Development Safety Update Report
3,4-methylenedioxymethamphetamine (MDMA)
US-IND 063384, 142908, 142690
Sequential Number 14

Reporting Period: 01 October 2020 to 30 September 2021
Date of Report: 30 November 2021

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USE	In conjunction with relevant regulatory and ethical guidance

This Development Safety Update Report does not contain confidential or unblinded information.

Executive Summary

This is the fourteenth annual report submitted by the MAPS Public Benefit Corporation (MAPS PBC) on behalf of the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization that is sponsoring nonclinical and clinical research of 3,4 methylenedioxymethamphetamine (MDMA)-assisted therapy for chronic psychiatric disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety associated with autism, anxiety related to a life-threatening illness, and eating disorders. European studies are sponsored by MAPS Europe B.V., a wholly owned subsidiary of MAPS, who has delegated certain trial organization responsibilities to MAPS PBC. The Development International Birth Date for the first authorization to conduct a clinical trial in any country worldwide was Oct 11, 2001. This report covers the period from 01 October 2020 through the data lock point of 30 September 2021 for all trials sponsored by MAPS, or its subsidiary MAPS Europe B.V., studying MDMA. The reporting period of all MDMA studies overseen by these sponsors has been harmonized globally and across United States Investigational New Drug Applications (US-INDs). This report does not include unblinded information for ongoing blinded studies. MDMA does not currently have marketing approval anywhere in the world.

As of the reporting period, 358 individuals are known to have been exposed to MDMA in sponsored studies, all under US-IND 063384. The sponsor does not have access to the primary data, but previous experience with MDMA includes an additional 1441 individuals by reference to scientific literature as of 01 October 2021, for a total of 1,799 research participants who have been exposed to MDMA in clinical or research studies conducted with or without sponsor support.

MDMA is a ring-substituted phenethylamine. MDMA, also known as 3,4-methylenedioxy-n-methylamphetamine and N-methyl-3,4- methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. The sponsor is developing the anhydrous form of the hydrochloride (HCl) salt for marketing, in the therapeutic dose range of 68 mg to 100 mg MDMA (equivalent to 80 mg to 120 mg MDMA HCl). The USAN council has adopted the generic name Midomafetamine and the short chemical name is MDMA.

MDMA is in the Entactogen class and produces anxiolytic and prosocial effects by increasing the synaptic levels of serotonin, as well as norepinephrine and to a lesser extent dopamine, through reuptake inhibition and release at monoaminergic transporters. MDMA has been shown to acutely decrease activity in the amygdala and increase blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin, arginine vasopressin, cortisol, prolactin, and adrenocorticotropic hormone in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. MDMA-assisted therapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of therapy. During marketing, MDMA in the proposed formulation is intended to be distributed to trained treatment providers for administration. Drug administration is only conducted under direct observation at medical offices, with no take-home doses permitted.

MDMA produces sympathomimetic effects that include significant transient, self-limited increases in heart rate, blood pressure, and body temperature that are likely to be well tolerated by healthy individuals. Serious Adverse Events (SAEs) involving administration of MDMA in MAPS-sponsored clinical trials have been rare. One cardiac Serious Adverse Reaction (SAR) has been reported in the Clinical Development Program through the end of the reporting period. Risks

posed by sympathomimetic effects of MDMA treatments are addressed in MAPS clinical trials by excluding people with pre-existing cardiovascular disease, cerebrovascular disease, or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse prior to each dose and at the end of experimental sessions.

In comparison to anxiolytics, antidepressants, and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to therapy. Up to three exposures to MDMA at a moderate initial dose of 68 mg to 100 mg MDMA (equivalent to 80 mg to 120 mg MDMA HCl) followed by a supplemental dose of 34 mg or 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl) within 1.5 to 2 hours, spaced approximately one month apart, are sufficient to obtain therapeutic results that have been seen in Phase 2 and Phase 3 studies. This single-dose regimen mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing.

Overall, the risks of SAEs and SARs have been addressed and constrained by limited, controlled exposure to the IMP to participants who have undergone adequate screening according to eligibility criteria defined in study protocols. There were no newly identified safety issues during the reporting period in ongoing or concluded clinical trials. There were no meaningful changes in adverse reactions, no clinically significant toxicities, no deaths related to an adverse event, no drug-drug interactions, no indications of lack of efficacy, no clinically significant medication errors or overdoses, and no evidence of drug misuse. Within the reporting period no new safety risks clearly attributable to MDMA have been identified. No high-level safety risks have been identified per the Risk Assessment and Characterization Tool (RACT) assessment in treatment with MDMA. Based on the previously reported data and the current state of scientific knowledge of therapeutic doses of MDMA, MDMA-assisted therapy demonstrates significant benefit that outweigh the risks using a 3-session treatment model combined with non-drug therapy sessions for preparation and integration in the treatment of PTSD.

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1.0 Introduction

This is the fourteenth annual report submitted by the MAPS Public Benefit Corporation (MAPS PBC) on behalf of the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization that is sponsoring clinical trials of 3,4 methylenedioxymethamphetamine (MDMA)-assisted therapy for chronic psychiatric disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety associated with autism, anxiety related to a life-threatening illness, and eating disorders. European studies are sponsored by MAPS Europe B.V., a wholly owned subsidiary of MAPS, who has delegated certain trial organization responsibilities to MAPS PBC. The Development International Birth Date for the first authorization to conduct a clinical trial in any country worldwide was Oct 11, 2001. This report covers the period from 01 October 2020 through the data lock point of 30 September 2021 for all trials sponsored by MAPS, or its subsidiary MAPS Europe B.V., studying MDMA. With this report, the reporting period of all MDMA studies overseen by these sponsors has been harmonized globally and across United States Investigational New Drug Applications (US-INDs). This report does not include unblinded information for ongoing blinded studies.

MDMA is a ring-substituted phenethylamine. MDMA, also known as 3,4 methylenedioxy-n-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of C11H15NO2. MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA. All clinical trials and nonclinical studies have used racemic MDMA. The sponsor is developing the anhydrous form of the hydrochloride (HCl) salt for marketing, in the therapeutic dose range of 68 mg to 100 mg MDMA (equivalent to 80 mg to 120 mg MDMA HCl). The USAN council has adopted the generic name Midomafetamine and the short chemical name is MDMA.

MDMA is in the Entactogen class and produces anxiolytic and prosocial effects by increasing the synaptic levels of serotonin, as well as norepinephrine and to a lesser extent dopamine, through reuptake inhibition and release at monoaminergic transporters. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin, arginine vasopressin, cortisol, prolactin, and adrenocorticotropic hormone, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. MDMA-assisted therapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of therapy.

The formulation of the investigational medicinal product (IMP) for early phase clinical trials included a gelatin capsule containing racemic white crystalline anhydrous MDMA, at doses ranging from 17 mg to 126 mg MDMA (equivalent to 20 mg to 150 mg MDMA HCl), compounded with alpha-lactose monohydrate, for oral administration. Phase 3 studies and the planned commercial presentation will include 34 mg to 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl) in hydroxypropylmethylcellulose (HPMC) capsules. The following excipients are included: magnesium stearate (1.0 % w/w) and mannitol (49.0 % w/w). MDMA in the proposed formulation would be distributed to treatment providers for administration after marketing authorization. Drug administration is only conducted under direct observation in a community-based healthcare setting with no take-home doses permitted.

MDMA produces sympathomimetic effects that include significant transient, self-limited increases in heart rate, blood pressure, and body temperature that are likely to be well tolerated by

healthy individuals. Most people do not experience elevations that exceed those seen after moderate exercise. Serious Adverse Events (SAEs) in MAPS-sponsored clinical trials have been rare.

Risks posed by sympathomimetic effects of MDMA treatments are addressed in MAPS clinical trials by excluding people with pre-existing underlying cardiovascular disease or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse prior to each dose and at the end of experimental sessions. MDMA may reduce responsiveness to changes in water/salt balance after normal and increased water consumption. MDMA is also a mild immunosuppressant.

Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the next 24 hours. The elimination half-life of a therapeutically active dose of MDMA is 7 to 9 hours. As MDMA and any active metabolites completely leave the body within 48 hours post-treatment, most reactions resolve within two to three days post-treatment. Reactions are monitored after each treatment and followed until resolution. Common adverse effects of an active dose of MDMA include anxiety, tight jaw or bruxism, headache, fatigue, lack of appetite, dizziness, insomnia, impaired gait or balance, and muscle tightness. MDMA is associated with medium risk of cardiovascular and cerebrovascular events due to sympathomimetic effects, and medium risk of psychological distress. No high-level risks have been identified to date.

In comparison to anxiolytics, antidepressants, and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to therapy. Up to three exposures to MDMA at a moderate initial dose of 68 mg to 100 mg MDMA (equivalent to 80 mg to 120 mg MDMA HCl) followed by a supplemental dose of 34 mg or 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl) within 1.5 to 2 hours, spaced approximately one month apart, are sufficient to obtain therapeutic results that have been seen in Phase 2 and Phase 3 studies. This single-dose regimen mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, the sponsor concludes that it remains favorable to pursue the research of MDMA as an adjunct to therapy.

2.0 Worldwide Marketing Approval Status

There have been no foreign marketing developments during the reporting period.

3.0 Actions Taken in the Reporting Period for Safety Reasons

The 13th Edition of the MDMA Investigator's Brochure (IB) was released on 22 March 2021 which included updated safety data from the sponsor's first Phase 3 trial. There were no new serious safety signals found in MAPP1, including no increase in reported adverse events of special interest in the categories of suicidal ideation or behavior, cardiovascular, or abuse potential in the MDMA group as compared to the therapy with placebo control group. This Phase 3 safety data, incorporated into the 13th Edition of the IB, added support to the favorable benefit/risk profile of MDMA-assisted therapy for the continuation of the development of this modality in the treatment of PTSD. This updated safety information was used to inform protocol updates to several protocols in the Sponsors clinical development program during this reporting period, including MAPP2 Amendment 4 Version 1, MPVA6 Amendment 3 Version 1, MED1 Amendment 3 Version 1, and EAMP1 Amendment 7 Version 1, as described in Section 5.0. With the exception of MAPP2, which is ongoing, the three other studies listed (MPVA6, MED1, and

EAMP1) are all in Start Up Phase and did not enroll any participants prior to implementing the specified amendments.

There was one amendment made to the MPVA6 protocol for safety reasons during the reporting period. The MPVA6 Amendment 3 Version 1, dated 08 April 2021 was submitted under US-IND 063384 Serial Number 0178 on 06 May 2021. The protocol was updated to include a tapering plan to ensure the safety of participant enrollment and corresponding adjustment of the Primary Outcome (CAPS-5) baseline assessment to ensure that participants meet all initial eligibility criteria prior to tapering off medication. Additional updates were also made to this protocol that were not for safety reasons, see Section 5.15.

There were two amendments made to the MED1 protocol for safety reasons during the reporting period. MED1 Amendment 2, Version 1, dated 20 November 2020 was submitted under US-IND 142980 Serial Number 0007 on 29 March 2021 and incorporated the FDA requirements for additional safety precautions for the anorexia nervosa-restricting subtype (AN-R) population, as agreed upon with Health Canada (HC). MED1 Amendment 3, Version 1, dated 22 March 2021 was submitted under US-IND 142980 Serial Number 0007 on 29 March 2021. Additional updates were also made to this protocol that were not for safety reasons, see Section 5.21.

There were two amendments made to the EAMP1 protocol for safety reasons during the reporting period. EAMP1 Amendment 5, Version 1, dated 16 October 2020 was submitted under US-IND 142980 Serial Number 0010 on 07 December 2020. The protocol was amended to add three additional administrations of the Columbia Suicide Severity Rating Scale (C-SSRS) by phone after each Experimental Session. Additionally, the protocol has been updated to include accommodations under the circumstance of the Coronavirus Disease 2019 (COVID-19) global pandemic, including a new recommendation for the order of screening activities and the use of electronic Informed Consent. EAMP1 Amendment 6, Version 1, dated 15 January 2021 was submitted under US-IND 142980 Serial Number 0012 on 01 February 2021. The protocol was amended to allow for echocardiograms to be used to assess patient eligibility. Additionally, the protocol has been updated to include an additional accommodation under the circumstance of the COVID-19 global pandemic, including remote monitoring. Additional updates were also made to this protocol that were not for safety reasons, see Section 5.25.

4.0 Changes to Reference Safety Information

The most recent version of the IB, the 13th Edition dated 22 March 2021, serves as the reference safety information (RSI) and was submitted under US-IND 063384 Serial Number 0173 on 29 March 2021. The RSI section has been updated to reflect the adoption of the European Economic Area (EEA) standard of including only SARs that have been observed at least twice in the sponsor's Clinical Development program in the RSI. The 12th Edition of the IB previously included an RSI table for regulatory reporting outside of the EEA region and has been removed in the 13th Edition to simplify reporting. Any SAE that is suspected to be attributable to MDMA will be considered unexpected and subject to expedited reporting for the Clinical Development Program worldwide. An updated edition will be submitted to the Agency and Investigators as an update anticipated early 2022.

5.0 Inventory of Clinical Trials Ongoing and Completed During the Reporting Period

See Appendix Table 1 for a cumulative listing of all clinical research studies using MDMA under the sponsorship of MAPS or subsidiaries.

5.1 Protocol MP-1

Title: Phase 2 Clinical Trial Testing the Safety and Efficacy of MDMA-Assisted Psychotherapy in Participants with Chronic Posttraumatic Stress Disorder (PTSD)

Purpose: This study was designed to test whether 125 mg MDMA-assisted psychotherapy can be safely administered to people with treatment-resistant PTSD and whether it will improve PTSD symptoms over placebo, 4 days after each of two experimental intervention sessions, and again at a 2-Month Follow-up after the second experimental session. In addition, findings from the MP-1 study were used to guide development of MDMA-assisted psychotherapy clinical trials and to define and standardize MDMA-assisted psychotherapy for PTSD patients.

First Participant First Visit: 30 March 2004

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants with chronic, treatment resistant PTSD aged 18 to 70 were eligible to enter the study. The number of participants reported below is final for this study.

Number of Participants Planned:	21
Number of Participants Enrolled and Treated:	23
Number of Participants Dropped Treatment:	2
Number of Participants Completed Experimental Sessions:	21
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	1
Number of Participants Completed Follow-up:	20

Demographics: See Appendix Table 2 for a cumulative summary of participant enrollment by demographic factors based on final, locked sponsor database.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.2 Protocol MP-2

Title: MDMA-Assisted Psychotherapy in 12 Patients with Treatment-Resistant Posttraumatic Stress Disorder

Purpose: This study was designed to test the safety and efficacy of MDMA-assisted psychotherapy conducted with 25 mg versus 125 mg MDMA in people with PTSD. In addition, findings from the MP-2 study were used to guide development of future studies to define and standardize MDMA-assisted psychotherapy for PTSD patients.

First Participant First Visit: 18 July 2006

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants with chronic, treatment resistant PTSD over the age of 18 were eligible to enter the study. The number of participants reported below is final for this study.

Number of Participants Planned:	12
Number of Participants Enrolled and Treated:	14
Number of Participants Dropped Treatment:	2
Number of Participants Completed Experimental Sessions:	12
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	2
Number of Participants Completed Follow-up:	10

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on final, locked sponsor database.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.3 Protocol MP-3

Title: Safety and Efficacy of MDMA-Assisted Psychotherapy in Participants with PTSD

Purpose: This study was designed to test the safety of MDMA-assisted psychotherapy conducted with 25 versus 125 mg MDMA in people with PTSD.

First Participant First Visit: 15 January 2008

Amendments During the Reporting Period: N/A. The study was terminated prior to the reporting period.

Participant Population: Participants with chronic, treatment-resistant PTSD over the age of 18 were eligible to enter the study. The number of participants reported below is final for this study.

Number of Participants Planned:	12
Number of Participants Enrolled and Treated:	5
Number of Participants Dropped Treatment:	1
Number of Participants Completed Experimental Sessions:	4
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	1
Number of Participants Completed Follow-up:	3

Demographics: See Appendix Table 2 for a cumulative summary of participant enrollment by demographic factors based on the site database.

Status: The study has been terminated early due to training issues with the clinical site staff and was subsequently relaunched as MP-9. The Abbreviated Final Clinical Study Report is in preparation.

5.4 Protocol MP-4

Title: A Randomized, Active Placebo-Controlled Pilot Study of MDMA-Assisted Psychotherapy in 12 Participants with Treatment-Resistant PTSD - Canada

Purpose: The overall objective of this study is to examine whether the full dose of MDMA versus the comparator dose used in conjunction with manualized psychotherapy will reduce or attenuate PTSD symptoms as evaluated by standard clinical measures and to collect safety data.

First Participant First Visit: 02 January 2015

Amendments During the Reporting Period: N/A. The study was terminated prior to the reporting period.

Participant Population: Participants with chronic, treatment-resistant PTSD over the age of 21 were eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	12
Number of Participants Enrolled and Treated:	6
Number of Participants Dropped Treatment:	0
Number of Participants Completed Experimental Sessions:	6
Number of Participants in Follow-up:	6
Number of Participants Dropped Follow-up:	0
Number of Participants Completed Follow-up:	6

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: This pilot study was terminated early due to study timelines extending beyond the End of Phase 2 Meeting with FDA. The Abbreviated Final Clinical Study Report is in preparation.

5.5 Protocol MP-8

Title: A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

Purpose: This protocol was designed to explore the safety and estimate the effect size of efficacy of MDMA-assisted psychotherapy, predominantly in veterans with service-related PTSD. The goal of this study was to test whether service-related PTSD is harder to treat than PTSD from other types of index trauma compared to prior investigations of this experimental treatment.

First Participant First Visit: 15 December 2010

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Veterans, firefighters, and police officers with chronic service-related treatment-resistant PTSD over the age of 18 were eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	24
Number of Participants Enrolled and Treated:	26
Number of Participants Dropped Treatment:	2
Number of Participants Completed Experimental Sessions:	24
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	1
Number of Participants Completed Follow-up:	24

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.6 Protocol MP-9

Title: A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy in People with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

Purpose: The objective of this study was to examine whether a full dose of MDMA versus an active placebo dose of MDMA used in conjunction with psychotherapy would reduce or attenuate PTSD symptoms and to collect safety data. The study started with an open-label lead-in of two participants in order to evaluate the psychotherapeutic approach based on the Treatment Manual for this experimental treatment.

First Participant First Visit: 27 March 2013

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants with chronic, treatment-resistant PTSD over the age of 18 are eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	10
Number of Participants Enrolled and Treated:	10
Number of Participants Dropped Treatment:	0
Number of Participants Completed Experimental Sessions:	10
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	1
Number of Participants Completed Follow-up:	9

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.7 Protocol MP-12

Title: A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Participants with Chronic, Treatment-Resistant PTSD

Purpose: The overall objective of this study was to compare effects of each of the active doses and the comparator dose of MDMA, used in conjunction with manualized psychotherapy, on reduction or attenuation of PTSD symptoms as evaluated by standard clinical measures and to collect safety data.

First Participant First Visit: 12 June 2013

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants with chronic, treatment-resistant PTSD over the age of 18 were eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	23
Number of Participants Enrolled:	29
Number of Participants Dropped Before Treatment:	1
Number of Participants Treated:	28
Number of Participants Dropped Treatment:	3
Number of Participants Completed Experimental Sessions:	26
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	1
Number of Participants Completed Follow-up:	25

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.8 Protocol MP1-E2

Title: An Open-Label Proof-of-Principle Study Testing the Use of an Additional MDMA-Assisted Psychotherapy Session in People Who Relapsed after Participating in a Phase 2 Clinical Trial of MDMA-Assisted Psychotherapy to Treat Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

Purpose: The objective of this study was to investigate whether a single session of MDMA-assisted psychotherapy could ameliorate the relapse of PTSD in those participants who had improved during participation in a Phase 2 clinical trial evaluating the safety and efficacy of MDMA-assisted psychotherapy but whose PTSD symptoms worsened over time during the follow-up period or after the initial study, MP-1.

First Participant First Visit: 20 January 2012

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants who completed MP-1 and relapsed after initial therapeutic gains were eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	3
Number of Participants Enrolled and Treated:	3
Number of Participants Dropped Treatment:	0
Number of Participants Completed Experimental Sessions:	3
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	0
Number of Participants Completed Follow-up:	3

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.9 Protocol MT-1

Title: A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers

Purpose: The overall objective of this study is to collect data regarding the psychological effects of manualized MDMA-assisted therapy in healthy volunteers, assess safety, and to expand the knowledge of therapists training to conduct MDMA-assisted therapy research.

First Participant First Visit: 21 April 2011

Amendments During the Reporting Period: There have been two protocol amendments during this reporting period.

MT-1 Protocol Amendment 6 Version 1, dated 19 January 2021, was submitted under US-IND 063384 Serial Number 0167 on 17 February 2021. The MT-1 protocol was amended to update the study drug dosing regimen. The MT-1 clinical research sites will be given a new GMP supply of MDMA and placebo to use for all newly enrolled participants. For each Experimental Session, participants will receive 100 mg MDMA (equivalent to 120 mg MDMA HCl) or placebo for their initial dose and 34 mg MDMA (equivalent to 40 mg MDMA HCl) or placebo for their supplemental dose. The protocol was also updated to provide additional guidance for measuring vital signs at the Experimental Sessions, add support person or study attendant expectations, and include accommodations in response to the coronavirus disease 2019 (COVID-19) pandemic or any other unforeseen emergency at clinic locations.

MT-1 Protocol Amendment 7 Version 1, dated 11 February 2021, was submitted under US-IND 063384 Serial Number 0167 on 17 February 2021. The MT-1 protocol was amended to update the video recording process for flexibility purposes and included general updates for clarity and standardization.

Participant Population: Healthy volunteers over the age of 18 are eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	120
Number of Participants Enrolled:	97
Number of Participants Treated:	96
Number of Participants Dropped Treatment:	0
Number of Participants Completed Experimental Sessions:	92
Number of Participants Completed Study:	92

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Ongoing.

5.10 Protocol MT2

Title: A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers

Purpose: The overall objective of this study is to collect data regarding the psychological effects of manualized MDMA-assisted psychotherapy in healthy volunteers, assess safety, and to expand the knowledge of therapists training to conduct MDMA-assisted psychotherapy research.

First Participant First Visit: N/A

Amendments During the Reporting Period: There have been no protocol amendments during this reporting period.

Participant Population: Healthy volunteers over the age of 18 are eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	150
Number of Participants Enrolled:	0
Number of Participants Treated:	0
Number of Participants Dropped Treatment:	0
Number of Participants Completed Experimental Sessions:	0
Number of Participants Completed Study:	0

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Study is in Start Up Phase.

5.11 Protocol MAA-1

Title: A Placebo-Controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA-Assisted Therapy for Social Anxiety in Autistic Adults

Purpose: The main objective of this study was to collect safety data to examine whether MDMA-assisted therapy would be tolerated and to estimate effect size of symptom reduction in social anxiety that is common in the adult autistic population as evaluated by standard clinical measures.

First Participant First Visit: 11 April 2014

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants must have a confirmed diagnosis of autism and 2 years of college-level education or comparable vocational training. Verbal and written proficiency in English will be required, including via text-to-speech technology. Participants must be 21 or over and MDMA naïve. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	12
Number of Participants Enrolled and Treated:	12
Number of Participants Dropped Treatment:	1
Number of Participants Completed Experimental Sessions:	11
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	0
Number of Participants Completed Follow-up:	11

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.12 Protocol MDA-1

Title: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness

Purpose: The overall objective of this study is to examine whether an active dose of MDMA versus a placebo used in conjunction with psychotherapy will reduce or attenuate anxiety and depression symptoms and improve quality of life as evaluated by standard clinical measures and to collect safety data.

First Participant Visit: 10 June 2015

Amendments During the Reporting Period: No amendments were made to the protocol during the reporting period.

Participant Population: Participants must have a diagnosis of a life-threatening illness, which may be ongoing or in remission but with the possibility of recurrence, as well as significant anxiety related to their diagnosis. Participants over the age of 18 were eligible to be enrolled. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	18
Number of Participants Enrolled:	21
Number of Participants Dropped Treatment:	3
Number of Participants Treated:	18
Number of Participants Completed Experimental Sessions:	17
Number of Participants in Follow-up:	0
Number of Participants Dropped Follow-up:	4
Number of Participants Completed Follow-up:	17

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.13 Protocol MPVA-1

Title: A Phase 1/2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in which 1 Member has Chronic PTSD

Purpose: The overall objective of this study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in conjunction with CBCT on PTSD symptoms and relationship functioning in participants with chronic PTSD and their partners.

First Participant Visit: 10 June 2015

Amendments During the Reporting Period: N/A. The study was terminated prior to the reporting period.

Participant Population: PTSD+ participants must have a diagnosis of PTSD and Concerned Significant Others must experience significant relationship distress due to the PTSD+ participant's PTSD diagnosis. Persons over the age of 18 are eligible to be enrolled. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

	Phase 1	Phase 2	Total
Number of Participants Planned:	10	10	20
Number of Participants Enrolled and Treated:	6	6	12
Number of Participants Dropped Treatment:	0	0	0
Number of Participants Completed Experimental Sessions:	6	6	12
Number of Participants in Follow-up:	0	0	0
Number of Participants Dropped Follow-up:	0	0	0
Number of Participants Completed Follow-up:	6	6	12

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is terminated early, and the Abbreviated Final Clinical Study Report is in preparation.

5.14 Protocol MPVA-4

Title: Evaluation of 3,4-methylenedioxymethamphetamine (MDMA) on Startle Response

Purpose: The study aims to evaluate the impact of MDMA on extinction of fear through learning following experimental startle and fear consolidation in healthy adults.

First Participant Visit: 14 March 2018

Amendments During the Reporting Period: During this reporting period, the institutional site's IRB was informed of an update to the number of screened participants, as the IRB considers all study participants who sign the ICF to be "enrolled." The full study protocol and the sponsor consider participants who pass screening and meet protocol eligibility criteria officially "enrolled." The site increased the target enrollment for screening in an IRB-approved amendment to account for the participants that failed screening in order to reach the enrollment goal of at least 30 participants.

Participant Population: Mentally healthy participants over the age of 21 who report prior recreational or research-based use of MDMA were eligible to be enrolled. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	30
Number of Participants Enrolled:	34
Number of Participants Dropped:	0
Number of Participants Treated:	34
Number of Participants Completed Experimental Session:	34
Number of Participants Completed Study:	34

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.15 Protocol MPVA6

Title: A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Therapy in U.S. Veterans with Chronic PTSD

Purpose: This objective of this study is to assess the comparative effectiveness of two versus three active MDMA-assisted therapy sessions in veterans with moderate chronic PTSD.

First Participant Visit: N/A

Amendments During the Reporting Period: There were three amendments made to the MPVA6 protocol for during the reporting period. These changes are described below.

The MPVA6 Amendment 3 Version 1, dated 08 April 2021 was submitted under US-IND 063384 Serial Number 0178 on 06 May 2021. The protocol was amended to reflect 13th Edition of the IB. Additionally, the protocol was updated to include a tapering plan to ensure the safety of participant enrollment and corresponding adjustment of the Primary Outcome (CAPS-5) baseline assessment from Screening to Visit 3 to ensure that participants meet all initial eligibility criteria prior to tapering off medication.

The MPVA6 Amendment 4 Version 1, dated 04 June 2021 was submitted under US-IND 063384 Serial Number 0182 on 10 June 2021. The protocol was amended to permit the supplemental dose to be 34 mg or 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl) according to IMP availability. Based on prior dose-finding studies, this potential decrease in the supplemental dose is not expected to have a substantive impact on safety or efficacy. Additional modifications were made to IMP handling and participant container assignment to better reflect the bulk presentation packaging.

The MPVA6 Amendment 5 Version 1, dated 10 September 2021 was submitted under US-IND 063384 Serial Number 0188 on 17 September 2021. The protocol was amended to indicate that only one participant for each therapy pair will be supervised during the lead-in portion of the protocol, and that participant will be randomized. Time points and frequency of collection of measures and blood draws were also clarified in this version. Following confirmation of IMP availability, details of the supplemental dosing procedures were confirmed such that all supplemental doses administered in the study will be 34 mg MDMA (equivalent to 40 mg MDMA HCl). Informed consent procedures were updated to allow flexibility for remote completion of the informed consent form using an electronic 21 CFR Part 11 compliant system due to COVID-19.

Participant Population: Participants that are military veterans over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a CAPS-5 Total Severity Score of 28 or greater at baseline are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	60
Number of Participants Enrolled:	0
Number of Participants Dropped:	0
Number of Participants Treated:	0
Number of Participants Completed Experimental Session:	0
Number of Participants Completed Study:	0

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Study is in Start Up Phase.

5.16 Protocol MP16

Title: An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder

Purpose: This open-label phase 2 study is designed to explore the safety and effectiveness of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA using the Clinician Administered PTSD Scale (CAPS-5) per the Diagnostic Statistical Manual for Mental Disorders Edition 5 (DSM-5) as the primary outcome measure 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. MP16 is a multi-site study with twelve clinical investigative sites across the U.S.

First Participant Visit: 08 December 2017

Amendments During the Reporting Period: There were no amendments made to the protocol during the reporting period.

Participant Population: Participants must have a diagnosis of posttraumatic stress disorder that is confirmed by a CAPS-5 Total Severity Score of 35 or greater at baseline. Persons over the age of 18 are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	60
Number of Participants Enrolled:	38
Number of Participants Treated:	33
Number of Participants Dropped Treatment:	1
Number of Participants Completed Study:	32

Status: The study is concluded. The sponsor has submitted an Interim Clinical Study Report, dated 17 February 2021 under US-IND 063384 Serial Number 0171 on 12 March 2021, based on interim locked data per FDA request. A Final Clinical Study Report will be submitted if deemed necessary.

5.17 Protocol MP17

Title: An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder

Purpose: This open-label phase 2 study is designed to explore the safety and effectiveness of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA using the CAPS-5 primary outcome measure 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. MP17 is a multi-site study currently with two sites across Canada.

First Participant Visit: 18 April 2018

Amendments During the Reporting Period: N/A. The study was terminated prior to the reporting period.

Participant Population: Participants must have a diagnosis of severe PTSD that is confirmed by a CAPS-5 Total Severity Score of 35 or greater at baseline. Persons over the age of 18 are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	5
Number of Participants Enrolled	4
Number of Participants Treated:	4
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	4

Status: The study was terminated early by the sponsor. The goal of this study was to provide a training opportunity to Phase 3 therapy teams in Canada. After each team treated one participant, the study objectives were met. The Abbreviated Final Clinical Study Report is in preparation.

5.18 Protocol MP18

Title: 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 Participants with Posttraumatic Stress Disorder

Purpose: The overall objective of this study is 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. MP18 is a multi-site study with 9 clinical sites in 6 countries in Europe.

First Participant Visit: 04 December 2020

Amendments During the Reporting Period: The protocol has been approved in the United Kingdom, Norway, Germany, the Netherlands, and Czechia (formerly known as Czech Republic). Regulatory submission to Portugal is in progress. Following assessment of country specific requirements and regulatory review, a harmonized version of the MP18 protocol was submitted during the reporting period. These changes are described below.

This consolidated protocol follows recommendations from RA/EC in The Netherlands, Czechia, Norway, United Kingdom and Germany. The updates include the latest safety information from the 13th Edition of the IB, clarification rationale for dose selection, advice related to ongoing mental healthcare, and use of the most accurate QT interval formula. Exclusion criterion for Dissociative Subtype of PTSD was removed. At home blood pressure and remote visits were added, and HIV test is no longer required.

The MP18 Protocol Version 6, dated 29 March 2021 was submitted under EudraCT # 2018-001718-13 for Regulatory Authorities/Ethics Committees (RA/EC) approval in Czechia, Norway, United Kingdom, and The Netherlands. In Czechia, MP18 Protocol Version 6 was approved by RA on 15 June 2021 and approved by EC on 05 May 2021. In Norway, MP18 Protocol Version 6 was approved by RA on 11 June 2021 and approved by EC on 08 June 2021. In United Kingdom, MP18 Protocol Version 6 was approved by RA on 14 October 2021 and approved by EC on 20 October 2021. In the Netherlands, MP18 Protocol Version 6 is pending approval by RA and was submitted for notification to the EC on 01 April 2021.

In Germany, the initial submission of MP18 Protocol Version 5.2 is pending approval by RA and was approved by the EC on 28 August 2021. MP18 Protocol Version 6 will be submitted once all approvals are received.

Participant Population: Participants must have a diagnosis of severe non-dissociative subtype of PTSD that is confirmed by a CAPS-5 Total Severity Score of 35 or greater at Baseline. Persons over the age of 18 are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	40
Number of Participants Enrolled:	8
Number of Participants Treated:	4
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	3

Status: Recruitment is ongoing in Norway, the Netherlands, and Czechia.

5.19 Protocol MPG1

Title: An Open-Label Feasibility and Safety Study of MDMA-Assisted Group Therapy for the Treatment of Posttraumatic Stress Disorder in Veterans

Purpose: The overall objectives of the protocol are to evaluate the feasibility and safety of MDMA-assisted group therapy for the treatment of PTSD in veterans.

First Participant Visit: N/A

Amendments During the Reporting Period: This study is in planning and the protocol has not yet been submitted.

Participant Population: Participants that are military veterans over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a CAPS-5 Total Severity Score of 28 or greater at baseline are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	18
Number of Participants Enrolled:	0
Number of Participants Treated:	0
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	0

Status: This study is in planning.

5.20 Protocol MPKH

Title: A Phase I, Open Label, Study of 3,4-Methylenedioxymethamphetamine (MDMA) Tolerability and Pharmacokinetics in Subjects with Moderate Hepatic Impairment Compared to Matched Control Subjects with Normal Hepatic Function

Purpose: The overall objectives of the protocol are to evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) of oral MDMA and its active metabolite, MDA, and to evaluate the effect of moderate hepatic impairment on the safety and tolerability of oral MDMA.

First Participant Visit: N/A

Amendments During the Reporting Period: The sponsor requested this study be deferred to a Phase 4, post-commercialization commitment. The initial product label would indicate the product has not been studied in patients with hepatic impairment. Based on published literature, the adverse consequences of hepatic impairment appear to be manageable in clinical settings where MDMA will be administered under direct observation with a limited number of exposures. Upon completion of the post-marketing commitment for this study, if the hepatic impairment data supports it, the sponsor would propose a labeling change.

The request was submitted by the sponsor in a Type B Meeting Request dated 15 March 2021, submitted under US-IND 063384 Serial Number 0176 on 12 March 2021, and background for the request was provided in the Meeting Briefing Packet for the Type B Written Response Only Meeting request dated 12 April 2021, submitted under US-IND 063384 Serial Number 0176 on 12 April 2021. In the context of COVID-19, many institutions are prioritizing their resources for COVID-19 treatments and for Phase 2/3 studies in patients with serious or life-threatening illnesses. As such, Phase 1 studies are designated lower priority for institutional resources, limiting both the staffing resources and site access to the inpatient ward for participants and the study team. In a Written Response to the meeting, dated 13 May 2021, the Agency found the request to defer the study as a post-marketing commitment reasonable and approved the study deferment to Phase 4.

Participant Population: Participants over the age of 18, of which 8 participants who meet the diagnosis of moderate hepatic impairment (class B according to Child-Pugh's criteria), and 8 participants with normal hepatic function are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	16
Number of Participants Enrolled:	0
Number of Participants Treated:	0
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	0

Status: Deferred to a Phase 4, post-marketing commitment.

5.21 Protocol MPKF

Title: A Phase 1, Single-Center, Open-Label, Randomized Sequence, 2-Period Cross-over Study to Determine the Effect of Food on the Relative Bioavailability of MDMA Oral Formulation in Healthy Volunteers

Purpose: The overall objectives of the protocol are to evaluate the food effect of a high calorie meal as compared to fasting conditions on the relative bioavailability of oral MDMA in healthy volunteers and to evaluate the effect of food on the safety and tolerability of oral MDMA.

First Participant Visit: N/A

Amendments During the Reporting Period: This study is in planning and the protocol has not yet been submitted.

Participant Population: Healthy volunteers over the age of 18 are eligible to enter the study. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	12
Number of Participants Enrolled:	0
Number of Participants Treated:	0
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	0

Status: This study is in planning.

5.22 Protocol MED1

Title: An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Therapy for Eating Disorders

Purpose: The overall objective of this study is to explore the safety and feasibility of open-label MDMA-assisted therapy with a flexible dose of MDMA and adjunctive caregiver support in reducing eating disorder symptoms for participants with AN-R or BED.

First Participant Visit: N/A

Amendments During the Reporting Period: There were two amendments made to the MED1 protocol during the reporting period. These changes are described below.

MED1 Amendment 2, Version 1, dated 20 November 2020 was submitted under US-IND 142980 Serial Number 0007 on 29 March 2021and incorporated the FDA requirements for additional safety precautions for the anorexia nervosa-restricting subtype (AN-R) population, as agreed upon with Health Canada (HC).

MED1 Amendment 3, Version 1, dated 22 March 2021 was submitted under US-IND 142980 Serial Number 0007 on 29 March 2021. The protocol was amended to update the IMP packaging in alignment with new standards and the supplemental dose regimen was updated to allow a lower dose of 34 mg MDMA (equivalent to 40 mg MDMA HCl) when participants are given an initial dose of 100 mg MDMA (equivalent to 120 mg MDMA HCl). Supplemental doses for any eating disorder participant (ED-P) will still not exceed half of the initial dose. Updates were also made to language for clarity and standardization of procedures and language with other MAPS studies and new information, including updates in accordance with the 13th Edition of the IB.

The sponsor also implemented a centralized Independent Rater (IR) to conduct the primary outcome measure assessments. Other updates include those for therapy team training requirements specific to the eating disorder population, an echocardiogram included as a screening procedure if deemed clinically indicated, and the removal of Human Immunodeficiency Virus (HIV) testing from screening procedures.

Participant Population: Participants over the age of 18 with an eating disorder, of which 12 participants who meet DSM-5 criteria for Anorexia Nervosa, Restricting-Type (AN-R), and 6 participants who meet DSM-5 criteria for Binge Eating Disorder (BED) are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Number of Participants Planned:	18
Number of Participants Enrolled:	0
Number of Participants Treated:	0
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	0

Status: Study is in Start Up Phase.

5.23 Protocol MAPP1

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder

Purpose: This multi-site, randomized, double-blind study assesses the efficacy and safety of MDMA-assisted psychotherapy versus psychotherapy with placebo control in participants diagnosed with at least severe PTSD. MAPP1 is a multi-site study currently with fifteen sites across the U.S., Canada, and Israel.

First Participant Visit: 24 December 2018

Amendments During the Reporting Period: N/A. The study was concluded prior to the reporting period.

Participant Population: Participants over the age of 18 with a diagnosis of at least severe PTSD that is confirmed by a CAPS-5 Total Severity Score of 35 or greater at baseline are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period at all study sites.

Number of Participants Planned:	100
Number of Participants Enrolled:	131
Number of Participants Treated:	90
Number of Participants Dropped Treatment:	11
Number of Participants Completed Study:	79

Demographics: See Appendix Table 2 for summary of participant enrollment by demographic factors based on data collected during the reporting period.

Status: The study is concluded. The Final Clinical Study Report is in preparation.

5.24 Protocol MAPP2

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder of Moderate or Greater Severity

Purpose: This multi-site, randomized, double-blind study assesses the efficacy and safety of MDMA-assisted psychotherapy versus psychotherapy with placebo control in participants diagnosed with at least moderate PTSD. MAPP2 is a multi-site study currently with fourteen sites across the U.S., Canada, and Israel.

First Participant Visit: 27 August 2020

Amendments During the Reporting Period: There was one amendment made to the MAPP2 protocol for during the reporting period. These changes are described below.

The MAPP2 Amendment 4 Version 1, dated 23 March 2021 was submitted under US-IND 063384 Serial Number 0173 on 29 March 2021. The MAPP2 protocol was amended to reflect the recent data from relevant nonclinical and clinical research described in the 13th Edition of the IB. Additionally, the protocol has been updated to include a Blinding Survey Measure to be completed at Study Termination.

Participant Population: Participants over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a CAPS-5 Total Severity Score of 28 or greater at baseline are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period at all study sites.

Number of Participants Planned:	100
Number of Participants Enrolled:	59
Number of Participants Treated:	41
Number of Participants Dropped Treatment:	3
Number of Participants Completed Study:	19

Status: Recruitment is ongoing.

5.25 Protocol MAPPUSX

Title: A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Therapy for the Treatment of Participants with Posttraumatic Stress Disorder

Purpose: This multi-site open-label safety extension study of manualized MDMA-assisted therapy for the treatment of participants with PTSD will be conducted in previous participants of Phase 3 parent studies who received placebo or were not treated due to COVID-19. MAPPUSX is a multi-site study currently with fifteen sites across the U.S., Canada, and Israel.

First Participant Visit: 22 March 2021

Amendments During the Reporting Period: There were two amendments made to the MAPPUSX protocol for during the reporting period. These changes are described below.

In keeping with agreements with the Division, the MAPPUSX Amendment 1 Version 1, dated 19 January 2021 was submitted under US-IND 063384 Serial Number 0165 on 03 February 2021. The MAPPUSX protocol was amended to add a Data Monitoring Committee. This amendment also included the addition of a flexible supplemental dose of either 34 mg or 50 mg MDMA (equivalent to 40 or 60 mg MDMA HCl).

The MAPPUSX Amendment 2 Version 1, dated 06 July 2021 was submitted under US-IND 063384 Serial Number 0184 on 14 July 2021. The MAPPUSX protocol was amended to reflect the recent data from relevant nonclinical and clinical research described in the 13th Edition of the IB. The protocol was also amended such that interim medical history and medication use will be collected via participant self-report unless the site physician deems it appropriate to collect medical records.

Participant Population: Participants over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a CAPS-5 Total Severity Score of 28 or greater at baseline are eligible to enroll. The number of participants reported below is the cumulative number of participants accrued as of the reporting period at all study sites.

Number of Participants Planned:	100
Number of Participants Enrolled:	7
Number of Participants Treated:	5
Number of Participants Dropped Treatment:	0
Number of Participants Completed Study:	1

Status: Recruitment is ongoing.

5.26 Protocol EAMP1

Title: An Intermediate-size Multi-site Expanded Access Program for MDMA-assisted Psychotherapy for Patients with Treatment-resistant PTSD

Purpose: The primary objective of this Expanded Access study is to provide MDMA-assisted psychotherapy on a compassionate basis to treatment-resistant PTSD patients. Supportive data on the safety and tolerability of open-label MDMA-assisted psychotherapy in clinical settings will be collected from patients with treatment-resistant PTSD.

First Participant Visit: N/A

Amendments During the Reporting Period: There were three amendments made to the EAMP1 protocol for during the reporting period. These changes are described below.

EAMP1 Amendment 5, Version 1, dated 16 October 2020 was submitted under US-IND 142980 Serial Number 0010 on 07 December 2020. The protocol was amended to add three additional administrations of the Columbia Suicide Severity Rating Scale (C-SSRS) by phone after each Experimental Session. Additionally, the protocol has been updated to include accommodations under the circumstance of the Coronavirus Disease 2019 (COVID-19) global pandemic, including a new recommendation for the order of screening activities and the use of electronic Informed Consent.

EAMP1 Amendment 6, Version 1, dated 15 January 2021 was submitted under US-IND 142980 Serial Number 0012 on 01 February 2021. The EAMP1 protocol was amended to allow for echocardiograms to be used to assess patient eligibility. Additionally, the protocol has been updated to include accommodations under the circumstance of the COVID-19 global pandemic, including remote monitoring.

EAMP1 Amendment 7, Version 1, dated 16 October 2020 was submitted under US-IND 142980 Serial Number 0015 on 13 September 2021. The EAMP1 protocol was amended to update information throughout the protocol based on the 13th Edition of the IB, to adjust inclusion and exclusion criteria, remove several patient measures, clarify enrollment review, update information regarding Audio/Video Recording responsibilities, and instate terminology changes and clarifications.

Participant Population: Participants over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a PTSD Checklist for DSM-5 (PCL-5) Total Score of 33 or greater at baseline are eligible to enroll. The number of patients reported below is the cumulative number of participants accrued as of the reporting period.

Number of Patients Planned:	50
Number of Patients Enrolled:	0
Number of Patients Treated:	0
Number of Patients Dropped Treatment:	0
Number of Patients Completed Treatment:	0

Status: Study is in Start Up Phase.

6.0 Estimated Cumulative Exposure

Through the end of the reporting period, there have cumulatively been a total of 458 participants treated in MAPS or MAPS Europe B.V.-sponsored studies, all under US-IND 063384, of which 358 participants are known to have been exposed at least once to MDMA at any dose.

6.1 Cumulative Participant Exposure in the Development Program

Table 1: Cumulative Known Exposure to MDMA in MAPS-Sponsored Clinical Trials

(Based on final data for completed studies and preliminary data for ongoing studies)

Study	Phase	Country	Study Population	Planned Enrollment	Participant Exposure to MDMA	Participant Exposure to Placebo
MP-1	2	US	PTSD	21	22 [A]	8
MP-2	2	Switzerland	PTSD	12	14	-
MP-3	2	Israel	PTSD	12	5	-
MP-4	2	Canada	PTSD	12	6	2
MP-8	2	US	PTSD	24	26	-
MP-9	2	Israel	PTSD	10	10	-
MP-12	2	US	PTSD	23	28	-
MP1-E2	2	US	PTSD	3 [B]	3 [B]	-
MT-1	1	US	Healthy Volunteer	120	96 [C]	96
MAA-1	2	US	Autistics with Social Anxiety	12	12	4
MDA-1	2	US	Anxiety Related to Life-threatening Illness	18	18	5
MPVA-1	1/2	US	PTSD and Concerned Significant Other	20	12	-
MPVA-4	1	US	Healthy Volunteer	30	17	17
MP16	2	US	PTSD	60	33	-
MP17	2	Canada	PTSD	5	4	-
MP18	2	EEA	PTSD	40	4	-
MAPP1	3	US/Canada/Israel	PTSD	100	46	44
MAPP2	3	US/Canada/Israel	PTSD	100	Blinded (41)	
MAPPUSX	3	US/Canada/Israel	PTSD	100	5	-
Total				719	358	176

[A] In MP-1, participants received either MDMA or an inactive placebo, but participants who took the option of continuing to the open-label crossover Stage 2 then received active dose MDMA as well (only one participant chose not to continue to Stage 2 in MP-1, due to a strong and sustained placebo response)
[B] In MP1-E2, participants were previously enrolled in MP-1. These participants were not counted again in the final summation.
[C] The MT-1 study uses a blinded full crossover design, with placebo administered in one session and MDMA in another session.

6.2 Participant Exposure from Marketing Experience

The IMP was not approved for marketing during this reporting period.

7.0 Data in Line Listings and Summary Tabulations

7.1 Reference Information

The most recent version of the MDMA Investigator's Brochure (IB), 13th Edition dated 22 March 2021 is used as the Reference Safety Information for this reporting period.

The Reference Safety Information was coded using MedDRA v17.1 or v20.0, depending on the study.

7.2 Line Listings of Serious Adverse Reactions During the Reporting Period

There were no SARs reported during the reporting period.

Cumulatively, one possibly related expected SAR of exacerbation of pre-existing ventricular extrasystoles was reported within the context of MAPS-sponsored study MP-8 and was presented in a prior DSUR. For a line listing and cumulative summary of all SARs in the Clinical Development Program, see Appendix Table 3.

7.3 Cumulative Summary Tabulations of Serious Adverse Events

The sponsor recorded one pre-dosing SAE in the clinical development program during this reporting period. In Study MP18, a participant reported increased suicidal ideation following information that based on initial site screening outcome they were ineligible for the study. Though the participant was not enrolled in the study, the sponsor conservatively recorded this as an SAE.

Cumulatively, 25 primary SAE cases have occurred across 16 MAPS-sponsored studies. For a cumulative summary of all SAEs in the Clinical Development Program, see Appendix Table 4.

8.0 Significant Findings from Clinical Trials During the Reporting Period

The sponsor's pivotal Phase 3 trial, MAPP1, concluded during this reporting period. This trial demonstrated that PTSD symptoms were significantly attenuated by MDMA-assisted therapy and confirm findings seen in Phase 2 studies. Manualized therapy in conjunction with MDMA was statistically superior for PTSD treatment in CAPS-5 severity scores from Baseline to 2 months after three blinded experimental sessions in comparison to therapy paired with an inactive placebo ($p<0.0001$, $d=0.91$). This finding was supported by a positive secondary efficacy result in reducing clinician-rated functional impairment (as measured by the Sheehan Disability Scale, SDS) of $p=0.0116$. There were no new serious safety signals found in MAPP1, including no increase in reported adverse events of special interest in the categories of suicidal ideation or behavior, cardiovascular, or abuse potential in the MDMA group as compared to the therapy with placebo control group. Responder analysis indicated that at the primary endpoint, 67% of participants in the MDMA group no longer met diagnostic criteria for PTSD, compared to 32% of the placebo group. This pivotal trial was published in Nature Medicine in 2021: Mitchell et al., 2021. "MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study." Nat Med. 2021 Jun;27(6):1025-1033.

The findings from two open-label studies (MP16 and MP17), testing the modality of MDMA-assisted therapy in multisite clinical trials to assess the feasibility of scaling this manualized therapy across 14 North American sites, were published during the reporting period. Cotherapist

dyads were trained in the manualized MDMA-assisted therapy protocol and administered three experimental sessions 3 to 5 weeks apart among participants with severe PTSD. PTSD symptom severity decreased following three MDMA-assisted therapy sessions at 18 weeks post baseline (mean Δ in CAPS-5 scores =−29.99, ΔSD=13.45, $p<0.0001$, n=37, Cohen's d = 2.2). Cotherapist dyads were provided clinical supervision and evaluated for protocol adherence by centralized raters. Adherence rating scores were high across cotherapist dyads (mean=95.08%, SD=3.70%) and sites (mean=95.23%, SD=2.20%). These two open-label studies show that a large treatment response to MDMA-assisted therapy can be scaled and replicated by newly trained cotherapist dyads across multiple sites. (Wang et al., 2021. "Scaling Up: Multisite Open-Label Clinical Trials of MDMA-Assisted Therapy for Severe Posttraumatic Stress Disorder." Journal of Humanistic Psychology, 00221678211023663.)

Additionally, in an unplanned pooled analysis of data from Phase 2 studies (MP-4, MP-8, MP-9, and MP-12), treatment-resistant PTSD participants who had not tapered from SSRI or SNRI medications had significantly lower CAPS-IV total scores at the primary endpoint (mean=45.7, SD=27.17, p=0.009) compared to participants who had tapered from these medications (mean=70.3, SD=33.60). (Feduccia et al., 2021. "Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy." Psychopharmacology (Berl). 2021 Feb;238(2):581-588.) This post hoc analysis suggests that recent exposure to antidepressant drugs that target reuptake transporters may reduce treatment response to MDMA-assisted therapy. This analysis needs to be further assessed in larger samples across studies.

As described in the IB issued during the reporting period, treatment emergent adverse events (TEAEs) with at least a twofold difference between the MDMA and placebo groups, in order of prevalence (>10%), include muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, restlessness, mydriasis, dizziness postural, bruxism, nystagmus, blood pressure increased, feeling jittery, noncardiac chest pain, and dry mouth. Based on their limited duration, these adverse events are not likely to have clinical significance beyond several days after treatment.

MDMA is associated with medium risk of cardiovascular and cerebrovascular events due to sympathomimetic effects, and medium risk of transient exacerbation of psychological distress. No high-level risks have been identified to date.

8.1 Completed Clinical Trials

During the reporting period, two clinical trials were concluded (MAPP1 and MPVA-4). The MAPP1 study database was locked on 27 October 2020 and the MPVA-4 study database was locked on 04 November 2020. The MP17 and MP16 studies finished data collection in a previous reporting period and the clinical database for studies MP17 and MP16 was interim locked on December 10, 2019 in order to provide FDA with an interim Clinical Study Report. For MP16, the sponsor submitted an Interim Clinical Study Report, dated 17 February 2021 under US-IND 063384 Serial Number 0171 on 12 March 2021.

8.2 Ongoing Clinical Trials

As of the reporting period there are three active clinical trials under US-IND 063384, which are studies MT-1, MAPP2, and MAPPUSX. In addition, under US-IND 063384, there is one Phase 2 study (MPVA6) in the start up phase anticipated to commence in late 2021, as well as one Phase 1 study (MPKF) and one Phase 2 study (MPG1) in planning, both anticipated to commence in early 2022.

There is one MAPS-funded study sponsored by MAPS Europe B.V. (MP18) outside of US-IND that is active and recruiting in Europe for treatment of PTSD and one Phase 3 study (MAPP3) in planning, anticipated to commence in 2022 in Europe. In addition, two studies are planned under separate US-INDs, an open label study of MDMA for treatment of eating disorders (MED1) under US-IND 142908 and an intermediate-sized Expanded Access study for treatment of treatment-resistant PTSD (EAMP1) under US-IND 142690. Both studies are in start up phase and are anticipated to commence in early 2022.

8.3 Long-Term Follow-up

For participants who received two to three active doses of MDMA (64 to 106 mg, equivalent to 75 mg to 125 mg MDMA HCl) during blinded or open-label therapy sessions with additional non-drug therapy sessions, PTSD symptoms were assessed using the Clinician-Administered PTSD Scale for DSM IV (CAPS-IV) at baseline, 1 to 2 months after the last active MDMA session (treatment exit), and at least 12 months post final MDMA session (LTFU). A mixed-effect repeated-measures (MMRM) analysis assessed changes in CAPS-IV total severity scores. The number of participants who met PTSD diagnostic criteria was summarized at each time point. Participants completed the long-term follow-up questionnaire covered by a Certificate of Confidentiality from FDA during participation in the following clinical trials: NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610. There was a significant reduction in CAPS-IV total severity scores from baseline to treatment exit (LS mean (SE) = − 44.8 (2.82), $p < .0001$), with a Cohen's d effect size of 1.58 (95% CI = 1.24, 1.91). CAPS-IV scores continued to decrease from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), $p < .05$), with a Cohen's d effect size of 0.23 (95% CI = 0.04, 0.43). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%). The majority of participants reported benefits, including improved relationships and well-being, and a minority reported harms from study participation. PTSD symptoms were reduced 1 to 2 months after MDMA-assisted therapy, and symptom improvement continued at least 12 months post-treatment. Phase 3 trials are investigating this novel treatment approach in a larger sample of participants with chronic PTSD. These results were published during the previous reporting period (Jerome et al., 2020. "Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials." Journal of Psychopharmacology (Berl). 2020 Aug;237(8):2485-2497).

As discussed with the Division during the Type B Guidance Meeting for Breakthrough Designated Therapy held on 24 February 2021 and outlined in the related meeting briefing package submitted under US-IND 063384 Serial Number 0164 on 22 January 2021, the MPLONG protocol will serve to provide long-term follow-up data on MDMA-assisted therapy clinical trials, with all participants having at least six months of follow-up beyond completion of their participation in the parent study. MPLONG will measure persistence of effectiveness after MDMA vs. placebo using the CAPS-5 and will additionally gather data to support health economics and cost-effectiveness analyses of MDMA-assisted therapy. The sponsor's initial NDA submission will include these long-term follow-up data following participants from both the MDMA and placebo groups of the pivotal Phase 3 Study MAPP1 to assess durability of treatment response from this placebo-controlled sample.

A similar study, MPELONG will serve as the observational long-term follow-up protocol for MDMA-assisted therapy clinical trials conducted in Europe and will measure persistence of effectiveness using the CAPS-5 and will additionally gather data to support health economics and cost effectiveness analyses of this treatment. MPELONG Version 2, dated 29 July 2021 was submitted to the Voluntary Harmonization Procedure (VHP) for multinational clinical drug trials

conducted in EEA on 15 October 2021. The sponsor received a list of grounds for non-acceptance (GNA) on 22 November 2021 and a response letter is currently in preparation.

8.4 Other Therapeutic Use of Investigational Drug

Other programs conducted by the sponsor that offer use of the investigational drug following a specific protocol and include solicited reporting as per ICH E2D include the sponsor's Expanded Access Program and the investigator-initiated trial programs.

The sponsor has received FDA authorization to establish an intermediate-sized Expanded Access Program under US-IND #142690 intended to provide early access to MDMA-assisted therapy to a limited group patients with treatment-resistant PTSD who cannot participate in Phase 3 studies due to demonstrated ineligibility, geographic factors, or lack of capacity in the Phase 3 protocols. Participants will be treated under a specific protocol (EAMP1) described in section 5.25 of this report. The program is in the development stage and expected to start in by the end of 2021 or early 2022.

The investigator-initiated trial (IIT) program facilitates the research of investigators who want to develop unique clinical trials as "sponsor-investigators" to study a new research question that may support expanding patient access or investigation into other conditions that MDMA-assisted therapy may be effective in treating by providing IMP. The investigational drug may be used under the specific investigator-initiated protocols in this program and all protocols include solicited reporting to the sponsor/manufacturer as per ICH E2D. During this reporting period there was one IIT trial open to enrollment (IVA1) titled "Open-label Phase 2 Study of MDMA-Assisted Psychotherapy in Veterans with Combat-Related, Refractory PTSD". No subjects received IMP in this program during this reporting period.

8.5 New Safety Data Related to Combination Therapies

The IMP is not part of a fixed combination product or a multi-drug regimen.

9.0 Safety Findings from Noninterventional Studies

No new safety information was obtained from noninterventional studies during the reporting period.

10.0 Other Clinical Trial/Study Safety Information

No new safety information was obtained from randomized clinical trials not supported by the sponsor during the reporting period.

11.0 Safety Findings from Marketing Experience

The IMP has not been approved for marketing in any country.

12.0 Nonclinical Data

No significant nonclinical sponsored studies were performed during the reporting period.

13.0 Literature

The 13th Edition of the IB, dated 22 March 2021, contains a summary of past and current findings for MDMA through October 1, 2020.

One scientific article related to safety of MDMA was published during the reporting period where the sponsor provided the IMP. This open-label study investigated the safety and tolerability proof-of-concept of MDMA-assisted therapy for treatment of alcohol use disorder (AUD) post-detoxification. The abstract stated, "Fourteen patients with AUD completed a community alcohol detoxification and received an eight-week course of recovery-based therapy. Participants received two sessions with MDMA (187.5 mg each session). Psychological support was provided before, during and after each session. Safety and tolerability were assessed alongside psychological and physiological outcome measures. Alcohol use behavior, mental well-being and functioning data were collected for nine months after alcohol detoxification. MDMA treatment was well tolerated by all participants. No unexpected adverse events were observed. Psychosocial functioning improved across the cohort. Regarding alcohol use, at nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox. This study provides preliminary support for the safety and tolerability of a novel intervention for AUD post detox." Relevant to safety, one participant with controlled hypertension experienced a transient abnormal rise in blood pressure (SBP/DBP of 183/118 mmHG) two hours after initial dose of 125 mg MDMA, attributed to the participant forgetting to take their hypertensive medication. The supplemental dose was withheld and the participant was asymptomatic with no medical intervention needed. The participant took their hypertensive medication prior to the subsequent second Experimental Session and did not experience abnormal changes in blood pressure. This supports the sponsor's mitigation strategy of maintaining participants on hypertensive medication during MDMA-assisted therapy treatment. (Sessa et al., 2021. "First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder." J Psychopharmacol. 2021 Apr; 35(4): 375-383)

Another paper was published during the reporting period that pooled data from 10 randomized, double-blind, placebo-controlled, cross-over studies performed in the same laboratory in 194 healthy subjects receiving doses of 75 or 125 mg of MDMA HCl. The authors investigated the influence of drug dose, body weight, sex, age, drug pre-experience, genetics, personality, and mental state before drug intake on the acute physiological and psychological response to MDMA. The abstract stated: "In univariable analyses, the MDMA plasma concentration was the strongest predictor for most outcome variables. When adjusting for dose per body weight, we found that (a) a higher activity of the enzyme CYP2D6 predicted lower MDMA plasma concentration, (b) a higher score in the personality trait "openness to experience" predicted more perceived "closeness", a stronger decrease in "general inactivation", and higher scores in the 5D-ASC (5 Dimensions of Altered States of Consciousness Questionnaire) scales "oceanic boundlessness" and "visionary restructuralization", and (c) subjects with high "neuroticism" or trait anxiety were more likely to have unpleasant and/or anxious reactions. Although MDMA plasma concentration was the strongest predictor, several personality traits and mood state variables additionally explained variance in the response to MDMA. The results confirm that both pharmacological and non-pharmacological variables influence the response to MDMA." Of particular relevance, after adjusting drug dose for body weight, the factors of sex, age, or previous MDMA experience did not significantly influence the physiological or psychological response to MDMA. (Studerus et al., 2021. "Prediction of MDMA response in healthy humans: a pooled analysis of placebo-controlled studies." J Psychopharmacol. 2021 May;35(5):556-565)

14.0 Other DSURs

No other DSURs related to the IMP were produced or submitted by the sponsor during the reporting period. This DSUR represents a harmonized report across all programs overseen by the sponsor and subsidiaries worldwide.

15.0 Lack of Efficacy

No data indicating a lack of efficacy was found for the IMP during this reporting period.

16.0 Region-Specific Information

16.1 IND Safety Reports Submitted During the Reporting Period

A total of 14 IND safety reports were submitted during this reporting period under US-IND 063384. Five of these reports reflected new events and the remaining nine contained follow-up information to previously reported events including updated clinical information from study closure monitoring and post-database lock unblinding. Cumulatively 30 total IND Safety Reports were submitted in the clinical program. In keeping with the FDA's November 1, 2019 Information Request, expedited IND Safety reports are submitted for Adverse Events of Special Interest related to suicidality for retroactive and ongoing adverse events of suicidal ideation judged to be serious or severe in the opinion of the investigator, suicidal behavior, or self-injurious behavior in the context of suicidal ideation, as well as ongoing instances of C-SSRS suicidal ideation scores of 4 or 5.

Of the 30 cumulative IND Safety reports submitted US-IND 063384, 1 report was for MT-1, 1 report was for MP17, 1 report was for MP16, 24 reports were for 11 MAPP1 participants, and 3 reports were for 2 MAPP2 participants. Of these IND Safety reports, 16 were primary reports in unique participants and 14 were follow up reports. One was reported as a SUSAR of preparatory suicidal behavior in MAPP1 participant 1103002 where relationship to IMP could not be ruled out due to temporal proximity to dosing. The condition assignment was placebo and was provided to FDA in Manufacturer Report #4. Four IND Safety Reports were submitted in total for this participant. Following study wide unblinding, this participant was determined to have received placebo and therefore the event is now categorized as an SAE.

These AESIs of suicidal ideation and behavior are disease related events with high incidence in populations of people with PTSD, especially those suffering from chronic PTSD, and therefore remain unexpected for MDMA but expected background events due to the underlying PTSD. The sponsor is committed to monitoring suicidal ideation and behavior in the clinical development program for MDMA-assisted therapy according to the Safety Plan specified in study protocols.

16.2 Cumulative summary tabulation of serious adverse reactions

Cumulatively, one possibly related expected SAR of exacerbation of pre-existing ventricular extrasystoles was reported within the context of MAPS-sponsored study MP-8 and was presented in a prior DSUR. For a line listing and cumulative summary of all SARs in the Clinical Development Program, see Appendix Table 3.

16.3 Participants Who Died During Reporting Period

There have been no deaths during the reporting period.

See Appendix Table 5 for cumulative data summary on deaths reported from studies described in this DSUR.

16.4 Participants Who Dropped Out of Study Due to An Adverse Event During the Reporting Period

During the reporting period, one participant in the MAPP2 Phase 3 trial chose to discontinue the intervention after Experimental Session 1 due to an AE of abdominal pain. The participant went to the Emergency Room and was diagnosed with ileitis, but declined care and was not admitted to the hospital. The participant discontinued study participation due to pain.

A comprehensive list of participants who dropped out of clinical trials in association with an AE is presented in Appendix Table 6.

16.5 Significant Phase 1 Protocol Modifications

One Phase 1 study is ongoing under this US-IND 063384. For MT-1, two protocol amendments were implemented during the reporting period which is described in Section 5.9.

16.6 Significant Manufacturing Changes

There have been significant changes to the manufacturing of the IMP during this reporting period.

Optimization of the API synthetic route was developed to manufacture the Phase 3 cGMP MDMA HCl. A high yielding process that reproducibly provides material within the specifications has been achieved. Following the manufacture of a small-scale batch (5 L) in August 2020 and a commissioning batch in October 2020, three consecutive process validation batches were manufactured with this optimized manufacturing process at the commercial scale (50 L) in November 2020. This cGMP API material was used to manufacture an additional cGMP IMP batch of each strength (40 mg and 60 mg) of MDMA HCl capsules. The details of the Chemistry Manufacturing and Controls (CMC) were submitted in Module 3 of the US-IND 063384 Serial Number 0189 as an information amendment on 12 October 2021. This formulation is the planned commercial formulation and the same process will be used to manufacture the primary stability batches for each dosage strength at the commercial batch size in keeping with the WRO meeting minutes received from the Agency on 13 October 2021.

Additional stability data were generated on the current cGMP IMP batches and cover, beside 6 months under accelerated storage conditions 40°C/75% RH, a period of 24 months under long term storage conditions 25°C/60% RH in cold form aluminum blister packs and 18 months under long term storage conditions 25°C/60% RH in HDPE wide mouth bottles (1, 2, 4, 6 and 9 count) with HDPE SecuRx child resistant closures. The stability protocols for storage under long-term conditions (25°C/60% RH) in cold form aluminum blister packs are complete whereas the stability protocols in 1 and 9 count bottle size, running for up to 36 months, are still ongoing.

In summary there is no evidence of change in appearance, assay, or impurities in the capsules. Moisture remains constantly at a low level. These data suggest that MDMA is very stable and unreactive. Isolated low or sporadic out-of-specification dissolution results are likely to be associated with suboptimal manufacturing or dissolution conditions and optimization of the capsule manufacturing process is ongoing. The most current stability results for 40 mg and 60 mg MDMA HCl after 24 months storage at 25°C/60% RH in aluminum blister strips and 18 months in HDPE bottles show that there is no trend of dissolution data, and all results comply with specification.

Based on these data a shelf life of 36 months and retest date 30 April 2024 is proposed for the clinical drug product with recommended storage at ambient temperature up to 30°C. If the stability data continue to show no significant changes in purity or other characteristics, the shelf life will be further extended.

16.7 General Investigational Plan

An End of Phase 2 Meeting occurred with the FDA on November 29, 2016. The Sponsor and FDA reached agreement through SPA on the design and primary endpoint of identical Phase 3 studies (MAPP1 and MAPP2) on July 28, 2017. On August 15, 2017, the FDA granted Breakthrough Therapy Designation to MDMA for the treatment of PTSD. The initial multidisciplinary Breakthrough Planning Meeting was conducted with FDA on December 20, 2017. Per the agreed upon communication plan per Breakthrough Meeting Minutes dated 19 January 2018, the Sponsor held a Type B Guidance meeting with the FDA on 24 February 2021 to discuss the findings in the Phase 3 trial MAPP1 and their impact on the Investigational Plan and New Drug Application (NDA). The Sponsor and FDA agreed that presenting the results of the long term follow up study to assess treatment durability of MAPP1 participants who received MDMA or placebo will be included in the initial NDA submission.

An additional Type B Written Response Only (WRO) Meeting was requested on 15 March 2021 to discuss the remaining matters posed in the Type B meeting request, relating to timelines for NDA and User Fees submissions, the status of certain planned pharmacology and toxicology studies, as well as Drug Product and Substance characterization, control, and stability strategies. A WRO Type B Meeting Briefing Packet was submitted by the sponsor on 12 April 2021. The Sponsor and FDA agreed on the deferral of the hepatic impairment study (MPKH) to Phase 4 as a post-marketing commitment and the inclusion of the food effects study (MPKF) with in vivo pharmacokinetic and ECG data in the initial NDA submission.

Additionally, per the agreed upon communication plan from the Breakthrough Meeting Minutes dated 19 January 2018, the sponsor submitted a high-level outline of initial thinking on a proposed Risk Evaluation and Mitigation Strategy (REMS) for general comments and high-level feedback from the Division. The Agency agreed to provide review and feedback on a high-level summary of the proposed REMS program and the sponsor submitted a Request for Comments and Advice on 31 August 2021. The Agency provided feedback to the request on 25 October 2021 and the sponsor is incorporating the feedback into an updated REMS proposal.

A Scientific Advice (SA) Pre-submission meeting was held on 01 March 2018 to discuss pivotal Phase 3 studies with the European Medicine Agency. This pre-submission meeting was followed by the initiation of the SA procedure during the week of May 14 to May 17, 2018, and an official SA discussion meeting between the sponsor and SAWP took place on June 12, 2018. The final SA letter was received from the Committee for Medicinal Products for Human Use (CHMP) on June 28, 2018.

MDMA has not been approved for marketing in any country to date. The sponsor will seek approval of MDMA as a novel adjunct to supportive therapy for treatment of PTSD from the US FDA with a rolling NDA submission beginning in 2021 and ending in 2023. Future planned MAAs will also be submitted to the Israeli Ministry of Health (MOH) and Health Canada. This will be followed by the EMA marketing authorization application through the Centralized Procedure in 2024.

On February 1, 2018, an initial Pediatric Study Plan was agreed to with the FDA. The sponsor and FDA agreed to a Partial Waiver for research involving neonates, infants, and children 6 years of age and under, and a Deferral request for children and adolescents 7 to 17 years of age in order to allow the sponsor to gain sufficient marketing experience and safety data in adults prior to testing in the pediatric population. The sponsor will submit a UK-PIP and EMA-PIP for RA review prior to launching the Phase 3 study (MAPP3) in Europe.

FDA has cleared an intermediate-sized Expanded Access Program intended to provide early access to MDMA-assisted therapy to patients with treatment-resistant PTSD who cannot participate in Phase 3 studies due to demonstrated ineligibility, geographic factors or lack of capacity in the Phase 3 protocols, under US-IND #142690. FDA has also cleared a new pilot study for the use of MDMA as an adjunct to therapy in patients with eating disorders, under US-IND #142908. Below is a table of completed, ongoing, and planned MAPS-sponsored clinical trials of MDMA-assisted therapy across indications.

Table 2: Investigational Plan of Concluded, Ongoing, and Planned Clinical Trials of MDMA-Assisted Therapy Across Indications

Study/ Phase	Start - End (Year)	Country	Study Population/ IND#	MDMA	Placebo	Pivotal Safety	Pivotal Efficacy
Concluded Studies							
MP-1/ Phase 2	2003-2009	US	PTSD/ US-IND 063384	22 [A]	8	Legacy	Legacy
MP-2/ Phase 2	2006-2011	Switzer-land	PTSD/ US-IND 063384	14	-	Legacy	Legacy
MP-3/ Phase 2	2007-2010	Israel	PTSD/ US-IND 063384	5	-	Legacy	Legacy
MP-4/ Phase 2	2013-2016	Canada	PTSD/ US-IND 063384	6	2	Legacy	Legacy
MP-8/ Phase 2	2011-2016	US	PTSD/ US-IND 063384	26	-	Legacy	Legacy
MP-9/ Phase 2	2013-2017	Israel	PTSD/ US-IND 063384	10	-	Legacy	Legacy
MP-12/ Phase 2	2013-2017	US	PTSD/ US-IND 063384	28	-	Legacy	Legacy
MP1-E2/ Phase 2	2012-2014	US	PTSD/ US-IND063384	3 [B]	-	Legacy	Legacy
MAA-1/ Phase 2	2014-2017	US	Autistics with Social Anxiety/ US-IND 063384	12	4	Not registration study	Not registration study
MDA-1/ Phase 2	2014-2018	US	Anxiety, Life-threatening Illness/ US-IND 063384	18	5	Not registration study	Not registration study
MPVA1/ Phase 1/2	2017-2018	US	Healthy and PTSD/ US-IND 063384	12	-	Not registration study	Not registration study
MP17/ Phase 2	2018-2019	Canada	PTSD/ US-IND 063384	4	-	Not registration study	Not registration study
MAPP1/ Phase 3	2018-2020	US, Israel, Canada	PTSD/ US-IND 063384	46	44	Pivotal Safety	Pivotal Efficacy

MPVA4/ Phase 2	2017-2020	US	Healthy/ US-IND 063384	15	15	Supportive	Mechanistic
MP16/ Phase 2	2017-2021	US	PTSD/ US-IND 063384	33	-	Pivotal Safety	Open label
Ongoing Studies							
MT-1/ Phase 1	2011-2022	US	Healthy/ US-IND 063384	120 [C]	120 [C]	Legacy	Legacy
MAPP2/ Phase 3	2020-2022	US, Israel, Canada	PTSD/ US-IND 063384	50	50	Pivotal Safety	Pivotal Efficacy
MAPPUSX/ Phase 2	2021-2022	US, Israel, Canada	PTSD/ US-IND 063384	100	-	Pivotal Safety	Open label
MP18/ Phase 2	2020-2022	EEA	PTSD/ Not under US-IND	40	-	Not registration study	Open label
MPVA6/ Phase 2	2021-2023	US	PTSD/ US-IND 063384	60	-	Not registration study	Pragmatic
Planned Studies							
MAPP3/ Phase 3	2022-2024	EEA	PTSD/ Not under US-IND	35	35	EMA registration study	EMA registration study
MPKF/ Phase 1	2022-2022	US	Healthy/ US-IND 063384	12	-	Pivotal Safety	Not in PTSD patients
MT2/ Phase 1	2022-2024	US	Healthy / US-IND 063384	150	-	Not registration study	Not registration study
EAMP1/ Phase 2	2021-2025	US	Treatment-resistant PTSD/ US-IND142690	50	-	Not registration study	Pragmatic RWE
MED1/ Phase 2	2022-2023	US, Canada	Eating Disorders/ US-IND 142908	15	-	Not registration study	Not registration study
MPG1/ Phase 2	2022-2023	US	PTSD/ US-IND 063384	18	-	Not registration study	Not registration study
Long-Term Follow-Up Studies [D]							
MPLONG	2021-2023	US, Israel, Canada	PTSD/ US-IND 063384	-	-	Observa-tional	Pivotal Efficacy
MPELONG	2022-2023	EEA	PTSD/ Not under US-IND	-	-	Observa-tional	EMA registration study

[A] In MP-1, participants received either MDMA or an inactive placebo, but participants who took the option of continuing to the open-label crossover Stage 2 then received active dose MDMA as well (only one participant chose not to continue to Stage 2 in MP-1, due to a strong and sustained placebo response).
[B] In MP1-E2, participants were previously enrolled in MP-1. These participants were not counted again in the final summation.
[C] The MT-1 study uses a blinded full crossover design, with placebo administered in one session and MDMA in another session.
[D] No drug is administered in long-term follow-up studies.

16.8 Log of Outstanding Business

At the time of this report there is no outstanding business.

17.0 Late-breaking Information

There is no late-breaking information to report for the IMP during this reporting period.

18.0 Overall Safety Assessment

18.1 Evaluation of the Risks

Overall, the risks of SAEs and SARs have been addressed and constrained by limited, controlled exposure to the IMP to participants who have undergone adequate screening according to eligibility criteria defined in study protocols.

There were no newly identified safety issues during the reporting period in ongoing or concluded clinical trials. There were no meaningful changes in adverse reactions, no clinically significant toxicities, no deaths related to an adverse event, no drug-drug interactions, no indications of lack of efficacy, no clinically significant medication errors or overdoses, and no evidence of drug misuse.

An internal aggregate safety review was conducted comprehensively across studies. MAPP2 aggregate safety reports were periodically reviewed by the Pivotal Program iDMC per the MAPP2 protocol. The FDA requested that a DMC be added to MAPPUSX for safety monitoring since PTSD population at risk for suicidality and therefore MAPPUSX was added to the scope of the Pivotal Program iDMC.

The Pivotal Program iDMC for the above referenced studies have met 1 time to review group unblinded ongoing safety data for this study, once during this reporting period (Data Review Meeting #6: on 27 July 2021). The iDMC reviewed suicidal ideation and behavior events (which are known consequences of PTSD) observed in the MAPP2 clinical trial in comparison to results from the MAPP1 clinical trial. In MAPP2, reported Lifetime C-SSRS prevalence rates, as of May 12, 2021, were less for suicidal ideation (88.9%), serious ideation (27.8%), and behavior (16.7%) than were reported in the MAPP1 clinical trial. During this reporting period, no SAEs have been reported for MAPP2, which excludes participants with current serious suicide risk in eligibility criteria. The iDMC found no concerns for either MAPP2 or MAPPUSX and reported that the studies can proceed as planned.

18.2 Benefit-Risk Considerations

Given the safety profile and the positive efficacy signals seen in MAPS' Phase 2 and Phase 3 studies, the sponsor concludes that the risk-benefit analysis of MDMA-assisted therapy weighs in favor of accelerating the clinical development program of MDMA-assisted therapy for the treatment of PTSD.

The sponsor has conducted a review of adverse events for MDMA. A total of 8 SAEs of suicidal ideation and/or behavior were cumulatively reported in all MDMA studies in 458 participants through the reporting period. Five SAEs were not related to study drug, as they were reported before dosing (one suicidal ideation and one suicidal behavior) or in the placebo group (one suicidal ideation, and two suicide attempts by the same participant). Three SAEs were reported by three participants randomized to MDMA (two suicidal ideation, one suicide attempt). The relative incidence of these SAEs were comparable between MDMA and Placebo (0.84% [3 of 358] participants following MDMA vs. 1.13% [2 of 176] following Placebo). Eligibility criteria for these studies are designed to be generalizable to the intended population of patients suffering

from chronic PTSD who exhibit frequent and highly prevalent history of suicidal ideation and behavior.

The IB will be updated if there is sufficient information to justify a change to Reference Safety Information. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, the sponsor concludes that it remains favorable to pursue the research of MDMA as a medicine used as an adjunct to enhance therapy.

19.0 Summary of Important Risks

Within the reporting period no new safety risks clearly attributable to MDMA have been identified. No high-level safety risks have been identified per the Risk Assessment and Characterization Tool (RACT) assessment in treatment with MDMA. Medium level risks do not indicate the likelihood the event will occur, but indicate that non-complex procedures are needed to adequately eliminate or manage the risk in the patient population. Based on this, two medium level risks continue to be monitored in clinical trials during the upcoming reporting period. These include risks of cardiovascular/cerebrovascular events and exacerbation of psychological distress. These risks were agreed with the Agency and appropriate risk mitigation procedures have been included within active study protocols. During the reporting period, no Adverse Events of Special Interest (AESIs) of abuse potential for the investigational product or cardiac AESIs potentially indicative of QT prolongation were reported in the MAPP2 Phase 3 trials. This is consistent with the MAPP1 Phase 3 data indicating that these AESIs do not occur at an elevated level in the MDMA group.

Medium Risk of Cardiovascular and Cerebrovascular Events: Consistent with previously reported data there is a medium risk of cardiovascular events as MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner. Typically, this increase is not problematic for physically healthy individuals and subsides as drug is excreted. An examination of safety data from the Phase 2 and Phase 3 studies of MDMA-assisted therapy detected a dose-dependent increase in systolic blood pressure but not diastolic blood pressure. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing in ongoing clinical trials. QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event.

Medium Risk of Exacerbation of Psychological Distress: A medium-level risk of exacerbation of psychological distress exists in participants with a psychiatric diagnosis. Data in PTSD patients from the sponsor's Phase 3 clinical trial (MAPP1) indicate treatment emergent adverse events (TEAE) related to psychological distress were similarly reported across both groups of blinded participants: anxiety (37.0% MDMA, vs 40.9% placebo), depressed mood (10.9% MDMA vs 9.1% placebo), and suicidal ideation (45.7% MDMA vs 50.0% placebo). These commonly reported AEs were observed in both treatment arms, transient in duration, mild to moderate in severity, and also overlap with symptoms of pre-existing conditions in medical history associated with PTSD, which might have influenced the frequency of events observed during clinical trials of MDMA-assisted therapy. While these data do not support that psychological distress is a specific risk of MDMA, psychological distress may be exacerbated in the presence of MDMA following the onset of MDMA effects until the last effects have dissipated. In previous studies, psychological symptoms have generally been self-limiting and have responded well to reassurance from the therapy team, with occasional use of benzodiazepines for anxiety. In the Phase 3 studies participants have the intention of confronting and working through traumatic experiences. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the

psychotherapeutic process. This risk is expected for the participant population with PTSD and will continue to be monitored in ongoing and upcoming clinical trials.

There are two low-level theoretical safety risks in thermoregulatory modulation (increased body temperature) and osmoregulatory modulation (dilutional hyponatremia) that continue to be mitigated in current studies. With the risk mitigation procedures put in place in study protocols, these risks are sufficiently controlled and have not been actualized in clinical trials. The sponsor will continue to monitor them in ongoing and upcoming clinical trials.

20.0 Conclusions

Based on the previously reported data and the current state of scientific knowledge, MDMA-assisted therapy demonstrates significant benefit that outweigh the risks using a 3-session treatment model combined with non-drug therapy sessions for preparation and integration in the treatment of PTSD.

Across Phase 2 and Phase 3 studies, the overall rates of AEs and reactions are acceptable and generally self-limiting. In addition, there was an absence of AEs supporting drug dependence, intentional drug misuse, and substance abuse in a controlled therapeutic setting. Proper preparation, testing, monitoring, and follow-up support is expected to mitigate cardiovascular events or exacerbation of psychological distress that have been noted as medium-level safety risks. Risk mitigation mechanisms have been incorporated into the Phase 3 study designs and will reduce the difficulties that participants might have with adverse reactions. The Phase 3 studies being conducted by the sponsor are intended to further develop abuse liability, safety, and efficacy data in support of a marketing application for MDMA-assisted therapy in the treatment of PTSD within a controlled clinical setting.

Appendix

Appendix Table 1: Cumulative listing of all clinical research studies using MDMA under the sponsorship of MAPS or subsidiaries

Protocol	Study Title	Phase	Country/IND	Participant Population	# of Participants Planned	Relevant Product, per USP Salt Policy [A]	Status During Reporting Period
MP-1	Safety and Efficacy of MDMA-Assisted Psychotherapy in Participants with Chronic PTSD	2	US/ US-IND 063384	Persons with PTSD aged 18 to 70	21 planned/ 23 actual	(8) Inactive placebo during two blinded experimental sessions, followed by open-label crossover of two to three experimental sessions with full dose MDMA, followed 1.5-2.5 hours later by optional half dose (15) Full dose 106 mg MDMA followed 2-2.5 hours later by optional 53 mg dose during two blinded experimental sessions, followed by one additional optional open-label experimental session with full dose MDMA, followed 1.5-2.5 hours later by optional half dose	Concluded, Clinical Study Report in progress
MP-2	Safety and Efficacy of MDMA-Assisted Psychotherapy in Participants with Treatment-Resistant PTSD	2	Switzerland/ US-IND 063384	Persons with PTSD over the age of 18	12 planned/ 14 actual	(5) Active placebo 21 mg MDMA followed 2-2.5 hours later by optional 11 mg dose during three blinded experimental sessions, followed by open-label crossover of three experimental sessions with 106 mg	Concluded, Clinical Study Report in progress

						MDMA, followed 1.5-2.5 hours later by optional half dose, followed by two optional open-label experimental sessions with 128 mg MDMA, followed 1.5-2.5 hours later by optional half dose, for non-responders (9) Full dose 106 mg of MDMA followed 2.5 hours later by optional 62.5 mg dose during three experimental sessions, followed by two optional open-label experimental sessions with 128 mg MDMA, followed 1.5-2.5 hours later by optional half dose, for non-responders	
MP-3	Safety and Efficacy of MDMA-Assisted Psychotherapy in Participants with PTSD	2	Israel/ US-IND 063384	Persons with PTSD over the age of 18	12 planned/ 5 actual	(2) Active placebo 21 mg MDMA followed 2-2.5 hours later by optional 11 mg dose, followed by open-label crossover of two experimental sessions with full dose MDMA, followed 1.5-2.5 hours later by optional half dose (3) Full dose 106 mg of MDMA followed 2.5 hours later by optional 53 mg dose during two	Study terminated early, Abbreviated Clinical Study Report in progress

						experimental sessions	
MP-4	A Randomized, Active Placebo-Controlled Pilot Study of MDMA-Assisted Psychotherapy in 12 Participants with Treatment-Resistant PTSD - Canada	2	Canada/ US-IND 063384	Canadian residents with PTSD over the age of 21	12 planned/ 6 actual	(2) Inactive placebo followed 1.5-2.5 hours later by optional supplemental half dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 84 mg or 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose (4) Full dose 106 mg of MDMA followed 1.5-2.5 hours later by optional 53 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	Study terminated early Abbreviated Clinical Study Report in progress
MP-8	A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant PTSD	2	US/ US-IND 063384	Veterans, firefighters, or police officers with PTSD over the age of 18	24 planned/ 26 actual	(7) Low dose 25 mg MDMA followed 1.5-2.5 hours later by optional 13 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 84 mg or 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose	Concluded, Clinical Study Report in progress

						(7) Medium dose 64 mg MDMA followed 1.5-2.5 hours later by optional 32 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 84 mg or 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose (12) Full dose 106 mg of MDMA followed 1.5-2.5 hours later by optional 53 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	
MP-9	A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy in People with Chronic, Treatment-Resistant PTSD	2	Israel/ US-IND 063384	Persons with PTSD over the age of 18	10 planned/ 10 actual	(3) Active placebo 21 mg MDMA followed 1.5-2.5 hours later by optional 11 mg dose in two blinded experimental sessions, followed by open-label crossover of two experimental sessions with full dose MDMA, followed 1.5-2.5 hours later by optional half dose (5) Full dose 106 mg of MDMA followed 1.5-2.5	Concluded, Clinical Study Report in progress

						hours later by optional 53 mg dose during two blinded experimental sessions (2) Full dose 106 mg of MDMA followed 1.5-2.5 hours later by optional 53 mg dose during two open-label lead-in experimental sessions	
MP-12	A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Participants with Chronic, Treatment-Resistant PTSD	2	US/ US-IND 063384	Persons with PTSD over the age of 18	23 planned/ 28 actual	(7) Comparator dose 34 mg MDMA followed 1.5-2.5 hours later by optional 17 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 84 mg or 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose (9) Active dose 84 mg MDMA followed 1.5-2.5 hours later by optional 42 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with active dose of 84 mg or 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose	Concluded, Clinical Study Report in progress

						(12) Active dose 106 mg MDMA followed 1.5-2.5 hours later by optional 53 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	
MP1-E2	An Open-Label Proof-of-Principle Study Testing the Use of an Additional MDMA-Assisted Psychotherapy Session in People Who Relapsed after Participating in a Phase 2 Clinical Trial of MDMA-Assisted Psychotherapy to Treat Chronic, Treatment-Resistant PTSD	2	US/ US-IND 063384	Participants who completed MP-1 and relapsed after initial improvement	Up to 3 planned/ 3 actual	(3) Full dose 106 mg of MDMA followed 1.5- 2.5 hours later by optional 53 mg dose during one open-label experimental session	Concluded, Clinical Study Report in progress
MT-1	A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers	1	US/ US-IND 063384	Healthy volunteers over the age of 18	120 planned/ 97 actual	(100) Full dose 106 mg of MDMA followed 1.5-2.5 hours later by optional 53 mg dose or inactive placebo crossover during two experimental sessions in randomized order	Ongoing
MT2	A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers	1	US/ US-IND 063384	Healthy volunteers over the age of 18	150 planned/ 0 actual	(150) Initial dose of 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later.	In Start Up Phase
MAA-1	A Placebo-Controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety	2	US/ US-IND 063384	MDMA-naïve persons on the autism spectrum	12 planned/ 12 actual	(4) Active dose 64 mg MDMA in one blinded experimental session,	Concluded, Clinical Study

	Study of MDMA-Assisted Psychotherapy for Social Anxiety in Autistic Adults			with social anxiety over the age of 21		escalating to 84 mg MDMA in second blinded experimental session (4) Active dose 84 mg MDMA in one blinded experimental session, escalating to 106 mg MDMA in second blinded experimental session (4) Inactive placebo in two blinded experimental sessions, followed by open-label crossover of 64 mg MDMA in one experimental session, then 106 mg of MDMA in second experimental session	Report in progress
MDA-1	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness	2	US/ US-IND 063384	Persons with anxiety related to a life-threatening illness over the age of 18	18 planned/ 21 actual	(5) Inactive placebo followed 1.5-2.5 hours later by optional placebo dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 106 mg MDMA, followed 1.5-2.5 hours later by optional half dose (13) Full dose 106 mg of MDMA followed 1.5-2.5 hours later by optional 53	Concluded, Clinical Study Report in progress

						mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	
MPVA-1	A Phase 1/2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in which 1 Member has Chronic PTSD	1/2	US/ US-IND 063384	Persons aged 18 or older including a PTSD+ participant and a Concerned Significant Other who does not have a current diagnosis of PTSD but is experiencing associated psychological distress	10 planned dyads (20 participants)/ 6 actual dyads (12 participants)	(12) 64 mg of MDMA followed 1.5 to 2 hours later by an optional dose of 32 mg in one experimental session, followed by a second session using either 84 or 64 mg of MDMA, supplemented with an optional half-dose 1.5 to 2 hours after the initial MDMA dose	Study terminated early, Abbreviated Clinical Study Report in progress
MPVA-4	Evaluation of 3,4-methylenedioxymethamphetamine (MDMA) on Startle Response	1	US/ US-IND 063384	Healthy volunteers over the age of 21 with prior MDMA use in a recreational or research setting	30 planned/ 34 actual	(17) Inactive placebo dose in one blinded experimental session (17) Active dose 84 mg of MDMA in one blinded experimental session	Concluded, Clinical Study Report in progress
MPVA6	A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Therapy in U.S. Veterans with Chronic PTSD	2	US/ US-IND 063384	Persons with moderate PTSD over the age of 18	60 planned/ 0 actual	Two or three open label Experimental Sessions, total amount to be administered per Experimental Session range from 100 mg to 134 mg.	In Start Up Phase

						(30) Sessions 1 and 2: initial dose of 100 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 1, 2 and 3: initial doses of 100 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later	
MP16	An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder	2	US/ US-IND 063384	Persons with severe PTSD over the age of 18	Up to 60 planned/ 38 actual	Three open label Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg (60) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	Concluded, Interim Clinical Study Report submitted
MP17	An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-	2	Canada/ US-IND 063384	Persons with severe PTSD	Up to 5 planned/ 4 actual	Two open label Experimental Sessions, total amount to be	Study terminated early,

	Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder			over the age of 18		administered per Experimental Session range from 84 mg to 159 mg MDMA (4) Session 1: 84 mg MDMA followed 1.5-2.5 hours later by supplemental dose of 42 mg MDMA Sessions 2 and 3: initial dose of 84 mg or 106 mg MDMA followed by an optional supplemental half-dose 1.5 to 2 hours later of 42 mg or 53 mg MDMA	Abbreviated Clinical Study Report in progress
MP18	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	2	Europe/ EudraCT# 2018-001718-13	Persons with non-dissociative subtype of PTSD Persons with severe PTSD over the age of 18	Up to 40 planned/ 8 actual	Two open label Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg MDMA (40) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Session 2: initial dose of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	Recruitment ongoing

MPKH	A Phase I, Open Label, Study of MDMA Tolerability and Pharmacokinetics in Subjects with Moderate Hepatic Impairment Compared to Matched Control Subjects with Normal Hepatic Function	1	US/ US-IND 063384	8 participants with hepatic impairment; 8 matched controls	16 participants planned/ 0 actual	(16) One Session with 68 mg MDMA	Anticipated to be included as Phase-4 post approval commitment
MPKF	A Phase 1, Single-Center, Open-Label, Randomized Sequence, 2-Period Cross-over Study to Determine the Effect of Food on the Relative Bioavailability of MDMA Oral Formulation in Healthy Volunteers	1	US/ US-IND 063384	Healthy persons over the age of 18	12 participants planned/ 0 actual	(12) Two open label Experimental Sessions (either fed or fasted), total amount to be administered per Experimental Session is 84 mg MDMA	In Planning
MED1	An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Therapy for Eating Disorders	2	US & Canada/ US-IND 142908	12 participants with Anorexia Nervosa, Restricting-Type (AN-R), and 6 participants with Binge Eating Disorder (BED)	18 participants planned/ 0 actual	Three open label Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg MDMA (18) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	In Start Up Phase

MAPP1	A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder	3	US, Israel & Canada/ US-IND 063384	Persons with severe posttraumatic stress disorder over the age of 18	100 planned at all sites, with potential sample size re-estimation based on interim analysis/ 90 actual	Three blinded Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg MDMA (44) Inactive placebo followed by supplemental half-dose 1.5 to 2 hours later (46) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	Concluded, Clinical Study Report in progress
MAPP2	A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder of Moderate or Greater Severity	3	US, Israel & Canada/ US-IND 063384	Persons with at least moderate posttraumatic stress disorder over the age of 18	100 planned at all sites, with potential sample size re-estimation based on interim analysis/ 59 actual	Three blinded Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg MDMA (50) Inactive placebo followed by supplemental	Recruitment ongoing

						half-dose 1.5 to 2 hours later (50) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	
MAPPUSX	A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Therapy for the Treatment of Participants with Posttraumatic Stress Disorder	3	US, Israel & Canada/ US-IND 063384	Persons with at least moderate posttraumatic stress disorder over the age of 18	100 planned at all sites/ 7 actual	Three open label Experimental Sessions, total amount to be administered per Experimental Session range from 68 mg to 150 mg MDMA (100) Session 1: initial dose of 68 mg MDMA followed by supplemental 34 mg MDMA 1.5 to 2 hours later Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	Recruitment ongoing

EAMP1	An Intermediate-size Multi-site Expanded Access Program for MDMA-assisted Psychotherapy for Patients with Treatment-resistant PTSD	Expanded Access	US/ US-IND 142690	Persons with treatment-resistant posttraumatic stress disorder over the age of 18	50 participants planned at all sites/ 0 actual	(50) Session 1: 68 mg MDMA followed 1.5-2.5 hours later by supplemental dose of 34 mg MDMA Sessions 2 and 3: initial doses of 68 mg or 100 mg MDMA followed by supplemental 34 mg or 50 mg MDMA 1.5 to 2 hours later	In Start Up Phase

[A] See Appendix Table 7: MDMA Conversion Chart.

Appendix Table 2: Cumulative Demographics from Participants Treated in MAPS-Sponsored Clinical Trials

(Based on final data for completed studies and preliminary data for ongoing studies)

Cumulative Age and Gender Demographics Among Participants Treated Across All Studies				
Age Range	**Male**	**Female**	**Non-Binary [A]**	**Total**
18-19	1	0	0	1
20-29	43	44	0	87
30-39	77	73	2	152
40-49	51	68	1	120
50-59	26	37	0	68
60-69	10	21	0	31
70-79	4	0	0	4
Total	**212**	**243**	**3**	**458**

Cumulative Racial and Ethnic Demographics Among Participants Treated Across All Studies	
Racial Group	**Number of Participants**
American Indian or Alaska Native	7
Asian	17
Black or African American	15
Native Hawaiian or Other Pacific Islander	0
White	377
Multiple	23
Other [B, C]	19
Total	**458**
Ethnicity [C]	**Number of Participants**
Hispanic or Latino	30
Not Hispanic or Latino	270
Unknown	158
Total	**458**

Cumulative Racial and Ethnic Demographics Among Participants Treated in Phase 3 Studies [D]	
Racial Group	**Number of Participants**
American Indian or Alaska Native	4
Asian	10
Black or African American	7
Native Hawaiian or Other Pacific Islander	0
White	100
Multiple	12
Other	0
Total	**133**
Ethnicity	**Number of Participants**
Hispanic or Latino	17
Not Hispanic or Latino	115
Unknown	1
Total	**133**

[A] Non-binary was added as a gender identity option starting in 2018 and has been collected in the following studies: MAPP1, MAPP2, MAPPUSX, and MP18, enrolling a total of 137 participants to date.
[B] Studies MT-1 and MPVA-4 incorrectly collected "Asian/Pacific Islander" as a single, combined racial group. 8 participants who selected "Asian/Pacific Islander" as their race are classified here as "Other" under racial group.
[C] Hispanic/Latino ethnicity was incorrectly collected as a racial category in the following studies: MP-1, MP-2, MP-3, MP-4, MP-8, MP-9, MP-12, MT-1, MAA-1, MDA-1, MPVA-1, and MPVA-4, in a total of 284 participants. Participants could select only one racial category. If a participant selected Hispanic/Latino

as their race in these studies, the participant's race is classified here as "Other" and ethnicity as "Hispanic/Latino." Participants who did not select Hispanic/Latino as their race are classified here as "Unknown" for ethnicity.

[D] Phase 3 studies consist of MAPP1, MAPP2, and MAPPUSX.

Appendix Table 3: Cumulative SARs in MAPS-Sponsored Clinical Trials

(Based on sponsor database listings for completed studies and preliminary data received from the sites for ongoing studies)

Study	Partic-ipant #	Country/ Gender/ Age	Adverse Event/ Preferred Term*	SOC	Onset Date/ Onset Time	Resolution Date	Severity	Expected-ness	Outcome	Suspect Drug [A]	Daily Dose [A]/ Route Formulation	Dates of Treatment/ Duration of Treatment
MP-8	0811	U.S. Male 46	Ventricular Extrasystoles (increase)	Cardiov ascular	08-Mar-2013 1 hour, 17 minutes post administra tion	09-Mar-2013	Moderate	Expected	Resolved/ Return to Baseline	106 mg MDMA	25 mg + 13 mg 25 mg + 13 mg 25 mg (no suppl) 106 mg + 53 mg 106 mg (no suppl) oral: gelatin capsule compounded with lactose	26-Oct-2012 30-Nov-2012 05-Jan-2013 08-Feb-2013 08-Mar-2013 Once a month for 5 months

[A] See Appendix Table 7: MDMA Conversion Chart.

Appendix Table 4: Cumulative Summary Tabulation of All SAEs (Event-Level) in MAPS-Sponsored Clinical Trials by Initial Dose

System Organ Class Preferred Term [A]	Before Dosing	68-106 mg MDMA [B]	25 mg MDMA [B]	Long-term Follow-up	Placebo
Cardiac Disorders					
Ventricular Extrasystoles		1 [C]			
Infections and Infestations					
Appendicitis				1	
Meningitis		1 [D1]			
Sepsis		1 [D1]			
Injury, Poisoning, and Procedural Complications					
Clavicle Fracture		1			
Lower Limb Fracture		1			
Nervous system disorders					
Syncope		1			
Spinal Cord Paralysis		1 [D1]			
Cerebrovascular Accident		1 [D1]			
Neoplasms Benign, Malignant, and Unspecified					
Invasive ductal breast carcinoma		1			
Chordoma		1 [D1]			
Intraductal proliferative breast lesion		1			
Metastases to Central Nervous System				1	
Breast Cancer Stage 1		1			
Psychiatric Disorders					
Depression				1 [D2]	
Suicidal Ideation	1	1 [D2]	1		1
Suicidal Behavior	1				
Suicide Attempt		1			2 [D3]
Reproductive System and Breast Disorders					
Ovarian Cyst Rupture		1			
Uterine Fibroids		1			

[A] Medical coding with MedDRA Version 17.1 or 20 depending on the study.
[B] See Appendix Table 7: MDMA Conversion Chart.
[C] Reported also as a SAR.
[D] Multiple SAEs occurred in single participant. D1: 51007 (MDMA): Five SAEs; Primary SAE is chordoma, secondary SAEs are meningitis, sepsis, spinal cord paralysis, and cerebrovascular accident. D2: 0805 (MDMA): Two SAEs of depression and suicidal ideation. D3: 1103002 (placebo): Two SAEs of suicide attempts.

Appendix Table 5: Cumulative Summary of Deaths in MAPS-Sponsored Clinical Trials

(Based on final data received from the sites)

Study	MDMA Dose [A]	Participant #	Adverse Event	Date Last Drug Admin	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Outcome	Relationship to Drug
MP-2	106 mg	0101	Metastases to central nervous system	04-Jan-2007	31-May-2007	18-Jul-2007	Yes	Continuous	Removed from Study	Hospitalization	Death	Not Related in opinion of investigator
MDA-1	106 mg	51007	Recurrence of chordoma	17-Dec-2015	30-Dec-2015	04-Sep-2016	Yes	Continuous	Delayed experimental session	Hospitalization; surgery; chemotherapy, radiation, as determined by patient's oncology and surgical teams	Death	Not Related in opinion of investigator

[A] See Appendix Table 7: MDMA Conversion Chart.

Appendix Table 6: Cumulative Summary of Treatment Drop-outs Due to Adverse Events in MAPS-Sponsored Clinical Trials

(Based on final data received from the sites)

Study	Participant #	Reason for Not Completing Treatment	Onset Timing of AE	Outcome	Date of Termination	Relationship to Study Drug
MDA-1	51007	Recurrence of chordoma, meningitis	13 days after dose 1 (MDMA)	Death	04-Sep-2016	Not Related in opinion of investigator
MP-1	0208	Major depression (relapse)	42 days after dose 1 (MDMA)	Early Term	7-Oct-2005	Not related in opinion of investigator
MP-2	105	Anxiety	0 days after dose 1 (MDMA)	Early Term	20-Sep-2007	Not Related in opinion of investigator
MP-2	101	Metastases to central nervous system	147 days after dose 3 (MDMA)	Death	18-Jul-2007	Not Related in opinion of investigator
MP16	1612002	Nightmare	0 days after dose 2 (MDMA)	Early Term	06-Mar-2019	Relationship to drug not collected from investigator per protocol
MAPP1	1102001	Anxiety	0 days after dose 1 (Placebo)	Early Term	19-Jun-2019	Not related Relationship to drug not collected from investigator per protocol
MAPP1	1103002	Suicide Attempt	0 days after dose 1 (Placebo)	Early Term	03-Jul-2019	Not Related in opinion of investigator
MAPP1	1104001	Suicidal Ideation	10 days after dose 2 (Placebo)	Dropout	30-Aug-2019	Not Related in opinion of investigator
MAPP1	1111002	Insomnia	20 days after dose 2 (Placebo)	Early Term	18-Sep-2019	Not Related Relationship to drug not collected from investigator per protocol
MAPP1	1113002	Depressed mood	5 days after dose 1 (MDMA)	Dropout	01-Apr-2020	Chose to discontinue due to triggering endpoint assessments, and AE. Relationship to drug not collected from investigator per protocol
MAPP2	2202009	Abdominal pain	18 days after dose 1 (Blinded)	Dropout	20-Aug-2021	Not Related Relationship to drug not collected from investigator per protocol

Appendix Table 7: MDMA Conversion Chart

Per USP Salt Policy, the strength of a drug product should be expressed in terms of the active moiety. As previous studies listed only the strength of MDMA as a hydrochloride (HCL) salt, this table provides a conversion chart of mg of MDMA HCl to mg of MDMA as the active moiety.

The molecular weight (MW) of MDMA as an anhydrous HCl salt (229.70 g/mol) and the MW of MDMA as a base (193.25 g/mol) were used to convert the mg of MDMA HCl to mg of MDMA, rounded to the nearest mg, per capsule. In studies where multiple capsules were administered, the converted amount per capsule was multiplied.

# of Capsules and Dose MDMA HCl (mg)	MDMA HCl (mg)	MDMA (mg)
	12.5	11
	15	13
	25	21
	30	25
	37.5	32
	40	34
	50	42
	60	50
	62.5	53
2 x 37.5	75	64
2 x 40	80	68
2 x 50	100	84
2 x 60	120	100
2 x 62.5	125	106
4 x 37.5	150	128
2 x 60 + 40	160	134
3 x 60	180	150
3 x 62.5	187.5	159