**MPELONG**
**Public Clinical Study Protocol**

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

| | |
|---|---|
| COMPOUND | No investigational compound |
| BRIEF TITLE | Long-term follow-up of MDMA-assisted therapy for posttraumatic stress disorder |
| STUDY ACRONYM | MPELONG |
| EudraCT NUMBER | 2021-005596-39 |
| SPONSOR NAME | MAPS Europe B.V. |
| SPONSOR LEGAL REGISTERED ADDRESS | Paxlaan 10, Unit #142, 2131 PZ, Hoofddorp, The Netherlands |
| VERSION AND DATE | Version 3, 18-JAN-2022 |

## Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Version 1 | 27 JULY 2021 |
| Version 2 | 29 JULY 2021 |
| Version 3 | 18 JAN 2022 |

### Version 3, 18 JAN 2022

This protocol amendment (Version 3, 18 JAN 2022) has been implemented to address changes requested by the Czech State Institute for Drug Control (reference National Competent Authority for the Voluntary Harmonisation Procedure).

### Version 2, 29 JULY 2021

This protocol amendment (Version 2, 29 JULY 2021) has been implemented prior to submission to any regulatory authority or ethics committee.

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## List of Abbreviations

| | |
|---|---|
| AE(s) | Adverse Event(s) |
| AUD | Alcohol Use Disorder |
| 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 |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5th edition |
| DSP-I | Dissociative Subtype of PTSD Interview |
| DUDIT | Drug Abuse Disorders Identification Test |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture system |
| EMA | European Medicines Agency |
| EQ-5D-5L | EuroQol Five Dimensions – Five Levels Questionnaire |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| HPA | Hypothalamic-pituitary-adrenal |
| IB | Investigator's Brochure |
| ICD | International Classification of Disease |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICD-10 | International Classification of Disease, 10th edition |
| IR | Independent Rater |
| IRB | Institutional Review Board |
| LTFU | Long-term Follow-up |
| MAPS | Multidisciplinary Association for Psychedelic Studies |
| MAPS Europe | MAPS Europe B.V. |
| MDMA | 3,4-methylenedioxymethamphetamine |
| MDMA-AT | MDMA-assisted Therapy |
| MINI | Mini-International Neuropsychiatric Interview |
| PCL-5 | PTSD Checklist for DSM-5 |
| PTSD | Posttraumatic Stress Disorder |
| SAE | Serious Adverse Event |
| SCS | Self-compassion Scale |
| SDS | Sheehan Disability Scale |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| SUD | Substance Use Disorder |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| UFEC | Utilization of Facility-based and Emergent Care |
| US | United States |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

# 1.0 Protocol Summary

## 1.1 Synopsis

### Protocol Title

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

### Brief Title

Long-term follow-up of MDMA-assisted therapy for PTSD

### Rationale

Data from a series of Phase 2 and 3 studies of MDMA-assisted therapy (MDMA-AT) conducted by the sponsor provide preliminary evidence that chronic posttraumatic stress disorder (PTSD), independent of cause, may be treatable with up to three sessions of MDMA-AT [1, 2]. A long-term follow-up of Phase 2 study participants at least 12 months after study completion found a low PTSD relapse rate (12.1%) and that benefits outweighed risks associated with treatment [2]. This study will serve as the long-term follow-up (LTFU) protocol for MAPS Europe sponsored MDMA-AT clinical trials for PTSD 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.

### Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| • Comparison of PTSD severity between groups who received MDMA vs. Placebo during parent study based on LTFU IR assessment | • CAPS-5 Total Severity Score |
| Secondary | |
| • Comparison of degree of functional impairment associated with PTSD between groups who received MDMA vs. Placebo during parent study based on LTFU IR assessment | • SDS for PTSD for MAPS Total score |

### Overall Design

Study participants who consent will participate in two assessment sessions, followed by a termination visit. The first session will be conducted by an Independent Rater (IR) who will administer the CAPS-5 assessment (primary endpoint) as well other measures. A second visit will be scheduled to complete the remaining measures, which will be either self-administered, or administered by a trained clinician. A termination visit will occur where a post-study plan will be agreed with the participant.

As there is no treatment in this long-term follow-up study, there is no blinding of participants, site staff or sponsor.

### Brief Summary

The purpose of this study is to measure the long-term safety and persistence of the

effectiveness of MDMA-AT in participants diagnosed with moderate to severe PTSD, who have previously participated in a MAPS Europe-sponsored protocol.

Study details include:

- After signing the informed consent, the study will collect data over two visits approximately one month apart. This will occur at least 6 months after completing the parent study.
- There will be no treatment provided as part of this long-term follow-up study. However, all participants will be provided with a post-study plan to ensure they have healthcare referrals as appropriate.
- After completion of two study visits, a study termination visit will occur.

**Number of Participants**

All participants who have previously participated in a MAPS Europe clinical study of MDMA-AT for PTSD and who received at least one dose of Investigational Medicinal Product (IMP) will be invited to join this long-term follow-up study. The number of participants in this study will therefore be determined by the number of eligible participants in other MAPS Europe studies.

All participants in the ongoing phase 2 study MP18 (EudraCT# 2018-001718-13) will be invited to participate in this long-term follow-up study. Additionally, participants from future MDMA-AT studies will also be invited to participate in this long-term follow-up study.

## 2.0 Introduction

MAPS Europe B.V. (MAPS Europe) is a small or medium-sized enterprise (SME) organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in patients with posttraumatic stress disorder (PTSD). MAPS Europe is a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), an American tax-exempt charity providing funding for the MDMA-assisted therapy (MDMA-AT) clinical development program.

MDMA-AT is a US FDA Breakthrough-Designated treatment for PTSD based on the potential for substantial improvement over available medications. MAPS-sponsored Phase 2 and Phase 3 studies are intended to gather data on the safety and effectiveness of MDMA-AT as a treatment for PTSD.

This long-term follow-up (LTFU) study will investigate the persistence of effectiveness of MDMA-AT after a participant has completed the parent study as measured by 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. As well as the CAPS-5 scores other data evaluating the persistence of effectiveness, and safety data will be collected. No Investigational Medicinal Product (IMP) or psychotherapy will be administered in this study. Eligible participants who received at least one dose of IMP in a MAPS Europe study protocol will be invited to enroll in this LTFU study.

## 2.1 Study Rationale

Data from a series of Phase 2 and 3 studies of MDMA-AT conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, may be treatable with up to three sessions of MDMA-AT [1, 3]. A long-term follow-up of Phase 2 participants at least 12 months after parent study completion found a low PTSD relapse rate (12.1%) and also concluded that overall the benefits outweighed the risks associated with treatment [2]. This non-interventional study will serve as the LTFU protocol for MDMA-AT clinical trials conducted in Europe 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.

## 2.2 Background

### 2.2.1 Posttraumatic Stress Disorder (PTSD)

PTSD is a serious debilitating disorder associated with increased mortality and cardiometabolic morbidity. PTSD is a stress-related psychiatric condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, and accidents. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 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.

In Europe, lifetime PTSD prevalence estimates range from 0.56% to 7.4% in the general population. The Netherlands was shown to be amongst the countries with the highest lifetime prevalence of PTSD followed by the United Kingdom (UK), France and Germany [4]. The lifetime PTSD prevalence in the general population in the Netherlands is 7.4% [5]. In Belgium, France, Germany, Italy, the Netherlands and Spain the lifetime prevalence was found to be 1.9% [95% CI: 1.7-2.1] of the adult population [6]. Occupational exposure to dangerous and high-risk situations increases the risk for PTSD. This applies to military personnel and police officers. In Dutch veterans the risk of developing PTSD is increased in the first 2 years after deployment [7] and the need for medical care is also increased [8]. In the UK, the cost of PTSD to the National Health Service and society is substantial, with a recent study in Northern Ireland estimating £172 million per year in direct and indirect costs within the country [9].

Available PTSD treatments, including medications and therapy, are effective in 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 European Medicines Agency (EMA) has approved sertraline and paroxetine for PTSD, both of which are selective serotonin reuptake inhibitors (SSRIs). PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which fully return upon discontinuation of treatment. Adverse effects of maintenance SSRI treatment that contribute to discontinuation include sexual dysfunction, weight gain, and sleep disturbance. Variable SSRI treatment outcomes have led to recommendations of trauma-focused psychotherapy as routine first-line treatment by the VA's National Center for PTSD in the U.S., as well as by the World Health Organization (WHO). Currently, there is evidence that the antidepressants paroxetine, venlafaxine, sertraline and fluoxetine can be effective in post-traumatic stress disorder, but the magnitude of effect is, unfortunately, small to medium (Cohen's d 0.13 – 0.43)[10]. An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but are minimally effective in reducing PTSD symptoms. PTSD carries a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [11, 12]. Given the chronicity of PTSD, low treatment compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients exhibit an unmet medical need.

### 2.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by Merck pharmaceutical company in 1912 [13, 14]. Similar to SSRIs, MDMA binds to the monoamine transporters, with the greatest affinity for the serotonin transport (SERT). MDMA also enhances synaptic levels of serotonin, and to a lesser extent norepinephrine and dopamine, by vesicular carrier-mediated release and reuptake inhibition of these neurotransmitters [15-21]. MDMA increases levels of affiliative neurohormones oxytocin and vasopressin, which is associated with increased trust and attenuation of reactivity to threatening cues, and cortisol and prolactin. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, which would treat the core psychopathology of PTSD for a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the initial dose. Effects of the initial dose last 3 to 6 hours, which is extended to 5 to 8 hours with a supplemental half-dose administered 1.5 to 2 hours post initial dose. Orally administered MDMA has a half-life of 7 to 9 hours in humans. Unlike approved PTSD medications, therapeutic effects of MDMA have a rapid onset, and do not require daily dosing or a steady state in the blood to be effective. Thus, the effects of MDMA are distinct from and work through different mechanisms than anxiolytics and SSRIs. Furthermore, there is no evidence that limited doses of MDMA in controlled clinical settings creates a physical dependence or drug seeking behavior. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [22, 23]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [24]. Hence, MDMA is said to have moderate abuse potential in non-medical settings, and low abuse potential in clinical settings.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MDMA is provided in the investigator's brochure.

### 2.2.3 MDMA-Assisted Therapy for PTSD

MDMA is capable of inducing unique psychopharmacological effects, including decreased fear and increased wellbeing, sociability, interpersonal trust, acceptance of self and others, and ability to address these issues without extreme disorientation or ego loss due to alert state of consciousness. These factors taken together can provide the opportunity for a corrective emotional experience.

A combined treatment of MDMA and psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [25-28]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [29]. Participants are able to experience and express fear, anger, and grief with less

likelihood of feeling overwhelmed by these emotions. In healthy controls, MDMA reduces reactivity to unpleasant memories [30]. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-AT may enable participants to restructure their intra-psychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

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

### 2.2.4 Previous Clinical Experience with MDMA

MDMA-AT is a novel treatment package that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct intended to enhance certain aspects of psychotherapy.

Intent-to-treat (ITT) analysis of primary efficacy and safety data from six MAPS-sponsored MDMA PTSD Phase 2 clinical trials worldwide (MP1, MP2, MP4, MP8, MP9, MP12) consisting of 107 blinded participants with chronic PTSD was completed in 2016. In these studies, PTSD, independent of cause, appears treatable with a two- to three-session treatment package of MDMA-AT. As of October 1, 2020, with 341 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1775 participants in MDMA research studies conducted without sponsor support, the sponsor has observed an acceptable risk-benefit ratio for MDMA-AT. Across Phase 2 studies initial doses of 75 mg-125 mg MDMA were statistically superior to 0 mg to 40 mg MDMA based on a t-test of difference in CAPS-4 severity scores from Baseline to 1 to 2 months after two to three blinded experimental sessions ($p<0.001$). The dropout rate across studies was 7.5% (8 of 107). Large placebo-subtracted effect sizes (Cohen's d 0.9), initial indications of efficacy, and favorable safety outcomes support continuation of the Phase 3 program.

The first randomized, double-blind, placebo-controlled multi-site Phase 3 study for MDMA-AT for severe PTSD in the United States, Canada and Israel included a total of 90 randomized participants (46 randomized to MDMA and 44 to placebo). 67% of the participants in the MDMA group no longer met the diagnostic criteria for PTSD after 3 experimental sessions as confirmed by the change in CAPS-5 total severity score [3]. A second randomized, double-blind, placebo-controlled multi-site Phase 3 study confirming the efficacy and safety of MDMA-AT for the treatment of PTSD is ongoing.

A comprehensive review of MDMA research can be found in the IB supplied by the sponsor.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Procedures** | | |
| Suicide and risk of self-harm | During administration 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. | Qualified site staff will administer the Columbia-Suicide Severity Rating Scale (C-SSRS) and by an IR as needed depending on clinical presentation of the participants during IR Assessments, to monitor for development and intensity of suicidal ideation and/or behavior. If the C-SSRS reveals current serious suicidal ideation or behavior, the participant will be referred for further management as appropriate according to clinical site standard procedure. For IR-led visits done off-site, a "warm handoff" will occur after each IR assessment to ensure the participant can speak with a qualified staff member about any distressing emotions they may have experienced during the assessment. |
| Discomfort related to video recording of sessions | All IR assessments will be recorded for research and training purposes. Participants may feel uncomfortable with having their session(s) recorded. | Video recordings are necessary for analyzing assessments and to ensure quality and consistency across assessors. This will be explained to participants during the informed consent process, at which time participants may decline to participate. |
| Loss of privacy related to security breach | As with any electronically stored data, a security breach may occur which could cause a loss of privacy. | The sponsor uses encrypted, secure technology to transfer and store recordings. The sponsor is committed to taking preventative measures to avoid any loss of privacy or a security breach. 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. |

### 2.3.2 Benefit Assessment

There is no direct benefit to participants in this non-interventional study. It is hoped that the data generated will enable significant insight into the persistence of response to MDMA-AT, and long-term impact on quality of life on individuals diagnosed with PTSD. If a need for external medical or psychiatric referral is identified during participation in this study, the investigator or designee will provide referrals and follow-up as outlined in Section 8.3.4 Post-study Plan.

### 2.3.3 Overall Benefit Risk Conclusion

This follow-up study will allow the sponsor to assess the long-term impact of MDMA-AT on PTSD symptom severity as well as multiple quality of life measures. The sponsor acknowledges the distress which may be caused by revisiting traumatic events during the IR assessments and when completing questionnaires and ensures there is a provision for a qualified staff member administering assessments to ensure appropriate care and referrals can be made. A post-study plan will be provided to each participant, to enable engagement with additional care if required. Secure technology is used to record and transfer data. The Sponsor believes this study has been designed with a favorable overall benefit-risk profile.

## 3.0 Objectives and Endpoints

| **Objectives** | **Endpoints** |
|---|---|
| Primary | |
| • Comparison of PTSD severity between groups who received MDMA vs. Placebo during parent study based on LTFU IR assessment | • CAPS-5 Total Severity Score |
| Secondary | |
| • Comparison of degree of functional impairment associated with PTSD between groups who received MDMA vs. Placebo during parent study based on LTFU IR assessment | • SDS for PTSD for MAPS Total score |
| Safety | |
| Evaluate Long-term safety of MDMA-AT since completion of parent study, by assessing:<br>• Incidence of new or resolving medical diagnoses<br>• Incidence of concomitant medication use<br>• Incidence of Ecstasy use<br>• Incidence of psychotherapy use<br>• Incidence of serious suicidal ideation and positive suicidal behavior<br>• Incidence of new alcohol and substance use disorders meeting DSM-V criteria | <br><br>• Interim medical history<br>• Interim concomitant medications<br>• Self-reported *Ecstasy* use per LTFUQ<br>• Documentation of psychotherapy use per LTFUQ<br>• MAPS-adapted C-SSRS<br>• MINI AUD and SUD modules |

| Objectives | Endpoints |
|---|---|
| Exploratory | |
| • Comparison of specified scores between groups who received MDMA vs. Placebo during parent study based on LTFU assessment using the following measures:<br>• Dissociative symptoms associated with PTSD<br>• Facility-based healthcare utilization<br>• Alcohol use<br>• Drug use<br>• Depression symptom severity<br>• Chronic pain<br>• Health Utility<br>• Workplace absenteeism and productivity<br>• Patient-reported outcome for PTSD severity<br>• Impact of new life events on PTSD severity<br>• Self compassion<br>• Economic factors and occupation | <br><br><br><br>• DSP-I<br><br>• UFEC<br>• AUDIT<br>• DUDIT<br>• BDI-II<br>• CPGS<br>• EQ-5D-5L<br>• Days Lost, Days underproductive per SDS for PTSD for MAPS<br>• PCL-5<br><br>• LEC-5<br><br>• SCS<br>• Sources and brackets of income, employment status, refugee or veteran status per social history |

## 4.0 Study Design

### 4.1 Overall Design

This multi-site study will assess the long-term safety and effectiveness of MDMA-AT in participants diagnosed with PTSD following participation in a MAPS Europe-sponsored study of MDMA-AT. Participants in this study will need to have received at least one dose of IMP in the parent study. The IR will assess PTSD symptoms using the CAPS-5 and participants will complete self-report measures. Safety data and changes in medications and therapy since the termination of parent study will be collected and reported.

For each participant, study participation will consist of:

- **Informed Consent:** Signing of informed consent form (ICF) and eligibility assessment. Participants may sign the ICF at any time after completing the parent study.
- **Long-term Follow-up Visits:** At least six months after completion of parent study, administration of CAPS-5 and self-report measures, and collection of safety data.
- **Termination:** Contact from study site informing participant that study participation is complete.

### 4.2 Scientific Rationale for Study Design

PTSD is a chronic and disabling stress-related condition associated with serious adverse health outcomes and identifying novel treatments with durable effectiveness is timely and important. Therefore, it is critical to assess the long-term impact of limited exposure to single-dose medications on PTSD symptoms as well as function and health-related quality of life. This long-term follow-up protocol will evaluate the persistence of treatment response to MDMA-AT and safety in individuals who have participated in a MAPS Europe-sponsored trial of MDMA-AT for PTSD. The decision to collect the follow-up data at least six-months after parent study completion was based on input from regulatory authorities. The CAPS-5 is considered the international gold standard for the diagnosis of PTSD and the assessment of PTSD symptom severity. The data collected in this study will be analyzed with condition assignment from the parent study protocol in which the individual previously participated.

### 4.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

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 a post-study plan. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with country regulations.

## 5.0 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

**Age**

1. At least 18 years of age at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Previously enrolled in a MAPS Europe sponsored study of MDMA-assisted therapy for the treatment of PTSD.
3. Have received at least one dose of Investigational Medicinal Product (IMP) in the parent study.
4. Agree to be contacted by a study team at least 6 months after parent study completion to schedule and participate in LTFU assessments.
5. Agree to have Independent Rater assessments video-recorded.

**Informed Consent**

6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

### 5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with study participation.

### 5.3 Lifestyle Considerations

No lifestyle modifications are required to participate in this study.

## 6.0 Study Intervention(s) and Concomitant Therapy

No study interventions are administered in this study.

### 6.1 Measures to Minimize Bias: Randomization and Blinding

#### 6.1.1 Ongoing Blinding

Participants who have participated in a blinded MAPS-Europe study protocol (also referred to as *the parent study protocol*) may not yet have been unblinded at the time of participation in this LTFU protocol. In this case, clinical sites will ensure no information is discussed or shared with the participant which could jeopardize the blind.

#### 6.1.2 Independent Rater

To minimize bias in measuring effect, the sponsor will use an observer-blind, centralized, reliable Independent Rater (IR) pool to administer the CAPS-5 and SDS measures via live video interviews. The IRs are all mental health professionals with graduate-level training in psychology, social work or counseling, at least 1 year of experience working with trauma-exposed populations, and have previous experience administering structured assessments. IRs are trained to administer these diagnostic assessments in a neutral, non-leading manner to minimize the chance for bias. Avoiding building a therapeutic or clinical rapport beyond the basic level of rapport needed to conduct the interview in the research setting also minimizes the chance for bias. Because a strong, therapeutic alliance is developed between the therapists and the participant during the therapeutic portion of the trial, site staff cannot function as IRs without risking the introduction of bias during the collection of data related to the primary endpoint.

Personal information, such as the participant's name, will be sent to the IR in advance of the assessment using a GDPR-compliant secure messaging service. This information is required, as the IR needs to make the participant feel comfortable and confirm the correct participant is being assessed. Personally identifiable information will never be shared

with the sponsor. Remote assessment assures that the IR collecting the clinician-administered outcome measures will not have any prior knowledge of the specific content of prior therapy sessions.

IRs will be assigned to participants based on availability, and the assessment will be conducted in the same language(s) used at each clinical site. Data will be entered into a dedicated IR database by someone who is not conducting other study assessments or procedures (e.g. IR coordinator).

### 6.2 Concomitant Therapy

Every effort should be made to record any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant has used since completing the parent study, along with:

- Reason for use
- Dates of administration including start and end dates

## 7.0 Discontinuation of Study and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

### 7.1 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- The participant will be permanently discontinued from the study participation at that time. The site team will provide the participant with a post-study plan as described in Section 8.3.4 Post-study Plan.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

### 7.2 Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and the investigator's team is unable to contact them.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The investigator or designee must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (e.g. 3 telephone calls or emails). In addition, they should reach out to the contact person (relative, spouse, close friend or other support person) provided by the participant. Finally, if necessary, a certified letter (or local equivalent method) should be sent to the participant's last known mailing address. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

## 8.0 Study Assessments and Procedures

- Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue the study.
- Adherence to the study design requirements is essential and required for study conduct.
- Study procedures may be performed over one or several visits, as determined by the investigator to best support the participant and to ensure completion of all study procedures wherever possible. Additionally, separate visits may be combined into a single visit as appropriate.

## 8.1 Screening Period

Individuals who have received at least one dose of IMP in a MAPS Europe-sponsored MDMA-AT protocol for treatment of PTSD will be contacted and invited to participate in this LTFU study. Potential participants will be contacted using the contact information provided as part of their participation in the parent study protocol.

If a participant refuses to participate in this study, then a note should be made in their parent study record and the participant should not be contacted again.

## 8.2 Enrollment

Once a participant has signed the ICF and the investigator or designee has confirmed the participant meets all eligibility criteria, they will be considered enrolled.

Upon enrollment, the participant should be asked to sign a release of information request in order to access their interim medical records pertaining to the time following the completion of the parent study until present day. Having these records available will facilitate the medical history collection. Please note, if no significant health changes have

occurred, the investigator or designee may omit this procedure. Additionally, the release of information may be signed on a different visit.

### 8.3 Assessment Period

During the Assessment Period, study participants will be asked to undergo the assessments. These assessments may be done in-person, via telephone, or via video conference.

#### 8.3.1 Independent Rater Assessments

For participants who completed CAPS-5 assessments in the parent study, an IR visit via teleassessment will be scheduled for completion of CAPS-5 and SDS. The IR interview will be recorded to assess reliability of ratings. If a participant reports suicidal ideation during this assessment, the IR will administer the C-SSRS and contact the therapy team after the call and share any concerns. The therapy team will follow-up with the participant to ensure safety, provide support, recommend treatment if appropriate, and schedule the next visit.

Participants will be strongly encouraged to complete the IR visit at the clinical site, with a trained therapist on-site for the participant to speak with following the assessment, to discuss any difficult feelings which may have emerged. In situations where a participant is not able to be physically present at the site (e.g. isolating at home due to COVID-19 exposure), upon completion of the assessment, a "warm hand-off" occurs where the IR ensures there is a member of the site study team to join the call, who can "debrief" with the participant after the assessment.

#### 8.3.2 Measures and Medical History

The participant will meet with study staff via teleassessment or in person to be guided in the completion of electronic self-report measures. Site staff will support the participant in completing the electronic self-report.

Measures completed at this visit 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 begin to develop a post-study plan, which may include a referral for additional medical or therapeutic care, if needed.

Any changes to the participant’s health since the last visit of the parent study protocol should be recorded as part of the participant’s interim medical history. This includes weight, any significant health changes, and any changes in mental health, including a worsening of preexisting symptoms. If the participant reports a clinically significant change in health requiring medical attention they will be asked to request medical records that have been generated since the parent study. If no clinically significant health changes have occurred, this will not be required. If the participant is being treated by a psychiatrist or therapist, the study team will ask for authorization to collect information

over the phone if records cannot be released. The site staff will record any changes in medications or therapy since completion of the parent study. The C-SSRS will only be administered by a trained study team member if there is any concern about suicidal ideation. Previously collected social and demographic data will be reviewed for accuracy and updated as necessary.

### 8.3.3 Study Termination

Study Termination will take place after all visits have been completed and all requested medical records have been received by the study site. The post-study plan will be reviewed with the participant, including a follow-up on any referrals made at prior visits.

### 8.3.4 Post-study Plan

At the Study Termination visit, participants will be provided with a post-study plan. This plan will summarize treatments completed, current medications, and contact information for more information about the study if needed. Participants may request a referral for further therapeutic or medical care if appropriate. Enrolled participants who terminate the study early will be offered a post-study plan at their last contact. Screen Failures will be provided a referral if requested.

## 8.4 Study Assessments

### 8.4.1 Primary Outcome Measure and Reliability

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

The past month CAPS-5 is a semi-structured interview that assesses index history of DSM-5-defined traumatic event exposure, including the most distressing event and time since exposure, to produce a diagnostic score (presence vs. absence) and a PTSD Total Severity score [31]. 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 an 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.

### 8.4.2 Secondary Outcome Measure

**Customized version of the Sheehan Disability Scale for PTSD for the MAPS studies (SDS for PTSD for MAPS)**

The SDS for PTSD for MAPS is an assessment of functional impairment [32]. The reporting period for this measure 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). The Total Score is derived from an average of the first three items of the measure. Items pertaining to Days Lost and Days Underproductive will be included [32, 33].

### 8.4.3 Exploratory Measures

**Mini-International Neuropsychiatric Interview (MINI): Alcohol Use Disorder (AUD) and Substance Use Disorder (SUD) modules**

This version of the MINI (7.0.2), a structured interview that was first developed in 1998 to be compatible with DSM and International Classification of Disease (ICD) criteria for psychiatric illnesses [34] is now compatible with DSM-5 and will be administered by a member of the Independent Rater Pool to screen for diagnosis of Alcohol and Substance Use Disorders. Each module of the MINI consists of two or three questions where the answer is either “Yes” or “No,” and decision-tree logic is used to determine whether to ask additional questions [35]. MINI items were highly reliable (interrater reliability between kappa of 0.8 and 0.99, test-retest reliability between 0.6 and 0.9 for all scales save “current mania”)`, and diagnosis via MINI was comparable to that made with the Composite Diagnostic Interview and the SCID [35, 36]. Testing on non-psychiatric samples did not create false positives [34].

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

The LEC-5 is a 17-item self-report instrument designed to determine the presence of traumatic life events in the assessment and diagnosis of PTSD. It is a companion measure to the PCL-5 and will be used to assess PTSD. The participant indicates whether each event listed has occurred since the end of the parent study, permitting the possibility of marking multiple new events [37].

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

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms in the past month, derived from the symptoms of PTSD per DSM-5 [38]. 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).

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

The DSP-I is a clinician-administered interview designed by an international team of PTSD researchers to detect and assess severity of the dissociative type of PTSD and recommended for use as an additional or complementary measure ("add-on") to the CAPS-5 [39-42]. Assessments of military veterans and civilians support the existence of a dissociative subtype of PTSD that is associated with PTSD severity and derealization and depersonalization. It consists of two parts, only Part 1 will be administered. Part 1 contains five items addressing depersonalization, four items addressing derealization, and a section that is administered if dissociative episodes are endorsed that assesses duration and perceived cause of episodes (seven items) and observer items (three items) addressing interviewee demeanor, including evidence of dissociation, such as forgetfulness or giving a statement that is bizarre within the context of the interview. If two or more items within this section are endorsed, this indicates the presence of other dissociative symptoms beyond depersonalization and derealization. The DSP-I was first developed in 2016 and revised in 2017.

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

The BDI-II is a revision of the BDI, a 21-item self-report measure [43, 44] that will serve as a measure of depression symptom severity [45]. 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 [45]. 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 [45, 46]. Higher scores indicate more severe depressive symptoms.

**Chronic Pain Grade Scale (CPGS)**

The CPGS is a seven-item measure of pain. Responses to six of the seven items are made on a 10-point Likert scale, and a response on the other item is the number of days in the past 6 months when pain prevented the respondent from carrying out everyday activities [47]. 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. The CPGS is a validated scale with high internal consistency (Cronbach's alpha = 0.90) and correlated with other instruments assessing pain [48].

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

The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions; mobility, self-care, usual activities, pain-discomfort and anxiety-depression, and one visual analog scale (VAS). Responses are made on each dimension by checking one of five 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") [49, 50]. In the second part of the EQ-5D-5L, current degree of health ("your health today") is indicated by marking a 100 mm line, with 100 considered "the best health you can imagine" and one "the worst health you can imagine". The EQ-5D-5L does not sum responses but treats each response on a dimension as a scale score, and the VAS (Visual Analogue Scale) is the location of the mark. The scale can permit comparison across groups on health profiles, and an index can be derived from matching the five-dimension scores and the VAS response with nation-specific datasets and calculator software or statistical software syntax designed for the measure. The EQ-5D-5L began as part of the EuroQoL measure, published in 1990 [51]. 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 [52].

**Self-Compassion Scale (SCS)**

The SCS is a 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience [53]. 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. 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 [54].

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

The AUDIT is a ten-item self-report test. Respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) [55]. The ninth item addresses occurrence of injury of self or other as a result of drinking and the tenth addresses others' concerns about the respondent's drinking, with only three responses provided (0=No, 2=Yes, but not during the last year, 3=Yes, during the last year). The measure can readily detect alcohol abuse disorders in a wide array of individuals [56].

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

The DUDIT is an 11-item measure designed to assess presence of substance use disorders [57]. Responses to items are made on a 5-point scale with exact responses varying across questions. When present, use can be described in monthly or less than monthly versus four times a week or daily. A list of substances is provided at the end of the measure. The DUDIT is reliable, with a Cronbach's alpha of 0.80. When compared with an interview based on ICD 10, the DUDIT had a sensitivity to detecting substance use disorders of 90% and a specificity of 80% [57].

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

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.

**Long-term Follow-up Questionnaire**

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

### 8.5 Safety Assessments

Additional visits or repeat assessments (in person, at home, by telephone, or via tele-assessment) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential participant.

#### 8.5.1 Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation is frequently observed in patients with PTSD.

Suicidal ideation and behavior will be monitored during the study using the MAPS-adapted C-SSRS.

If the screening MAPS-adapted C-SSRS indicates active suicidal ideation or behavior, participants will be monitored appropriately and observed closely for increases in suicidal ideation and behavior (SIB) or any other unusual changes in behavior via additional MAPS-adapted C-SSRS assessments as required. Participants who experience increases in SIB should undergo a risk assessment.

**Table 1: Suicidal Ideation and Behavior Measure**

| Objective | Measure | Measure Type | Administration |
|---|---|---|---|
| Assess incidence of positive or serious ideation and suicidal behavior. | MAPS-adapted C-SSRS | Safety | Tele-assessment (IR screening) and Site (if required) |

The MAPS-adapted C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [59]. It consists of a Past 2 Weeks version and a Since Last Visit version that assess suicidal ideation, ideation intensity, and behavior. The MAPS-adapted C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The Past 2 Weeks version will be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. The C-SSRS Intensity scale for Lifetime obtained a Cronbach's alpha of 0.93 and 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI "suicide thoughts" item [60].

### 8.6 Serious Adverse Events (SAEs) and Other Safety Reporting

SAEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an SAE and remain responsible for following up of all SAEs.

#### 8.6.1 Time Period and Frequency for Collecting SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) until study termination.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

#### 8.6.2 Method of Detecting SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

#### 8.6.3 Follow-up of SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

### 8.6.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [IB/IDFU/package insert or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

### 8.6.5 Pregnancy

- Pregnancy information will be collected as a part of the interim medical history.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

## 8.7 Pharmacokinetics

PK parameters are not evaluated in this study.

## 8.8 Genetics

Genetics are not evaluated in this study.

### 8.9 Biomarkers

Biomarkers are not evaluated in this study.

### 8.10 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

### 8.11 Medical Resource Utilization and Health Economics

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits, and
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

## 9.0 Appendices

### Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### Informed Consent Process

- The investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Participants must be freely able to provide informed consent, and not have any freedoms restricted due to institutionalization or court order.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written

consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A signed copy of the ICF(s) must be provided to the participant.

**Data Protection**

- The Sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.
- The Sponsor serves as Data Controller according to the General Data Protection Regulation (GDPR) on the protection of individuals with regard to the processing of personal data and on the free movement of such data confirms herewith compliance with GDPR in all stages of Data Management.
- Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Data will be securely transferred to remote and secure servers. Clinical trial data other than video data will be hosted on an EDC system compliant with Title 21 Part 11 policies of the Code of Federal Regulations in the United States and with EU Directives. The data system includes password protection and internal quality checks.
- The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy. The sponsor will train the study staff on EDC procedures.
- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. Source worksheets and patient contact information will be retained at study centers per GCP. All source documents will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by

the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- With regard to any personal data processed in context of this study, MAPS Europe and MAPS PBC serve as Joint Data Controllers according to the General Data Protection Regulation (GDPR). MAPS Europe is responsible for exercising the rights of data subjects. The legal basis for data transfer between MAPS Europe and MAPS PBC, including responsibilities related to cross-border data transfers, is described in a controller-to-controller agreement with Standard Contractual Clauses.

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