MP18 Protocol Synopsis
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An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder

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USE	In conjunction with relevant regulatory and ethical guidance

MP18 Protocol Synopsis

Rationale

MAPS Europe B.V. is a small medium enterprise organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in patients with posttraumatic stress disorder (PTSD). MAPS Europe B.V. is a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), a tax-exempt charity providing funding for the clinical development program. The Multidisciplinary Association for Psychedelic Studies (MAPS) Data from a series of Phase 2 studies of MDMA-assisted psychotherapy sponsored by MAPS provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy. This open-label Phase 2 study will serve as the lead-in to the planned Phase 3 study in Europe and to validate assumptions made for statistical power calculations supporting the planned Phase 3 clinical trial. This study will also provide cross-cultural validation data on the updated version of the Primary Outcome measure, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), which will be used in the Phase 3 study. In addition, the study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy while providing an opportunity for clinical supervision to planned Phase 3 therapy teams. This study will be the first multicenter study of MDMA-assisted psychotherapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated Phase 2 trials to confirm the Phase 3 study design.

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

Study Design

This multicenter, open-label, lead-in study assesses the safety and effectiveness of MDMA-assisted psychotherapy in participants diagnosed with at least severe PTSD. All safety data will be included in the global safety database for MDMA maintained by MAPS. Some sites will participate in the imaging sub-study.

A flexible dose of MDMA, followed by a supplemental half-dose unless contraindicated, is administered during the Treatment Period with manualized psychotherapy in two open-label Experimental Sessions spaced approximately a month apart. This 8-week Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug psychotherapy. The Primary Outcome measure, the Clinician Administered PTSD Scale (CAPS-5) is assessed by a blinded centralized Independent Rater (IR) pool multiple times throughout the study. The IR pool will be blinded to visit number and number of treatments received and will not have access to data collected by the sites during the active treatment period.

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

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

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

Study Design Overview

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

Preparatory Period with Enrollment Confirmation From Preparatory Session 1 to Preparatory Session 3 : ~6 weeks (+5/-4 weeks)			
Study Visit/		**Visit Duration/ Visit Timing/ (Scheduling Window)**	**Brief Description of Events**
Preparatory Period	Preparatory Session 1	1.5 hours/ Within 1 week (-7/+5 days) after Enrollment 0 to 12 days after Enrollment	90-minute Preparatory Session. Target visit timing on tapering needs. If needed, schedule calls between Preparatory Sessions 1 and 2 if indicated for tapering, safety, or further questions about medical history.
	Preparatory Session 2	1.5 hours/ At least 2 days after Preparatory Session 1; within 3 weeks of Preparatory Session 1 2 to 21 days after Preparatory Session 1	90-minute Preparatory Session/ongoing assessment. If tapering is complete or not needed, check eligibility and schedule Baseline CAPS-5 and Preparatory Session 3. If tapering is ongoing, schedule post taper call for ongoing assessment.
	Phone Call End Taper	1 hour/ Within 1 week of planned taper end & stabilization off medications; 0 to 56 days after Enrollment; within 7 days of the end of tapering and stabilization; prior to Baseline CAPS-5.	If needed, confirm medication taper and stabilization is complete and participant is eligible for Baseline CAPS-5. Schedule Baseline CAPS-5 and Preparatory Session 3.
Baseline & Enrollment Confirmation	Baseline CAPS-5	1.5 hours/ Post Preparatory Session 2 & confirmation of Medication Taper and stabilization; before Preparatory Session 3. At least 7 days after Preparatory Session 2	CAPS-5, SDS, and DSP-I completed by an IR via tele-assessment after taper is complete. CAPS-5 scores sent ASAP to the therapy team/Principal Investigator.
	Preparatory Session 3 & Enrollment Confirmation	3 hours: (90 minutes of measures, 90-minute therapy) Within 6 days of Baseline CAPS-5	Prior to visit, ensure CAPS-5 confirms PTSD diagnosis and confirm enrollment by reassessing specified eligibility criteria. Complete Baseline self-report measures. Complete 3-hour Preparatory Session (~90-minute measures, 90-minute therapy) and schedule Experimental Session 1. If enrollment is not confirmed, do not perform visit; complete termination.

Treatment Period From Experimental Session 1 to Integrative Session 2.3: 8 weeks (-3/+4)			
Study Visit/ Visit #		**Visit Duration/ Visit Timing/ (Scheduling Window)**	**Brief Description of Events**
Treatment 1	Experimental Session 1	8 hours + overnight/ Within 1 week of Baseline CAPS-5 and Preparatory Session 3 and Enrollment Confirmation	First Experimental Session is within 1 week of the Baseline CAPS-5 and 2 weeks after Preparatory Session 2; it lasts 8 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless contraindicated.
	Integrative Session 1.1	1.5 hours/ Morning after Experimental Session 1 1 day after Experimental Session 1	90-minute Integrative Session the morning after Experimental Session 1. Followed by 4 phone check-ins over the 7 days post Experimental Session 1.
	Integrative Session 1.2	1.5 hours/ At least 3 days after Experimental Session 1; at least 2 days after Integrative Session 1.1; within 2 weeks after Experimental Session 1 3 to 14 days after Experimental Session 1; at least 2 days after Integrative Session 1.1	Approximately 2 weeks after Experimental Session 1, a 90-minute Integrative Session is completed.

	Integrative Session 1.3	1.5 hours/ 3 to 5 weeks after Experimental Session 1 ; at least 2 days after Integrative Session 1.2; 1 to 7 days before Experimental Session 2	90-minute Integrative. Can occur 1 to 7 days before Experimental Session 2.

Study Visit/ Visit #		**Visit Duration/ Visit Timing/ (Scheduling Window)**	**Brief Description of Events**
Treatment 2	Experimental Session 2	8 hours + overnight/ 3 to 5 weeks after Experimental Session 1; at least 2 weeks after Integrative Session 1.3	3 to 5 weeks after Experimental Session 1, and 2 weeks after Integrative Session 1.1. The second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.
	Integrative Session 2.1	1.5 hours/ Morning after Experimental Session 2	90-minute Integrative Session the morning after Experimental Session 2. Followed by 4 phone check-ins over 7 days post Experimental Session 2.
	Integrative Session 2.2	1.5 hours/ At least 3 days after Experimental Session 2; at least 2 days after Integrative Session 2.1; within 2 weeks after Experimental Session 2	Approximately 2 weeks after Experimental Session 2, a 90-minute Integrative Session is completed.
	Integrative Session 2.3	1.5 hours/ 3 to 5 weeks after Experimental Session 2	90-minute Integrative Session.
Follow-up Period and Study Termination From Integrative Session 2.3 until Study Termination: 4 weeks (+/-2).			
Study Visit		**Visit Duration/ Visit Timing/ (Scheduling Window)**	**Brief Description of Events**
Study Termination	Study Termination	2 hours	Complete self-reported and safety measures; create an exit plan for participant.

Dose Regimen of MDMA

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

Dose Regimen of MDMA

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

* Unless contraindicated

Protocol Objective

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

Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted psychotherapy for treatment of PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score.

Secondary Objective

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

Safety Objectives

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

- Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
- Assess incidence of AEs by severity.
- Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
- Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after IP administration.
- Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
- Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.
- Assess incidence of SAEs.
- Assess incidence of psychiatric concomitant medications taken during an Experimental Session and through 2 days after IP administration.
- Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.

- Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

Exploratory Objectives

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

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

Recruitment and Participant Population

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

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

Eligibility Criteria

At the completion of Screening, participants must meet all eligibility criteria and agree to all lifestyle modifications to be enrolled. Each participant will then enter the Preparatory Period

which includes medication tapering, if needed, and non-drug Preparatory Sessions. The Preparatory Period ends with Enrollment Confirmation. A participant's enrollment will be confirmed once they have completed medication tapering, have a confirmed PTSD diagnosis per the CAPS-5 assessment, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria

Inclusion Criteria

- Are at least 18 years old.
- Are fluent in speaking and reading the predominantly used or recognized language of the study site.
- Are able to swallow pills.
- Agree to have study visits video-recorded, including Experimental Sessions, Independent Rater assessments, and non-drug psychotherapy sessions.
- Must provide a contact (relative, spouse, close friend or other support person) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal or unreachable.
- Must agree to inform the investigators within 48 hours of any medical treatments and procedures.
- Women of childbearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile), must have a negative pregnancy test at study entry and prior to each Experimental Session, and must agree to use adequate birth control through 10 days after the last Experimental Session. Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, abstinence, oral hormones plus a barrier contraception, vasectomized sole partner. Not of childbearing potential is defined as permanent sterilization or assigned male at birth.
- Agree to the following lifestyle modifications: comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not participate in any other interventional clinical trials during the duration of the study, remain overnight at the study site after each Experimental Session and be driven home after, and commit to medication dosing, therapy, and study procedures.

Medical History

- At Screening, meet DSM-5 criteria for current PTSD
- May have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease.
- May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed.
- May have a history of or current Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the Medical Monitor.
- May have hypothyroidism if taking adequate and stable thyroid replacement medication.
- May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.

Exclusion Criteria

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

- Are not able to give adequate informed consent.
- Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation.
- Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist.
- Require ongoing concomitant therapy with a disallowed psychiatric medication.
- Weigh less than 48 kilograms (kg).
- Are pregnant or nursing or are of childbearing potential and are not practicing an effective means of birth control.

Lifestyle Modifications

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

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

Leading up to Experimental Sessions

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

Post Experimental Session

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