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Public Benefit
Corporation

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USE

In conjunction with relevant FDA guidance

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1.0 Executive Summary

This is the eighth annual report submitted for the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization sponsoring clinical trials of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for chronic psychiatric disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety related to autism, and anxiety related to a life-threatening illness, conducted under US-IND 063384. This report covers the period from 02 October 2014 through 01 October 2015. There were no MAPS-sponsored studies for MDMA conducted that were not under US-IND during the reporting period. MDMA does not currently have marketing approval anywhere in the world.

MDMA is a ring-substituted phenethylamine in the entactogen drug class that produces anxiolytic and prosocial effects by release of monoaminergic neurotransmitters and reuptake inhibition, likely through transporter occupancy and altering transporter configuration, with the greatest effect on serotonin, followed by norepinephrine and dopamine. 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 and arginine vasopressin in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues, as well as physiological effects of MDMA. 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 psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of psychotherapy.

The formulation of the investigational product consists of a gelatin capsule consisting of racemic white crystalline MDMA, at doses ranging from 12.5 mg to 150 mg, compounded with alpha-lactose, for oral administration. Due to a wide range of responses to identical milligram per kilogram (mg/kg) dosing between individuals, possibly as a result of nonlinear relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses that are equivalent to between 1 mg/kg and 3 mg/kg (cumulative active doses ranging from 112.5 mg to 225 mg with supplemental dosing) to achieve a more consistent response between subjects.

Unexpected and expected Serious Adverse Events (SAEs) related to administration of MDMA in MAPS-sponsored clinical trials have been rare and none have been life threatening. MDMA produces sympathomimetic effects that include significant transient, self-limited increases in heart rate and blood pressure that are likely to be well tolerated by healthy individuals. Most people do not experience elevations that exceed those seen during moderate exercise. During this reporting period there were two new Serious Adverse Events reported, neither related to receiving study drug. As previously reported, one probably drug-related expected SAE has occurred to date in this clinical development program. This event was an increase in frequency of ventricular extrasystoles experienced during treatment, which resolved with full recovery to baseline after the study drug's effects ceased. No cardiac damage occurred and hospitalization during this SAE was a cautionary measure. As of the reporting period, there have been 122 people exposed to MDMA, and a total of 362 exposures, in MAPS-sponsored studies conducted under US-IND. As of the reporting period, MDMA has been administered to over 1180 individuals for research purposes in studies sponsored by MAPS or others without publications or reports of unexpected drug-related SAEs.

Risks posed by sympathomimetic effects of MDMA treatments are addressed in MAPS clinical trials by excluding people with pre-existing cardiovascular disease or uncontrolled hypertension,

and by monitoring blood pressure, body temperature, and pulse during experimental sessions. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the next 24 hours. Once the drug leaves the body 2 to 3 days post-treatment, most reactions diminish. Reactions are monitored daily for a week after each treatment and followed until resolution. On the day of and during the week following each experimental session, the most commonly reported severe reactions were anxiety, insomnia, fatigue, muscle tightness, nausea, and depressed mood in the 125 mg dose groups across studies. Other common severe reactions include headache, decreased appetite, and irritability. MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these reactions are not likely to have clinical significance beyond several days after treatment.

In comparison to anxiolytics, antidepressants, and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy. A limited number of exposures to MDMA, spaced approximately a month apart at moderate doses, are sufficient to obtain therapeutic results, as found in [MP-1](#), [MP-2](#), and now [MP-8](#). This infrequent dosing 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 appears favorable to pursue the research of MDMA as an adjunct to psychotherapy.

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

None taken.

4.0 Changes to Reference Safety Information

The most recent version of the Investigator's Brochure, the 7th edition dated 01 August 2013, has been submitted to FDA.

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

The following table is a cumulative listing of all studies using MDMA under MAPS' US-IND 063384.

Table 1: Summary of Clinical Trials

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MP-1	Safety and Efficacy of MDMA-Assisted Psychotherapy in Subjects with Chronic PTSD	2	US	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 125 mg MDMA followed 2-2.5 hours later by optional 62.5 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	Complete

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MP-2	Safety and Efficacy of MDMA-Assisted Psychotherapy in Subjects with Treatment-Resistant PTSD	2	Switzerland	Persons with PTSD over the age of 18	12 planned/ 14 actual	<p>(5) Active placebo 25 mg MDMA followed 2-2.5 hours later by optional 12.5 mg dose during three blinded experimental sessions, followed by open-label crossover of three experimental sessions with 125mg MDMA, followed 1.5-2.5 hours later by optional half dose, followed by two optional open-label experimental sessions with 150mg MDMA, followed 1.5-2.5 hours later by optional half dose, for non-responders</p> <p>(9) Full dose 125 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 150mg MDMA, followed 1.5-2.5 hours later by optional half dose, for non-responders</p>	Complete

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MP-3	Safety and Efficacy of MDMA-Assisted Psychotherapy in Subjects with PTSD	2	Israel	Persons with PTSD over the age of 18	12 planned/ 5 actual	(2) Active placebo 25 mg MDMA followed 2-2.5 hours later by optional 12.5 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 125 mg of MDMA followed 2.5 hours later by optional 62.5 mg dose during two experimental sessions	Study Terminated after five subjects treated
MP-4	A Randomized, Active Placebo-Controlled Pilot Study of MDMA-Assisted Psychotherapy in 12 Subjects with Treatment-Resistant PTSD - Canada	2	Canada	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 100 mg or 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose (4) Full dose 125 mg of MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	Enrollment Concluded

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
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	Veterans, firefighters, or police officers with PTSD over the age of 18	24 planned/ 26 actual	<p>(7) Low dose 30 mg MDMA followed 1.5-2.5 hours later by optional 15 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 100 mg or 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose</p> <p>(7) Medium dose 75 mg MDMA followed 1.5-2.5 hours later by optional 37.5 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 100 mg or 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose</p> <p>(12) Full dose 125 mg of MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose</p>	Enrollment Completed

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
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	Persons with PTSD over the age of 18	10 planned/ 8 actual	(3) Active placebo 25 mg MDMA followed 1.5-2.5 hours later by optional 12.5 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 (7) Full dose 125 mg of MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose during two blinded experimental sessions	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MP-12	A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects with Chronic, Treatment-Resistant PTSD	2	US	Persons with PTSD over the age of 18	23 planned/ 28 actual	<p>(7) Comparator dose 40 mg MDMA followed 1.5-2.5 hours later by optional 20 mg dose in two blinded experimental sessions, followed by open-label crossover of three experimental sessions with active dose of 100 mg or 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose</p> <p>(9) Active dose 100 mg MDMA followed 1.5-2.5 hours later by optional 50 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with active dose of 100 mg or 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose</p> <p>(12) Active dose 125 mg MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose</p>	Enrollment Completed

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MP-1-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 Posttraumatic Stress Disorder (PTSD)	2	US	Subjects who completed MP-1 and relapsed after initial improvement	Up to 3 planned/ 3 actual	(3) Full dose 125 mg of MDMA followed 1.5- 2.5 hours later by optional 62.5 mg dose during one open-label experimental session	Complete
MT-1	A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers	1	US	Healthy volunteers over the age of 18	20 planned/ 7 actual	(20) Full dose 125 mg of MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose or inactive placebo crossover during two experimental sessions in randomized order	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
MAA-1	A Placebo-Controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA-Assisted Psychotherapy for Social Anxiety in Autistic Adults	2	US	Persons on the autism spectrum with social anxiety over the age of 21	12 planned/ 7 actual	<p>(4) Active dose 75 mg MDMA in one blinded experimental session, escalating to 100 mg MDMA in second blinded experimental session</p> <p>(4) Active dose 100 mg MDMA in one blinded experimental session, escalating to 125 mg MDMA in second blinded experimental session</p> <p>(4) Inactive placebo in two blinded experimental sessions, followed by open-label crossover of 75 mg MDMA in one experimental session, then 125 mg of MDMA in second experimental session</p>	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned/Actual	Relevant Product	Status During Reporting Period
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	Persons with significant anxiety related to a life-threatening illness over the age of 18	18 planned/ 4 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 125 mg MDMA, followed 1.5-2.5 hours later by optional half dose (13) Full dose 125 mg of MDMA followed 1.5-2.5 hours later by optional 62.5 mg dose in two blinded experimental sessions, followed by a third open-label experimental session with same dose	Recruiting

Protocol MP-1

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

Purpose: This study is designed to test whether MDMA-assisted psychotherapy can be safely administered to people with treatment-resistant PTSD and whether it will improve PTSD signs and symptoms 4 days after each of two experimental intervention sessions and again at a follow-up evaluation conducted two months 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 Subject First Visit: 30 March 2004

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

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

Number of Subjects Planned:	<u>21</u>
Number of Subjects Enrolled and Treated:	<u>23</u>
Number of Subjects Dropped Treatment:	<u>2</u>
Number of Subjects Completed Experimental Sessions:	<u>21</u>
Number of Subjects in Follow-up:	<u>0</u>
Number of Subjects Dropped Follow-up:	<u>1</u>
Number of Subjects Completed Follow-up:	<u>20</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on final, locked sponsor database.

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

Protocol MP-2

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

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

First Subject First Visit: 18 July 2007

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

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

Number of Subjects Planned:	<u>12</u>
Number of Subjects Enrolled and Treated:	<u>14</u>
Number of Subjects Dropped Treatment:	<u>2</u>
Number of Subjects Completed Experimental Sessions:	<u>12</u>
Number of Subjects in Follow-up:	<u>0</u>
Number of Subjects Dropped Follow-up:	<u>2</u>
Number of Subjects Completed Follow-up:	<u>10</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on final, locked sponsor database.

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

Protocol MP-3

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

Purpose: This study is designed to test the safety of MDMA-assisted psychotherapy conducted with 25 versus 125 mg MDMA in people with PTSD and will not produce serious adverse effects in this population.

First Subject First Visit: 15 January 2008

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

Subject Population: Persons with chronic, treatment-resistant PTSD over the age of 18 are eligible to enter the study. The number of subjects reported below is final for this study.

Number of Subjects Planned:	<u>12</u>
Number of Subjects Enrolled and Treated:	<u>5</u>
Number of Subjects Dropped Treatment:	<u>1</u>
Number of Subjects Completed Experimental Sessions:	<u>4</u>
Number of Subjects in Follow-up:	<u>0</u>
Number of Subjects Dropped Follow-up:	<u>1</u>
Number of Subjects Completed Follow-up:	<u>3</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on the site database.

Status: The study has been terminated. The Final Abbreviated Clinical Study Report is in preparation.

Protocol MP-4

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

Purpose: This study is designed to investigate the effect size of safety and efficacy for MDMA-assisted psychotherapy in 12 people with chronic, treatment-resistant PTSD.

First Subject First Visit: 02 January 2015

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

Subject Population: Persons with chronic, treatment-resistant PTSD over the age of 21 are eligible to enter the study. The number of subjects reported below is the cumulative number of subjects accrued as of the reporting period.

Number of Subjects Planned:	<u>12</u>
Number of Subjects Enrolled and Treated:	<u>6</u>
Number of Subjects Dropped Treatment:	<u>0</u>
Number of Subjects Completed Experimental Sessions:	<u>6</u>
Number of Subjects in Follow-up:	<u>6</u>
Number of Subjects Dropped Follow-up:	<u>0</u>
Number of Subjects Completed Follow-up:	<u>0</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Enrollment has been closed at this site. As of 22 November 2015 all subjects are in Long Term Follow-up.

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

First Subject First Visit: 15 December 2010

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

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

Number of Subjects Planned:	<u>24</u>
Number of Subjects Enrolled and Treated:	<u>26</u>
Number of Subjects Dropped Treatment:	<u>2</u>
Number of Subjects Completed Experimental Sessions:	<u>24</u>
Number of Subjects in Follow-up:	<u>4</u>
Number of Subjects Dropped Follow-up:	<u>2</u>
Number of Subjects Completed Follow-up:	<u>20</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Enrollment is completed.

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: This protocol is designed to investigate the effect size of safety and efficacy for MDMA-assisted psychotherapy in 10 people with chronic, treatment-resistant PTSD. The study starts with an open-label lead-in of two subjects in order to standardize the psychotherapeutic approach based on the Treatment Manual under development for this experimental treatment.

First Subject First Visit: 27 March 2013

Amendments During the Reporting Period: The Protocol was amended once during the reporting period. Amendment 3 Version 1 dated 30 March 2015 was approved by the IRB on 14 May 2015 and the Israeli Ministry of Health on 9 July 2015, submitted to FDA on 16 September 2015.

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

Number of Subjects Planned:	<u>10</u>
Number of Subjects Enrolled and Treated:	<u>7</u>
Number of Subjects Dropped Treatment:	<u>0</u>
Number of Subjects Completed Experimental Sessions:	<u>4</u>
Number of Subjects in Follow-up:	<u>1</u>
Number of Subjects Dropped Follow-up:	<u>1</u>
Number of Subjects Completed Follow-up:	<u>2</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Recruitment is ongoing.

Protocol MP-12

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

Purpose: This protocol is designed to investigate the effect size of safety and efficacy of MDMA-assisted psychotherapy in 23 people with chronic, treatment-resistant PTSD.

First Subject First Visit: 12 June 2013

Amendments During the Reporting Period: The protocol was amended once during the reporting period. Amendment #6, Version 1, dated 10 April 2015: approved by IRB of record on 25 June 2015, submitted to FDA on 18 June 2015. This amendment includes an expansion of the number of subjects to be treated from 23 to 26, allowing the site to enroll three additional subjects to replace subjects who had been inappropriately enrolled.

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

Number of Subjects Planned:	<u>23</u>
Number of Subjects Enrolled and Treated:	<u>26</u>
Number of Subjects Dropped Treatment:	<u>2</u>
Number of Subjects Completed Experimental Sessions:	<u>22</u>
Number of Subjects in Follow-up:	<u>13</u>
Number of Subjects Dropped Follow-up:	<u>1</u>
Number of Subjects Completed Follow-up:	<u>8</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Enrollment is complete.

Protocol MP-1-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: This protocol will investigate the effects of an additional MDMA-assisted psychotherapy session with associated preparatory sessions and integrative sessions on subjects who relapsed after initial improvement experienced in the sponsor's first U.S. Phase 2 pilot study, MP-1.

First Subject First Visit: 20 January 2012

Amendments During the Reporting Period: The protocol was not amended during the reporting period.

Subject Population: Subjects who completed MP-1 and relapsed after initial therapeutic gains are eligible to enter the study. The number of subjects reported below is the cumulative number of subjects accrued as of the reporting period.

Number of Subjects Planned:	<u>3</u>
Number of Subjects Enrolled and Treated:	<u>3</u>
Number of Subjects Dropped Treatment:	<u>0</u>
Number of Subjects Completed Experimental Sessions:	<u>3</u>
Number of Subjects in Follow-up:	<u>0</u>
Number of Subjects Dropped Follow-up:	<u>0</u>
Number of Subjects Completed Follow-up:	<u>3</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

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

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: This protocol is designed to collect quantitative data on mood, psychological symptoms, personality traits, and self-reported interpersonal closeness in up to 20 healthy volunteers after placebo and MDMA administration within a therapeutic setting.

First Subject First Visit: 21 April 2011

Amendments During the Reporting Period: The protocol was not amended during the reporting period.

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

Number of Subjects Planned:	<u>20</u>
Number of Subjects Enrolled and Treated:	<u>7</u>
Number of Subjects Dropped Treatment:	<u>0</u>
Number of Subjects Completed Experimental Sessions:	<u>7</u>
Number of Subjects in Follow-up:	<u>0</u>
Number of Subjects Dropped Follow-up:	<u>0</u>
Number of Subjects Completed Follow-up:	<u>7</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Recruitment is ongoing.

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: This is a double-blind, randomized, placebo-controlled, dose-finding Phase 2 pilot study designed to explore the safety and the therapeutic potential of MDMA-assisted therapy for treating social anxiety in 12 MDMA-naïve adults on the autism spectrum. This study will provide an estimate of effect size based on response to two experimental sessions of MDMA-assisted therapy in autistic adults on measures of safety, social anxiety, social perception, psychiatric symptoms, and biomarkers modulating social behavior in comparison to a placebo control group.

First Subject First Visit: 11 April 2014

Amendments During the Reporting Period: The protocol was not amended during the reporting period.

Subject Population: Subjects 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. Subjects must be 21 or over and MDMA naïve. The number of subjects reported below is the cumulative number of subjects accrued as of the reporting period.

Number of Subjects Planned:	<u>12</u>
Number of Subjects Enrolled and Treated:	<u>9</u>
Number of Subjects Dropped Treatment:	<u>1</u>
Number of Subjects Completed Experimental Sessions:	<u>7</u>
Number of Subjects in Follow-up:	<u>2</u>
Number of Subjects Dropped Follow-up:	<u>0</u>
Number of Subjects Completed Follow-up:	<u>5</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Recruitment is ongoing.

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: This is a double-blind, randomized, placebo-controlled, Phase 2 pilot study designed to explore the effect size of safety and the therapeutic potential of MDMA-assisted psychotherapy for treating social anxiety in 18 adults with anxiety associated with a life-threatening illness, which may be ongoing or in remission but with the possibility of recurrence.

First Subject Visit: 10 June 2015

Amendments During the Reporting Period: The protocol was amended once during the reporting period. Amendment #1, Version 1, dated 29 April 2015: approved by IRB of record on 3 June 2015, submitted to FDA on 4 August 2015. This amendment includes an expansion expanded descriptions of the Informed Consent process, patient eligibility, and study site location in the protocol, changes to the administration timepoint for baseline measures, and correction of minor inconsistencies between protocol sections. A semi-structured qualitative interview has also been added to the follow up visit one month after the third experimental session.

Subject Population: Subjects 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. Persons over the age of 18 are eligible to be enrolled. The number of subjects reported below is the cumulative number of subjects accrued as of the reporting period.

Number of Subjects Planned:	<u>18</u>
Number of Subjects Enrolled and Treated:	<u>4</u>
Number of Subjects Dropped Treatment:	<u>0</u>
Number of Subjects Completed Experimental Sessions:	<u>1</u>
Number of Subjects in Follow-up:	<u>1</u>
Number of Subjects Dropped Follow-up:	<u>0</u>
Number of Subjects Completed Follow-up:	<u>0</u>

Demographics: See [Appendix A](#) for summary of subject enrollment by demographic factors based on preliminary data collected during the reporting period.

Status: Recruitment is ongoing.

6.0 Estimated Cumulative Exposure

Table 2: Cumulative Subject Exposure in the Development Program

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

Study	Phase	Country	Study Population	Planned Enrollment	Subject Exposure to MDMA
MP-1	2	USA	PTSD	21	22*
MP-2	2	Switzerland	PTSD	12	14
MP-3	2	Israel	PTSD	12	5
MP-4	2	Canada	PTSD	12	6
MP-8	2	USA	PTSD	24	26
MP-9	2	Israel	PTSD	10	7
MP-12	2	USA	PTSD	23	26
MP1-E2	2	USA	PTSD	3	3**
MT-1	1	USA	Healthy Volunteer	20	7***
MAA-1	2	USA	Autistics with Social Anxiety	12	7
MDA-1	2	USA	Anxiety Related to Life-threatening Illness	18	2
Total					122

*In MP-1, subjects received either MDMA or an inactive placebo, but subjects who took the option of continuing to the open-label crossover Stage 2 then received active dose MDMA as well (only one subject chose not to continue to Stage 2 in MP-1, due to a strong and sustained placebo response)

**In MP1-E2, subjects previously participated in MP-1 and are not re-counted in cumulative exposure.

***In MT-1, subjects receive either MDMA or an inactive placebo in a blinded randomized crossover, so all subjects receive MDMA

7.0 Significant Findings from Clinical Trials During the Reporting Period

7.1 Clinical Safety

7.1.1 Summary of Serious Adverse Events (SAE)

During this period two new Serious Adverse Events were reported, neither related to receiving study drug.

The first SAE was a diagnosis of Breast Cancer in [MP-12](#) subject 12016. This was not related to study drug. The subject received an initial and supplemental cumulative dose of 187.5 mg MDMA on 24 Oct 2014, 21 Nov 2014, and 19 Dec 2014. On 28 Jan 2015 the study staff was informed that the subject had found a lump on her breast. On 17 Feb 2015 the subject notified the site staff that she had been diagnosed with Stage 1 Breast Cancer. On 27 Mar 2015 the subject underwent a double mastectomy. The surgery was successful with no need for chemotherapy or radiation. The subject is due for her final study visit for long term follow-up in the middle of December 2015.

The second SAE was a Fracture of the Left Tibial Plateau (PT: Lower Limb Fracture) with a secondary non-serious diagnosis of Blood Clot in Left Leg in [MP-12](#) subject 12019. This was not related to study drug. The subject received an initial and supplemental cumulative dose of 150 mg MDMA on 9 Jan 2015 and 6 Feb 2015. The injury occurred while skiing on 15 Feb 2015. During treatment for the tibial fracture it became evident that a blood clot had formed in his left leg. A filter was inserted into his vein to stabilize the blood clot. On 22 Feb 2015 the subject went to the emergency room due to severe headaches. The prescribing physician realized the subject had been prescribed Lovenox (enoxaparin) in the incorrect dosage, based on weight of 160 kg rather than the correct weight of 160 lbs. The subject was not admitted to the hospital. The subject was scheduled for tibial plateau repair surgery on 2 Mar 2015. The subject had his last experimental session on 5 Apr 2015. There were no complications during the treatment session. The blood clot persists and the subject is on a regimen of Xarelto (rivaroxaban) 10 mg and Lovenox (enoxaparin) 80 mg. The subject is due for his final study visit for long term follow-up at the beginning of April 2016.

See [Appendix B](#) for cumulative data on Serious Adverse Events reported to MAPS from studies conducted under US-IND.

7.1.2 Summary of Severe Adverse Events (AE)

During the reporting period, 32 subjects were treated in six studies under this IND. During this period, seven severe AEs were reported, with two that were judged to be possibly related to the study drug. Two possibly related severe AEs included depressed mood (1) and migraine headache (1).

Subject 12019 experienced severe depressed mood. The subject had experienced depressed mood as moderate on the day of the experimental session. The subject experienced moderate depressed mood again on days 2, 3 and 4 after the 2nd Experimental Session. Days 5 and 6 were noted as mild. On day 7 the subject experienced severe depressed mood on 13 Feb 2015 which resolved on 15 Feb 2015. The subject was contacted by the therapists an additional two days to ensure the subject got proper support. The AE has resolved and the subject's mood has returned to baseline.

Subject 08024 has a medical history of migraine headaches dating back to 2009. This subject experienced a severe migraine headache on the day after the second experimental session on 18 April 2015. The migraine resolved on 20 April 2015. The subject received an intramuscular injection of ketorolac and oral sumatriptan on 19 Apr 2015. The subject started a course of oral ondansetron on the same date and is continuing to take this medication. No further migraine headaches have been reported.

None of these severe AEs were considered SAEs (see [Section 7.1.1](#)). (see [Appendix C](#)).

AEs expected to occur on the day of and seven days after the experimental session were collected as Spontaneously Reported Reactions (see [Appendix E](#)). These reactions were initially compiled from the literature in a healthy volunteer population. During the reporting period, thirty-seven severe spontaneously reported reactions were reported. Seven of these reactions persisted beyond seven days after drug administration in the reporting period.

See [Appendix C](#) for cumulative listings of severe Adverse Events reported to MAPS during the reporting period from studies conducted under US-IND. See [Appendix D](#) for cumulative frequency of severe AEs listed by body system.

7.1.3 Summary of IND Safety Reports

There have been no IND Safety Reports during the reporting period.

7.1.4 Summary of Deaths

No deaths were reported during the reporting period. See [Appendix F](#) for a cumulative data summary.

7.1.5 Summary of Dropouts

Two subjects dropped out during the reporting period. Treatment for [MAA-1](#) subject A106 was discontinued by the Investigator due to inappropriate enrollment. The Investigator received medical records from an external treatment provider that indicated a previously undisclosed history of polysubstance and alcohol abuse, which may not have been in remission at the time of enrollment, as well as a history of hypertension. The medical records were inconsistent with self-report at screening, and these observations called into question the validity of study data. Treatment was discontinued after completion of integrative non-drug therapy following the single experimental session. [MDA-1](#) subject 51004 chose to discontinue treatment prior to the first experimental session due to exacerbation of anxiety caused by tapering of prestudy medications. This subject did not receive study drug.

Table 3: Summary of Treatment Dropouts
(Based on preliminary data received from the sites)

Study	Investigator	Subject #	Reason for Not Completing Treatment	Condition Assignment	Outcome	Relationship to Study Drug
MAA-1	Charles Grob, MD	A106	Inappropriate Enrollment	UNK	Early Terminated	Not related
MDA-1	Phillip Wolfson, MD	51004	Exacerbation of Anxiety	Prior to Dosing	Early Terminated	Not related

8.0 Safety Findings from Non-Interventional Studies

No new safety information was obtained from non-interventional studies during the reporting period.

9.0 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.

10.0 Safety Findings from Marketing Experience

The investigational product has not been approved for marketing in any country.

11.0 Nonclinical Data

No new non-clinical studies were performed during the reporting period.

12.0 Literature

No new safety findings were published during the reporting period.

13.0 Other Annual Reports

No other annual reports about MDMA were submitted by the sponsor during the reporting period.

14.0 Overall Safety Assessment

14.1 Evaluation of the Risks

The sponsor has analyzed the cumulative frequency of AEs and found the most frequent severe possibly or probably related AEs to be anxiety or distress (N = 3, 2% of subjects), depressed mood (N = 2, 2% of subjects), and panic attacks (N = 2, 2% of subjects). Severe AEs were treated with prescription medications and followed by additional phone contact and psychotherapy to ensure that the subjects returned to baseline or were stabilized. These AEs are listed in the Investigator's Brochure and informed consent materials as expected adverse effects of MDMA.

The sponsor has also analyzed the cumulative frequency of AEs commonly reported on the day of and 7 days after the experimental session, collected as Spontaneously Reported Reactions. These reactions were initially compiled from the literature in a healthy volunteer population. Despite the increase in exposures in the reporting period (146 experimental sessions, 28 subjects), the sponsor's cumulative analysis of these results across completed and ongoing studies of MDMA-assisted psychotherapy has remained consistent with reports from the previous year. This frequency analysis combines blinded and open-label data for safety purposes and percentages are based on the number of experimental sessions to account for low dose or placebo subjects also receiving 100 or 125 mg MDMA during the open-label crossover. The most frequently reported severe reactions related to 240 experimental sessions, across phase 2 studies, with 125 mg MDMA in 100 people were anxiety (N = 24, 10%), fatigue (N = 11, 5%), insomnia (N = 11, 5%), muscle tightness (N=11, 5%), depressed mood (N=9, 4%), and nausea (N=9, 4%). The highest dose group of 150 mg MDMA in MP-2 was only administered during 4 experimental sessions and was associated with reports of insomnia (N = 2), muscle tightness (jaw) (N = 2), and fatigue (N = 1). The following severe reactions were reported in less than 2% of experimental sessions with 125mg MDMA on the day of administration and the following week: diarrhea, dizziness, restlessness, asthenia, feeling cold, hypersomnia, judgment impaired, disturbance in attention, obsessive rumination, and parasthesia. These reactions may be of less concern than previously proposed in the scientific literature on MDMA.

Among the subset of adverse events collected as commonly reported severe reactions, anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood were reported in 4% or more subjects. Anxiety was reported the most by both inactive placebo (22%) and MDMA recipients (5-10%, depending on dose). These reactions also overlap with symptoms of pre-existing conditions in medical history associated with PTSD (depression, somatic symptoms, insomnia, anxiety), which may influence the frequency observed in MAPS-sponsored clinical trials of MDMA-assisted psychotherapy. Common severe reactions more likely to be associated with MDMA than underlying medical history include headache, decreased appetite, and irritability, reported in 2% of people receiving 125mg MDMA to date.

The 25 mg MDMA dose was only administered during 22 experimental sessions in 10 subjects and was associated with reports of insomnia (N = 4), fatigue (N=1), hypersomnia (N=1), and

decreased appetite (N=1). In studies where the active placebo is a low dose of 25-40mg MDMA, isolated reports of anxiety, hypersomnia, fatigue, and decreased appetite were observed, with insomnia (N=4) being reported more frequently. In comparison, 14 subjects who received an inactive placebo in 27 experimental sessions reported anxiety (N=6), insomnia (N=1), hyperhidrosis (N=1), and fatigue (N=1). Taking into consideration that the 125 mg MDMA dose has been administered by far the most frequently, the sponsor concludes that the frequency of severe spontaneously reported reactions are likely to be most accurate in the 125mg dose experimental sessions that have been administered to date in these studies. The higher number of experimental sessions at this dose also creates a greater opportunity to report severe reactions. While 125mg MDMA was associated with more severe reactions overall, these reactions were self-limiting and generally did not persist beyond the 7-day window after experimental sessions.

Any reactions that continued beyond the 7-day window were tracked as unexpected AEs until return to baseline. In all studies to date, 18 severe reactions lasted beyond the 7-day window: insomnia (N=2, maximum duration 26 days), anxiety (N=6, maximum duration 53 days), restlessness (N=2, maximum duration 18 days), obsessive rumination (N=1, duration 4 days) and depressed mood (N=4, maximum duration 51 days), headache (N=1, duration 13 day), muscle tightness (jaw) (N=1, duration 20 days), and muscle tightness (N=1, duration 20 days). These reactions were tracked as AEs until resolution and subjects experiencing them were provided with prescription medication and additional therapy. Seven of these were noted during the current reporting period.

MDMA is expected to produce statistically significant but transient, self-limited increases in blood pressure and heart rate. The supplemental half dose, when administered 1.5-2.5 hours after the initial dose, is not expected to cause further increases above those resulting from the initial dose of MDMA. Systolic blood pressure above 160 mmHg, the cut-off above which more frequent measurements are required by the protocols, was detected in 27% (93 of 343) of experimental sessions where MDMA was administered, and in 35% (55 of 157) of subjects receiving MDMA in sponsor-supported trials. Maximum duration above systolic blood pressure cut-off was 6 hours in two separate subjects with respective peak values of 172 and 174, where 125 mg MDMA was administered as the initial dose. Diastolic blood pressure exceeded 110 mmHg, the cut-off for more frequent measurement, in only 4% (15 of 343) of experimental sessions at any MDMA dose, and in 7% (11 of 157) of subjects receiving MDMA. Maximum duration above diastolic blood pressure cut-off was 5 hours in **MP-2** subject 112, with a peak of 114, where 125 mg MDMA was administered as the initial dose. This subject had a high pre-drug diastolic blood pressure reading of 96, and also experienced the highest systolic blood pressure observed to date in sponsor-supported studies of 200. This subject had a medical history of controlled hypertension, and the traumatic event that caused PTSD was medical malpractice, with a secondary diagnosis of white coat hypertension. This subject was only enrolled after 24-hour monitoring of blood pressure at baseline to confirm this diagnosis. In contrast, 14 subjects receiving 27 experimental sessions with placebo did not experience any elevations in blood pressure above cut-off. In experimental sessions with 25-30 mg MDMA elevations in blood pressure above cut-off were not observed either, supporting a dose-dependent effect of MDMA on blood pressure.

Heart rate elevation above 110 bpm, the cut-off for more frequent measurement, was detected in 31% (106 of 343) experimental sessions at any MDMA dose, and in 39% (61 of 157) of subjects receiving MDMA. Maximum peak pulse was 160 bpm reported in a subject who received 125 mg MDMA, with pulse remaining above cut-off for 60 minutes. At final reading 3.75 hours later, pulse had returned to below cut-off levels of 93 bpm. The maximum duration above cut-off was 9.5 hours in **MP-1** subject 218, where 125 mg MDMA was administered as the initial dose. This subject experienced a peak pulse of 121, which dropped at final reading to 119. Subject 218 had

no cardiovascular risk factors in medical history. In cases where blood pressure or heart rate was above cut-off, vitals were monitored more frequently. No subjects receiving MDMA in sponsor-supported clinical trials have required any clinical interventions for elevated blood pressure or pulse, as all values returned to normal as the effects of MDMA diminished.

Based on the literature, MDMA is also expected to produce elevations in body temperature with some influence of the ambient temperature. Body temperature above the cut-off of 1°C above baseline was detected in 33% (114 of 343) of experimental sessions where MDMA was administered, in 46% (72 of 157) of subjects receiving each dose in sponsor-supported trials. Maximum body temperature observed to date was 38.7°C in [MP-2](#) subject 107 lasting 3 hours, where 125mg MDMA was administered as the initial dose. This subject had no risk factors reported in medical history. Maximum duration above cut-off was 9.2 hours in [MP-9](#) subject 09007, where 125 mg MDMA was administered as the initial dose. This subject experienced a maximum of 38.0°C temperature, which dropped to 37.6°C at final reading. In contrast, in 7% (2 of 27) of experimental sessions where inactive placebo was administered, and in 14% (2 of 14) of subjects receiving inactive placebo, elevation of body temperature above cut-off was observed. Although body temperature was elevated for many of the subjects receiving MDMA, subjects receiving the placebo dose also had elevations. Adjustments were made to the ambient temperature and to air circulation in the room, but no subjects required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. In conclusion, it is best to ensure that the controlled setting for treatments with MDMA-assisted psychotherapy have the capacity to control ambient temperature.

Suicidal ideation and behavior were formally measured in [MP-4](#), [MP-8](#), [MP-9](#), [MP-12](#), [MT-1](#), [MAA-1](#), and [MDA-1](#) with the Columbia Suicide Severity Rating Scale ([C-SSRS](#)). There is high incidence of positive suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment resistant PTSD. In order to determine if suicidal ideation and behavior worsens or improves after treatment in MAPS-sponsored trials, the C-SSRS is given repeatedly throughout the study. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, therapeutic way, thoughts of ending one's life may surface during this process. However, evidence from ongoing studies indicates that these thoughts are most often transient, returning to baseline, or even improving during the acute period following MDMA treatment. C-SSRS scores have escalated during the preparatory sessions (before any drug administration), which is thought to be a result of preparatory discussion of traumatic experiences, and/or of subjects tapering off long-prescribed medications, such as SSRIs and benzodiazepines, which are known to induce suicidal ideation or behavior during withdrawal. During both non-drug and MDMA-assisted psychotherapy sessions, subjects are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with psychotherapy, the distress associated with psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies is low, occurring in only a few subjects post-MDMA treatment, and returning to non-life-threatening scores while subjects were closely monitored. Given that severe PTSD sufferers are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e. exacerbation of PTSD symptoms or from MDMA-stimulated effects). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. When positive serious ideation or behavior occurred after study enrollment, the investigators made follow-up observations of [C-SSRS](#) to ensure subject safety, and tracked scores until they returned to non-serious levels. Only two incidences of suicidal ideation have been considered clinically significant and tracked as severe AEs, but they were reported during the long-term follow-up period and were not related to study drug.

14.2 Benefit-Risk Considerations

Data from completed and ongoing studies of MDMA-assisted psychotherapy in people with chronic, treatment-resistant PTSD, social anxiety in autistic adults, and anxiety associated with terminal illness indicate that MDMA can be administered with an acceptable risk/benefit ratio in a therapeutic setting, as described in the Investigator's Brochure. In comparison to inactive placebo, MDMA administered according to the dosing regimen of an initial dose followed by a supplemental half dose appears to transiently elevate systolic blood pressure and heart rate but not diastolic blood pressure. Despite differences in frequency and procedures of monitoring vitals across sponsor-supported studies, all vitals return to acceptable values at the end of each experimental session, both in sponsor-supported studies and in other studies reported in the literature. This suggests that in future studies, it would be appropriate to measure vital signs less frequently during experimental sessions of MDMA-assisted psychotherapy, while monitoring for clinical signs and symptoms of hypertension and adding more frequent measurements of blood pressure and pulse only if clinically indicated. Rigorous screening should be maintained prior to enrollment to exclude subjects with uncontrolled cardiovascular risk. Symptoms that would call for more frequent vital sign measurement during an experimental session include: severe headache, confusion or focal neurologic signs, vision problems, chest pain, difficulty breathing, or palpitations.

In the sponsor-conducted placebo-controlled studies to date, MDMA does not produce greater psychological distress than placebo. MDMA has not adversely affected cognitive function in sponsor-supported studies to date. Scores on an established measure of PTSD symptoms declined to a statistically and clinically significant degree following MDMA-assisted psychotherapy in the per protocol set of [MP-1](#) subjects (N = 20), lending support to the rationale for continued research into this potentially promising treatment (Mithoefer et al. 2011). Improvements in PTSD symptoms observed in MP-1 were maintained an average of 3.8 years later (N = 16) (Mithoefer et al. 2013). Results from [MP-2](#) (N = 12) comparing 125 mg MDMA to 25 mg MDMA as an active placebo with different therapists in a Swiss sample were clinically but not statistically significant, although trends toward symptomatic improvement were noted in both primary and secondary measures of PTSD severity (Oehen et al. 2011). In the recently completed study of chronic PTSD in veterans, firefighters, and police officers ([MP-8](#), N=26), clinically and statistically significant results were also obtained in an intent to treat analysis, indicating that this treatment is generalizable to service-related trauma. Cohen's *d* effect size of this treatment is estimated to be 1.0 or greater, and three small pilot studies have generated reproducible results. In a previous reporting period, there has been one probably drug-related SAE reported in MAPS studies and none in research studies not supported by MAPS (see [Appendix B](#)). Two new SAEs have been

reported in MAPS-sponsored studies during the current reporting period, both unrelated to study drug. Both MAPS and the investigators conclude that the MDMA-assisted psychotherapy protocols appear to be sufficiently safe, well tolerated, and have an acceptable risk/benefit ratio.

15.0 Summary of Important Risks

To date, the important risks that have been identified and are expected are primarily cardiovascular in nature. This is the case with the single probably drug-related SAE observed to date. Risks posed by elevated blood pressure during treatment are addressed in clinical trials by excluding people with pre-existing uncontrolled hypertension or known cardiovascular or cerebrovascular disease, conducting EKGs, physical exams, and collecting careful medical history at baseline, and by monitoring blood pressure and pulse during experimental sessions. In all MAPS-sponsored studies, vitals always returned to baseline spontaneously without requiring medical intervention. In [MP-8](#), frequent vital sign measurements were taken during blinded MDMA-assisted sessions for subjects without a history of hypertension, the investigators were blinded to all blood pressure and pulse measurements except at baseline. In these sessions, there was never a need to break the blind for medical reasons. Elevations in blood pressure, pulse, and body temperature were observed above pre-determined cut-offs across MDMA doses, but these did not require medical intervention to return to baseline. Based on these results, in future studies, it would be appropriate to routinely measure vital signs only at baseline, prior to supplemental dose administration, and at the end of the session or until vitals have returned to baseline, with the option for more frequent measurements at the investigators' discretion if any medical indication arises.

Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the following week. Common severe reactions to MDMA-assisted psychotherapy in the treatment of anxiety disorders include anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood. Because of their limited duration, these changes are not likely to have clinical significance beyond several days after treatment.

16.0 Conclusions

MAPS is working towards implementing Phase 3 studies and submitting an NDA for the use of MDMA-assisted psychotherapy in patients with chronic, treatment-resistant PTSD. The sponsor and the investigators conducting the studies have published results in peer-reviewed scientific journals of the [MP-1](#) and [MP-2](#) studies indicating sustained improvements in PTSD severity after MDMA-assisted psychotherapy (Mithoefer et al. 2011, Mithoefer et al. 2013, Oehen et al. 2013). MAPS is currently sponsoring two US-based Phase 2 PTSD trials: one treating U.S. military veterans, firefighters, and police officers with service-related chronic, treatment-resistant PTSD ([MP-8](#)) and one treating individuals with treatment-resistant PTSD who are not necessarily military members or first responders ([MP-12](#)). MAPS is also currently sponsoring two international Phase 2 clinical trials: a study in Israel ([MP-9](#)) and a study in Vancouver, BC ([MP-4](#)) also treating individuals with chronic, treatment-resistant PTSD. These studies have completed enrollment as of the reporting period and results will be analyzed in preparation for an End of Phase 2 meeting with FDA to be requested in 2016. Additionally, MAPS is sponsoring a Phase 2 pilot feasibility study in association with Los Angeles Biomedical Research Institute at the Harbor-UCLA Medical Center and Stanford University investigating the safety and efficacy of MDMA-assisted therapy in the treatment of social anxiety in adults on the autism spectrum, and a Phase 2 pilot study in San Anselmo, California on the safety and efficacy of MDMA-assisted psychotherapy in the treatment of a new indication, anxiety associated with life-threatening illness. Taken together, these pilot studies will help to gather preliminary data and effect size estimates of the safety and efficacy of MDMA-assisted psychotherapy that will inform the design of possible Phase 3 multi-site studies.

17.0 Appendix A: Demographics

Table 4: All Studies Cumulative Demographics

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

Treatment by Initial Dose Received	Number of Subjects Receiving Dose at Least Once		
Inactive Placebo	21		
25 mg MDMA	10		
30 mg MDMA	7		
40 mg MDMA	7		
75 mg MDMA	13		
100 mg MDMA	25		
125 mg MDMA	107		
150 mg MDMA	3		
Unknown (still blinded)	2		
Total exposed to any dose of MDMA	122		
Age Range	Number of Subjects		
	Male	Female	Total
20-29	15	10	25
30-39	17	20	37
40-49	18	21	39
50-59	10	11	21
60-69	1	8	9
Racial Group	Number of Subjects Enrolled		
Asian	1		
Black	0		
Caucasian	111		
Middle Eastern	5		
Hispanic/Latino	4		
Native American	2		
Other	8		
Total	131		

18.0 Appendix B: Cumulative Serious Adverse Events

Table 5: All Studies Cumulative Serious Adverse Reactions

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

Study	Subject #	Country/ Gender/ Age	Adverse Event	Onset Date/ Onset Time	Resolution Date	Severity	Outcome	Drug	Daily Dose/ Route Formulation	Dates of Treatment/ Duration of Treatment
MP-8	0811	U.S. Male 46	Increase in Ventricular Extrasystoles	08-Mar-2013 1 hour, 17 minutes post-drug	09-Mar-2013	Moderate	Full Recovery/ Return to Baseline	125 mg MDMA	30 mg + 15 mg 30 mg + 15 mg 30 mg (no suppl) 125 mg + 62.5 mg 125 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

Table 6: Cumulative Summary Tabulation of Serious Adverse Events (SAEs) through End of Reporting Period

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

System Organ Class Preferred Term*	125 mg MDMA	100 mg MDMA	30 mg MDMA	Before Dosing
Gastrointestinal disorders				
Appendicitis	1			
Investigations				
Psychiatric Hospitalization				1
Fractured Clavicle (auto accident)	1			
Nervous System Disorder				
Vasovagal Syncope	1			
Neoplasms Benign, Malignant, and Unspecified				
Brain Metastasis (frontal brain syndrome)	1			
Breast Cancer	1			
Reproductive System and Breast Disorders				
Ovarian Cyst Ruptured		1		
Psychiatric Disorders				
Suicidal Ideation	1		1	
Major Depressive Episode	1			
Injury, Poisoning, and Procedural Complications				
Lower Limb Fracture				
Cardiac Disorders				
Increase in Ventricular Extrasystoles	1			

* Medical coding with MedDRA Version 15, 16, or 17 depending on the study

19.0 Appendix C: Severe Adverse Events within Reporting Period

Table 7: All Studies Severe Adverse Events within the Reporting Period

(Based on preliminary data received from the sites)

Study	Initial Dose (mg)	Subject #	Adverse Event	Date Last Drug Admin	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-8	30	0824	Migraine Headache	18-Apr-2015	19-Apr-2015	20-Apr-2015	No	Single/Intermittent	None	Prescription Medication	None	Full Recovery	Possibly Related
MP-8	125	0812	Appendicitis	15-Feb-2013	UN-April 2014	UN-April-2014	Yes	Single/Intermittent	None	Hospitalization	None	Full Recovery	Not Related
MP-12	125	12016	Breast Cancer	19-Dec-2014	17-Feb-2015	27-Mar-2015	Yes	Single/Intermittent	Delayed Experimental Session	Hospitalization	Surgery Double Mastectomy	Full Recovery	Not Related
MP-12	100	12019	Depressed Mood	06-Feb-2015	13-Feb-2015	15-Feb-2015	No	Continuous	None	Other	Phone consult PRN additional 2 days	Full Recovery	Possibly Related
MP-12	100	12019	Lower Limb Fracture	06-Feb-2015	15-Feb-2015	22-Apr-2015	Yes	Continuous	Delayed Experimental Session	Procedure or Therapy, Prescription Medication	None	Full Recovery	Not Related
MAA-1	100	A103	Psychiatric Symptom	27-Sep-2014	30-Oct-2014	6-Nov-2014	No	Continuous	None	Therapy	None	Resolved Back to Baseline	Not Related
MAA-1	100	A103	Dissociation	27-Sep-2014	30-Oct-2014	6-Nov-2014	No	Continuous	None	Therapy	Second Opinion from Treating Psychiatrist	Resolved Back to Baseline	Not Related

20.0 Appendix D: Severe Adverse Events by Relatedness

Table 8: Cumulative Frequency of Severe Adverse Events by Relatedness

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

Adverse Event	MP-1		MP-2		MP-4		MP-8		MP-9		MP-12		MP1-E2		MT-1		MDA-1		MAA-1		Total	
	Number of Subjects	23	14	6	26	7	26	3	7	4	9	127**										
Number of Sessions	67	56	22	101	14	82	3	7	8	19	399											
Relatedness	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR
Psychiatric																						
Re-experiencing Episode	1																				1 (1%)	0
Panic Attack	1		1																		2 (2%)	0
Major Depressive Episode		1					1														0	2 (2%)
Depressed Mood										2											2 (2%)	0
Obsessive rumination										1											1 (1%)	0
Anxiety, Distress			2							1											3 (2%)	0
Insomnia				2																	0	2 (2%)
Agoraphobia		1																			0	1(1%)
Suicidal Ideation							1							1							0	2(2%)
Psychiatric Symptoms																				1	0	1 (1%)
Dissociation																				1	0	1 (1%)
Nervous System																						
Headache			1				1														1 (1%)	1 (1%)
Sciatica		1																			0	1 (1%)
Gastrointestinal																						
Abdominal Cramps/Pain				1			1														1 (1%)	1 (1%)

Adverse Event	MP-1		MP-2		MP-4		MP-8		MP-9		MP-12		MP1-E2		MT-1		MDA-1		MAA-1		Total	
	Number of Subjects	23	14	6	26	7	26	3	7	4	9	127**										
Number of Sessions	67	56	22	101	14	82	3	7	8	19	399											
Relatedness	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR
General																						
Benzodiazepine Withdrawal		1																			0	1 (1%)
Restlessness									1												1 (1%)	0
Body Pain			1																		0	1 (1%)
Musculoskeletal & Connective Tissue																						
Musculoskeletal Chest Pain	1																				1 (1%)	0
Muscle Spasms										1											0	1 (1%)
Injury, Poisoning, and Procedural Complications																						
Lower Limb Fracture										1											0	1 (1%)
Infections and Infestations																						
Sinusitis		1																			0	1 (1%)
Appendicitis							1														0	1 (1%)
Neoplasms																						
Brain Metastasis			1																		0	1 (1%)
Breast Cancer										1											0	1 (1%)
Reproductive System and Breast Disorders																						
Ovarian Cyst Ruptured										1											0	1 (1%)

PR = Possibly or Probably Related to drug, NR = Not Related to drug, in the opinion of the investigator prior to breaking blind

** Percentages were calculated based on number of subjects experiencing the AE (each subject receives between two and six experimental sessions, depending on the study protocol and their condition assignment)

21.0 Appendix E: Commonly Reported Adverse Events (Spontaneously Reported Reactions)

Table 9: Severe Spontaneously Reported Reactions (reported during and 7 days after Experimental Sessions) by Dose Within the Reporting Period

(Based on preliminary data received from the sites for ongoing studies)

Study	Dose (mg)	Subject #	Preferred Term	Date Last Drug Admin	Onset Date at Any Severity	Resolution Date at Any Severity	Number of Days Severe	Serious	Frequency
MP-4	0	4002	Anxiety	18-Mar-2015	19-Mar-2015	25-Mar-2015	1	No	Intermittent
MP-4	0	4002	Hyperhidrosis	18-Mar-2015	19-Mar-2015	20-Mar-2015	1	No	Continuous
MP-4	125	4002	Judgment Impaired	22-May-2015	24-May-2015	29-May-2015	1	No	Intermittent
MP-4	125	4002	Depressed Mood	22-May-2015	24-May-2015	27-May-2015	1	No	Continuous
MP-4	0	4004	Insomnia	24-Mar-2015	25-Mar-2015	29-Mar-2015	1	No	Continuous
MP-4	125	4005	Muscle Tightness (jaw)	26-Jun-2015	26-Jun-2015	27-Jun-2015	1	No	Continuous
MP-4	125	4005	Depressed Mood	26-Jun-2015	28-Jun-2015	3-Jul-2015	3	No	Continuous
MP-4	125	4005	Obsessive Rumination	26-Jun-2015	28-Jun-2015	3-Jul-2015	3	No	Continuous
MP-4	125	4005	Headache	18-Jul-2015	18-Jul-2015	31-Jul-2015	1	No	Intermittent
MP-4	125	4005	Muscle Tightness (jaw)	18-Jul-2015	18-Jul-2015	7-Aug-2015	1	No	Intermittent
MP-4	125	4005	Restlessness	18-Jul-2015	20-Jul-2015	7-Aug-2015	2	No	Continuous
MP-4	125	4005	Muscle Tightness	18-Jul-2015	18-Jul-2015	7-Aug-2015	2	No	Continuous
MP-4	125	4005	Headache	14-Aug-2015	14-Aug-2015	20-Aug-2015	1	No	Intermittent
MP-4	125	4005	Feeling Cold	14-Aug-2015	14-Aug-2015	21-Aug-2015	1	No	Intermittent
MP-4	125	4005	Insomnia	14-Aug-2015	15-Aug-2015	10-Sep-2015	1	No	Intermittent
MP-4	125	4005	Nausea	14-Aug-2015	14-Aug-2015	18-Aug-2015	2	No	Intermittent
MP-4	125	4005	Parasthesia	14-Aug-2015	17-Aug-2015	19-Aug-2015	1	No	Intermittent
MP-4	125	4006	Nausea	3-Jul-2015	3-Jul-2015	10-Jul-2015	1	No	Intermittent
MP-9	125	9007	Dizziness	27-Aug-2015	27-Aug-2015	29-Aug-2015	1	No	Continuous
MP-9	125	9007	Insomnia	27-Aug-2015	28-Aug-2015	31-Aug-2015	1	No	Intermittent
MP-9	125	9007	Anxiety	17-Sep-2015	17-Sep-2015	23-Sep-2015	2	No	Intermittent
MP-9	125	9007	Depressed Mood	17-Sep-2015	19-Sep-2015	23-Sep-2015	1	No	Intermittent
MP-9	125	9007	Muscle Tightness	17-Sep-2015	17-Sep-2015	22-Sep-2015	1	No	Intermittent
MP-9	125	9007	Restlessness	17-Sep-2015	17-Sep-2015	23-Sep-2015	1	No	Intermittent
MP-9	125	9007	Asthenia	17-Sep-2015	20-Sep-2015	23-Sep-2015	2	No	Intermittent
MP-9	125	9007	Irritability	17-Sep-2015	17-Sep-2015	23-Sep-2015	1	No	Intermittent

Study	Dose (mg)	Subject #	Preferred Term	Date Last Drug Admin	Onset Date at Any Severity	Resolution Date at Any Severity	Number of Days Severe	Serious	Frequency
MP-9	125	9007	Decreased Appetite	17-Sep-2015	17-Sep-2015	23-Sep-2015	1	No	Intermittent
MP-12	100	12013	Depressed Mood	12-Oct-2014	13-Oct-2014	14-Oct-2014	1	No	Continuous
MP-12	125	12017	Anxiety	2-Jan-2015	2-Jan-2015	8-Jan-2015	1	No	Intermittent
MP-12	100	12019	Depressed Mood	6-Feb-2015	6-Feb-2015	15-Feb-2015	1	No	Intermittent
MP-12	125	12020	Diarrhea	10-Apr-2015	12-Apr-2015	14-Apr-2015	1	No	Intermittent
MP-12	125	12021	Anxiety	22-Mar-2015	24-Mar-2015	29-Mar-2015	1	No	Continuous
MP-12	125	12022	Anxiety	26-Jun-2015	29-Jun-2015	4-Jul2015	1	No	Intermittent
MP-12	125	12024	Dizziness	10-Jul-2015	10-Jul-2015	10-Jul-2015	1	No	Continuous
MP-12	125	12025	Anxiety	14-Aug-2015	14-Aug-2015	19-Aug-2015	1	No	Continuous
MP-12	125	12025	Anxiety	16-Sep-2015	16-Sep-2015	22-Sep-2015	1	No	Intermittent
MDA-1	125	51003	Diarrhea	24-Aug-2015	26-Aug-2015	29-Aug-2015	1	No	Intermittent

Table 10: Cumulative Frequency of Severe Spontaneously Reported Reactions Reported During and 7 days after Experimental Sessions by Dose

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

MDMA Dose	0 mg	25 mg	30 mg	40 mg	75 mg	100 mg	125 mg	150 mg
Number of Subjects	14	10	7	7	13	25	100	3
Number of Experimental Sessions*	27	22	15	12	20	42	240	4
Psychiatric								
Anxiety	6 (22%)	0	1(7%)	0	1(5%)	4 (10%)	24 (10%)	0
Depressed Mood	0	0	0	0	0	3 (7%)	9 (4%)	0
Insomnia	1 (4%)	4 (18%)	1 (7%)	1 (8%)	0	0	11 (5%)	2 (50%)
Obsessive Rumination	0	0	0	0	0	1 (2%)	1 (0.4%)	0
Restlessness	0	0	0	0	0	1 (2%)	3 (1%)	0
Irritability	0	0	0	0	0	1 (2%)	4 (2%)	0
Nervous System								
Headache	0	0	0	0	0	0	4 (2%)	0
Disturbance in Attention	0	0	0	0	0	0	1 (0.4%)	0
Dizziness	0	0	0	0	0	0	2 (1%)	0
Parasthesia	0	0	0	0	0	0	1 (0.4%)	0
Judgment Impaired	0	0	0	0	0	0	1 (0.4%)	0
Hypersomnia	0	1 (5%)	1 (7%)	0	0	0	0	0
Gastrointestinal System								
Nausea	0	0	0	0	0	0	9 (4%)	0
Diarrhea	0	0	0	0	0	0	2 (1%)	0
General								
Fatigue	1 (4%)	1 (5%)	0	0	0	0	13 (5%)	1 (25%)
Asthenia	0	0	0	0	0	0	1 (0.4%)	0
Feeling Cold	0	0	0	0	0	0	1 (0.4%)	0
Musculoskeletal & Connective Tissue								
Muscle Tightness	0	0	0	0	0	1(2%)	11 (5%)	2 (50%)
(jaw)	0	0	0	0	0	1(2%)	7 (3%)	2 (50%)
Metabolism and Nutrition								
Decreased Appetite	0	1(5%)	0	0	0	0	5 (2%)	0
Skin and Subcutaneous Tissue								
Hyperhidrosis	1 (4%)	0	0	0	0	0	0	0

* Reactions are collected on the day of and 7 days after each experimental session (percentages are calculated based on number of experimental sessions completed by initial MDMA dose during the studies)

22.0 Appendix F: Deaths

Table 11: All Studies Cumulative Deaths

(Based on final data received from the sites)

Study	Dose	Subject #	Adverse Event	Date Last Drug Admin	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relation-ship to Drug
MP-2	125 mg	0101	Brain meta-stasis (frontal brain syn-drome)	04-Jan-2007	31-May-2007	18-Jul-2007	Yes	Continuous	Removed from Study	Hospital-ization	None	Death	None