

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized overall and by treatment group. 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-IMP administration, prior to the supplemental dose, and at the end of each Experimental Session by treatment group.

7.8.1 Analysis of Exposure

The total mg exposure of participants will be summarized. Data will be tabulated for the Safety Set.

7.8.2 Analysis of Adverse Events

The primary measure of safety will be the reporting of unsolicited AEs. All AEs collected from Enrollment to Termination will be categorized as follows:

- Pretreatment AEs are defined as AEs that occur during the Preparatory Period prior to the first dose in the first Experimental Session
- Treatment Emergent AEs are defined as AEs that occur during the Treatment Period from the first Experimental Session to final study visit
- AEs that occur one and two days after MDMA administration
- AESIs are defined as AEs specified in the protocol related to cardiac function, serious suicidal ideation/behavior, and abuse liability
- Follow-up Period AEs are defined as AEs that occur during the Follow-up Period after the last Integrative Session through Termination
- AEs leading to discontinuation of IMP
- SAEs

Verbatim terms on case report forms will be mapped to preferred terms (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0

Frequency and incidence of AEs will be displayed by PT, sorted by SOC, severity, and seriousness. AEs will be analyzed and presented as follows:

- If a participant has more than one AE mapped to the same PT, that AE will be reported once using the highest severity
- Relationship as determined by the Clinical Investigator
- AEs that occur on day of Experimental Sessions and two days after IMP administration will be presented separately.

7.8.3 Concomitant Medications

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by treatment group.

7.8.4 Analysis of Suicidal Ideation and Behavior

A positive response for suicidal ideation is counted when a participant answers "yes" to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS (i.e., a score >0 for suicidal ideation). Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a participant answers "yes" to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by treatment group and time period (lifetime, screening, baseline, each Experimental Session (pre- and post-IMP), Integrative Sessions, and endpoints). Frequency and incidence of positive or serious ideation and suicidal behavior will be presented using descriptive statistics in tabular format. A Shift table of changes in suicide ideation since baseline will be presented.

7.8.5 Summary of Vital Signs

Vital signs (heart rate, BP, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IMP, prior to the supplemental dose, and at the end of each Experimental Session.

8.0 Timing of Analyses

The final analysis will be conducted after the database is locked.