Multidisciplinary Association for Psychedelic Studies (MAPS)

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Table 1: Summary of Clinical Trials

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	Relevant Product	Status During Reporting Period
MP-1	Safety and Efficacy of MDMA-assisted Psychotherapy in Subjects with Chronic PTSD	2	US	Males and females with PTSD aged 18 to 70	21 planned	8- Inactive placebo during 2 blinded experimental sessions, followed by open label crossover of 2-3 experimental sessions with full dose MDMA, followed 1.5-2.5 hrs later by optional half dose 13- Full dose 125 mg MDMA followed 2-2.5 hrs later by optional 62.5 mg dose during 2 blinded experimental sessions, followed by one additional open label experimental session with full dose MDMA, followed 1.5-2.5 hrs later by optional half dose	Complete
MP-2	Safety and Efficacy of MDMA-assisted Psychotherapy in Subjects with Treatment-resistant PTSD	2	Switzerland	Males and females with PTSD over the age of 18	12 planned	4- Active placebo 25 mg MDMA followed 2-2.5 hrs later by optional 12.5 mg dose during 3 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with full dose MDMA, followed 1.5-2.5 hrs later by optional half dose 8- Full dose 125 mg of MDMA followed 2.5 hrs later by optional 62.5 mg dose during 3 experimental sessions.	Complete

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	Relevant Product	Status During Reporting Period
MP-3	Safety and Efficacy of MDMA-assisted Psychotherapy in Subjects with PTSD	2	Israel	Males and females with PTSD over the age of 18	12 planned	4- Active placebo 25 mg MDMA followed 2-2.5 hrs later by optional 12.5 mg dose, followed by open label crossover of 2 experimental sessions with full dose MDMA, followed 1.5-2.5 hrs later by optional half dose 8- Full dose 125 mg of MDMA followed 2.5 hrs later by optional 62.5 mg dose during 2 experimental sessions.	Study Terminated after 5 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	Males and female Canadian residents with PTSD over the age of 21	12 planned	5- XXX followed 1.5-2.5 hrs later by optional supplemental half dose in 2 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with active dose of 100 or 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 7- Full dose 125 mg of MDMA followed 1.5-2.5 hrs later by optional 62.5 mg dose in 2 blinded experimental sessions, followed by a third open label experimental session with same dose	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	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	Male and female veterans, firefighters or police officers with PTSD over the age of 18	24 planned	6- Low dose 30 mg MDMA followed 1.5-2.5 hrs later by optional 15 mg dose in 2 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with active dose of 100 or 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 6- Medium dose 75 mg MDMA followed 1.5-2.5 hrs later by optional 37.5 mg dose in 2 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with active dose of 100 or 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 12- Full dose 125 mg of MDMA followed 1.5-2.5 hrs later by optional 62.5 mg dose in 2 blinded experimental sessions, followed by a third open label experimental session with same dose	Recruiting
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	Males and females with PTSD over the age of 18	10 planned	3- Active placebo 25 mg MDMA followed 1.5-2.5 hrs later by optional 12.5 mg dose in 2 blinded experimental sessions, followed by open label crossover of 2 experimental sessions with full dose MDMA, followed 1.5-2.5 hrs later by optional half dose 7- Full dose 125 mg of MDMA followed 1.5-2.5 hrs later by optional 62.5 mg dose during 2 blinded experimental sessions.	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	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	Males and females with PTSD over the age of 18	23 planned	5-Comparator dose followed 1.5-2.5 hrs later by optional half dose in 2 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with active dose of 100 or 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 9-Active dose 2 followed 1.5-2.5 hrs later by optional half dose in 2 blinded experimental sessions, followed by a third open label experimental session with active dose of 100 or 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 9- Active dose 1 followed 1.5-2.5 hrs later by optional half dose in 2 blinded experimental sessions, followed by a third open label experimental session with same dose	Recruiting
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	20- Full dose 125 mg of MDMA followed 1.5-2.5 hrs later by optional 62.5 mg dose, or inactive placebo crossover during 2 experimental sessions in randomized order	Recruiting

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	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	Males and Females on the autism spectrum with social anxiety over the age of 21	12 planned	4- Active dose 75 mg MDMA in one blinded experimental session, escalating to 100mg MDMA in second blinded experimental session 4- Active dose 100mg MDMA in one blinded experimental session, escalating to 125 mg MDMA in second blinded experimental session 4- Inactive placebo in 2 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	Recruiting
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	Males and females with significant anxiety related to a life-threatening illness over the age of 18	18 planned	5- Inactive placebo followed 1.5-2.5 hrs later by optional placebo dose in 2 blinded experimental sessions, followed by open label crossover of 3 experimental sessions with active dose of 125mg MDMA, followed 1.5-2.5 hrs later by optional half dose 18- Full dose 125 mg of MDMA followed 1.5-2.5 hrs later by optional 62.5 mg dose in 2 blinded experimental sessions, followed by a third open label experimental session with same dose	Initiation pending DEA approval

Protocol	Study Title	Phase	Country	Subject Population	# of Subjects Planned	Relevant Product	Status During Reporting Period
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 Posttraumatic Stress Disorder (PTSD)	2	US	Subjects who completed MP-1 and relapsed after initial improvement	Up to 3 planned	3- Full dose 125 mg of MDMA followed 1.5- 2.5 hours later by optional 62.5mg dose, during one open label experimental session .	Complete

1.0 EXECUTIVE SUMMARY

This is the seventh annual report submitted by the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization that is sponsoring clinical trials of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for chronic psychiatric disorders such as Posttraumatic Stress Disorder (PTSD) and social anxiety related to autism conducted under U.S. IND #63,384. This report covers the period from October 2, 2013 through October 1, 2014. There were no MAPS-sponsored studies for MDMA conducted that were not under U.S.-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 class that produces anxiolytic and prosocial effects by release of monoaminergic neurotransmitters through reuptake inhibition 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. 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 12.5mg to 150mg, compounded with alpha-lactose, and administered orally. Due to a wide range of responses to identical milligram per kilogram (mg/kg) dosing between individuals, possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses that are equivalent to between 1 and 2 mg/kg (active doses ranging from 125mg to 187.5mg with supplemental dosing) to achieve a more consistent response between subjects.

Unexpected and expected Serious Adverse Events (SAEs) involving administration of MDMA in MAPS-sponsored clinical trials have been rare and non-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 after moderate exercise. During the reporting period, no SAEs were reported to the sponsor. Prior to the reporting period, one probably drug-related expected SAE was reported to the sponsor, that was an increase in frequency of premature ventricular contractions experienced during treatment, which resolved with full recovery to baseline after the study drug's effects ceased. No acute cardiac damage occurred and hospitalization during this SAE was a cautionary measure. As of the reporting period, there have been 94 people exposed to MDMA and a total of 259 exposures in MAPS-sponsored studies conducted under US-IND. As of the reporting period, MDMA has been administered to over 1133 individuals for research purposes in studies sponsored by MAPS or otherwise without the occurrence 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 uncontrolled hypertension and by monitoring blood pressure, body temperature, and pulse. 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 3-4 days post-treatment, most reactions diminish. Reactions are monitored daily for a week after each treatment and followed until resolution. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, impaired gait or balance, dry mouth, ruminations, muscle tension and thirst. Less common reactions include restlessness, parasthesias, impaired judgment, perspiration, drowsiness, and nystagmus. While anxiety, headache, fatigue, insomnia and lack of appetite were reported by more than half the subjects in both placebo and MDMA conditions in MAPS study MP-1 and MP-2 (N=37), restlessness, tight jaw, and sensitivity to cold were more often reported by subjects in the 125mg MDMA condition. During the week following each experimental session, the most commonly reported reactions were fatigue, insomnia, low mood, anxiety, and difficulty concentrating in the 125mg dose groups across studies. 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 comparable or better results than other medications that require daily dosing. 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 a medicine used 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 August 1, 2013, has been submitted to FDA. No significant safety-related changes were made in this revision.

5.0 INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

The following is a cumulative listing of all studies using MDMA under MAPS' US IND # 63,384 in Table 1: Summary of Clinical Trials.

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 four 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: March 30, 2004

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

Subject Population: Males and females 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:	21
Number of Subjects Enrolled and Treated:	23
Number of Subjects Dropped Treatment:	2
Number of Subjects Completed Experimental Sessions:	21
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	1
Number of Subjects Completed Follow-up:	20

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 protocol is for a randomized, double-blind, active placebo-controlled study of the safety and efficacy of MDMA-assisted psychotherapy in patients with treatment-resistant 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: July 18, 2007

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

Subject Population: Males and females 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:	12
Number of Subjects Enrolled and Treated:	14
Number of Subjects Dropped Treatment:	2
Number of Subjects Completed Experimental Sessions:	12
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	2
Number of Subjects Completed Follow-up:	10

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: MDMA-assisted Psychotherapy in people with Posttraumatic Stress Disorder (PTSD)

Purpose: This protocol is designed to demonstrate that the use of MDMA-assisted psychotherapy in people with treatment-resistant PTSD is well-tolerated and will not produce serious adverse effects in this population.

First Subject First Visit: January 15, 2008

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

Subject Population: Males and females 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:	12
Number of Subjects Enrolled and Treated:	5
Number of Subjects Dropped Treatment:	1
Number of Subjects Completed Experimental Sessions:	4
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	1
Number of Subjects Completed Follow-up:	3

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, Double-Blind, Controlled Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-resistant Posttraumatic Stress Disorder (PTSD)-Canada

Purpose: This protocol 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: Pending medication tapering

Amendments During the Reporting Period: The protocol was amended twice during the reporting period. Amendment #2, Version 1, dated February 4, 2014: Approved by IRB of record on February 14, 2014, approved by Health Canada on March 14, 2014, submitted to FDA on February 6, 2014. This amendment revised the study design from a dose comparison study to a XXX study by replacing the XXX active placebo control with XXX as a comparator.

Amendment #2, Version 3, dated June 20, 2014: Approved by IRB of record on July 4, 2014, submitted to Health Canada on July 2, 2014, submitted to FDA on July 9, 2014. This administrative amendment included addition of a sub-investigator and co-therapist as a second therapist team, allowance for telemedicine visits, clarification of visit windows and medication tapering procedures for opiates taken for pain management.

Subject Population: Males and females 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:	12
Number of Subjects Enrolled and Treated:	0
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	0
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	0

Demographics: Enrollment started after the reporting period.

Status: First subject enrolled after reporting period on December 3, 2014, recruitment is ongoing.

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: December 15, 2010

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

Subject Population: Male and female 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:	24
Number of Subjects Enrolled and Treated:	22
Number of Subjects Dropped Treatment:	2
Number of Subjects Completed Experimental Sessions:	18
Number of Subjects in Follow-up:	4
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	13

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-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 2 subjects in order to standardize the psychotherapeutic approach based on the Treatment Manual under development for this experimental treatment.

First Subject First Visit: March 27, 2013

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

Subject Population: Males and females 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:	10
Number of Subjects Enrolled and Treated:	4
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	4
Number of Subjects in Follow-up:	2
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	2

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: June 12, 2013

Amendments During the Reporting Period: The protocol was amended twice during the reporting period. Amendment #4, Version 1, dated April 27, 2014 approved by IRB of record May 6, 2014, submitted to FDA on May 1, 2014. This amendment includes an expansion of the number of subjects to be treated from 17 to 23, clarification about the baseline CAPS measure, and clarification about reproductive risks as described in the IB.

Amendment #5, Version 1, dated August 19, 2014, approved by IRB of record August 29, 2014, and submitted to FDA on August 28, 2014. This amendment includes allows Stage 1 subjects who received Active Dose 2 during their first two experimental sessions in Stage 1 to receive either 100mg or 125mg MDMA plus an optional half dose in their third, open label experimental session.

Subject Population: Males and females 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:	23
Number of Subjects Enrolled and Treated:	14
Number of Subjects Dropped Treatment:	2
Number of Subjects Completed Experimental Sessions:	10
Number of Subjects in Follow-up:	10
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	1

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 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: April 21, 2011

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

Subject Population: Healthy males and females 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:	20
Number of Subjects Enrolled and Treated:	7
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	7
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	7

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 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: This protocol will investigate the effects of an additional MDMA-assisted psychotherapy session with associated preparatory 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: January 20, 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:	Up to 3
Number of Subjects Enrolled and Treated:	3
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	3
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	3

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 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: April 11, 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 two 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:	12
Number of Subjects Enrolled and Treated:	3
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	2
Number of Subjects in Follow-up:	2
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	0

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: No subjects have been enrolled.

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

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. Males and females over the age of 18 are eligible to be enrolled.

Number of Subjects Planned:	18
Number of Subjects Enrolled and Treated:	0
Number of Subjects Dropped Treatment:	0
Number of Subjects Completed Experimental Sessions:	0
Number of Subjects in Follow-up:	0
Number of Subjects Dropped Follow-up:	0
Number of Subjects Completed Follow-up:	0

Demographics: No subjects have been enrolled.

Status: Study initiation is pending approval from DEA.

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
MP1	2	USA	PTSD	21	22*
MP2	2	Switzerland	PTSD	12	14
MP3	2	Israel	PTSD	12	5
MP4	2	Canada	PTSD	12	0
MP8	2	USA	PTSD	24	22
MP9	2	Israel	PTSD	10	4
MP12	2	USA	PTSD	23	16
MT1	1	USA	Healthy Volunteer	20	7**
MAA1	2	USA	Autistics with Social Anxiety	12	4
MDA1	2	USA	Anxiety related to life-threatening illness	18	0
Total					**94**

In MAPS-sponsored studies other than MP1 and MT1, subjects receive either an active dose or a low dose of MDMA. So all subjects who are enrolled and treated have been exposed to the investigational product.
*In MP1, 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 MP1, due to a strong and sustained placebo response.
**In MT1, subjects receive either MDMA or an inactive placebo in a blinded randomized crossover, so all subjects ultimately 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)

No new SAEs occurred during the reporting period.

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, 31 subjects were treated in five studies under this IND. During this period, five severe Adverse Events were reported that were judged to be possibly or probably related to the study drug. Seven severe AEs (anxiety (3), low mood (2), restlessness (1), and ruminations (1)) occurred. Two severe AEs of anxiety were judged unrelated to study drug and resolved with complete recovery to baseline after treatment with therapy and prescription medication. One severe AE of low mood in subject 12008 was judged probably related to study drug, and after one day decreased to moderate severity and resolved with recovery to baseline after resuming therapy for almost two months. This subject had a medical history of dysthymia comorbid with PTSD and had received therapy for treatment pre-study. The remaining four severe AEs (restlessness, anxiety, low mood, ruminations) judged possibly related to study drug all occurred in the same subject (12012), who had a medical history of attachment disorder. None of these severe AEs were considered SAEs (See Section 7.1.1). Of these seven severe AEs, six were treated with additional therapy, one was treated with medications and none resulted in hospitalization (Please see Appendix C).

AEs expected to occur on the day of and 7 days after the experimental session were collected as Spontaneously Reported Reactions (Please see Appendix E). These reactions were initially compiled from the literature in a healthy volunteer population. During the reporting period, seven severe spontaneously reported reactions were reported. These reactions all persisted beyond seven days and were reported as unexpected AEs described above.

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. MP-12 subject 12008 chose to discontinue treatment due to difficulty tolerating the emotional content of his treatment sessions. The subject chose to resume pre-study therapy, did not complete an exit CAPS assessment, and does not plan to return for the 12-month follow-up visit. MP-12 subject 12015 did not start treatment because she became pregnant prior to receiving any drug administration.

Table 3: Summary of Treatment Dropouts*

Study Number	Investigator	Subject Number	Reason for Not Completing Treatment	Condition Assignment	Outcome	Relationship to Study Drug
MP-12	Marcela Ot'alora G.	12008	Emotional Distress	UNK	In Follow-up	Possibly Related
MP-12	Marcela Ot'alora G.	12015	Pregnancy	No treatment	In Follow-up	Not related

* Based on preliminary data received from the sites.

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 unexpected AEs and found the most frequent severe AEs to be anxiety or distress (N=5, 6% of subjects), depressed mood (N=4, 5% of subjects), panic attacks (N=2, 3% of subjects), restlessness (N=2, 3% of subjects), and ruminative cognition (N=2, 3% of subjects) (Please see Appendix D). These 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 expected to occur 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. Since seven severe reactions were reported to the sponsor during this reporting period, the sponsor's cumulative analysis of these results across completed and ongoing studies of MDMA-assisted psychotherapy for PTSD subjects has remained consistent with reports from the previous year, with prevalence slightly decreasing overall due to more and more treatments being completed. Based on reactions that were observed in these studies, the sponsor intends to hone in on an accurate list of side effects for the PTSD subject population. 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 125mg MDMA during the open label crossover. The most frequently reported severe reactions related to 168 experimental sessions with 125mg MDMA were anxiety (N=15, 9%), fatigue (N=12, 7%) and insomnia (N=9, 5%). The highest dose group of 150 mg MDMA was only administered during 4 experimental sessions and was associated with reports of insomnia (N=2), muscle tightness (tight jaw) (N=2), and fatigue (N=1). The 25 mg MDMA dose was only administered during 15 experimental sessions and was associated with reports of insomnia (N=3), fatigue (N=1) and lack of appetite (N=1). In comparison, subjects who received an inactive placebo in 16 experimental sessions reported anxiety (N=5) and fatigue (N=1). In studies where the active placebo is a low dose of MDMA, differences between groups are attributed to differences in MDMA dose received, and similarities between groups are attributed to MDMA-assisted psychotherapy. Taking into consideration that the 125mg MDMA dose has been administered by far the most frequently, the sponsor concludes that the spontaneously reported reactions are comparable between the various dose groups that have been administered to date in these studies.

Any reactions that continued beyond the 7-day window were tracked as unexpected AEs. In all studies to date, 11 severe reactions lasted beyond the 7-day window: insomnia (N=1, duration 12 days), anxiety (N=5, maximum duration 53 days), restlessness (N=1, duration 3 days), ruminations (N=1, duration 4 days) and low mood (N=3, maximum duration 51 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.

While full dose MDMA was associated with more severe expected reactions overall (N=57), these reactions were self-limiting and generally did not persist beyond the 7-day window after experimental sessions. The higher number of subjects receiving this dose in open-label experimental sessions also creates more opportunity to report reactions.

The 125 mg dose, alone or followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hours later, is expected to produce significant but transient, self-limited increases in systolic blood pressure and heart rate. Systolic blood pressure above the cut-off of 160 mmHg was detected in 25% (68 out of 273) experimental sessions where MDMA was administered at any dose, in 40% (38 of 95) of subjects in sponsor-supported trials. Maximum duration above systolic blood pressure cut-off was six hours in two separate subjects with respective peak values of 172 and 174, where 125mg MDMA was administered as the initial dose. Diastolic blood pressure exceeded the cut-off of 110 mmHg in only 2% (7 out of 273) of experimental sessions with MDMA in 6% (6 of 92) of

subjects. Maximum duration above diastolic blood pressure cut-off was five hours in one subject, with a peak of 114. In contrast, 8 subjects receiving 16 experimental sessions total did not experience any elevations in blood pressure above cut-off. Heart rate elevation above the cut-off of 110 BPM was detected in 30% (81 out of 273) experimental sessions where MDMA was administered at any dose, in 41% (39 of 95) of subjects in sponsor-supported trials. Maximum peak pulse was 156 BPM reported in a subject who received 125 mg MDMA, with pulse returning to 97 BPM during final measurement. The same subject had maximum duration of approximately six hours (367 minutes). Both blood pressure and heart rate above cut-off were monitored more frequently and returned to baseline without medical intervention. No subjects receiving MDMA in sponsor-supported clinical trials have required any clinical interventions for elevated blood pressure or pulse, and all values returned to normal as the effects of MDMA diminished.

14.2 Benefit-Risk Considerations

Data from completed studies of MDMA-assisted psychotherapy in people with chronic, treatment resistant PTSD 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 in MAPS studies and 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 BP and pulse only if clinically indicated. Rigorous screening would 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 studies to date, MDMA does not produce greater psychological distress than placebo. Nor did MDMA did adversely affect cognitive function. Scores on an established measure of PTSD symptoms declined to a statistically and clinically significant degree following MDMA-assisted psychotherapy in MP-1 (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. 2012). Results from MP-2 (N=12) comparing 125mg to 25mg MDMA as an active placebo 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 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). No new SAEs have been reported in MAPS-sponsored studies during the current reporting period. 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 at baseline, and by monitoring blood pressure and pulse during experimental sessions. In the first two MAPS-sponsored studies (MP-1 and MP-2) BP and pulse always returned to baseline spontaneously without requiring medical intervention. In a current, nearly completed study (MP-8), frequent vital sign measurements are taken, but during blinded MDMA-assisted sessions for subjects without a history of hypertension the investigators are blinded to all BP and pulse measurements except at baseline. In these sessions there has never been a need to break this blind for medical reasons. Based on these results, in future studies it may 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 next week. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, impaired gait or balance, dry mouth, ruminations, muscle tension and thirst. 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 to obtain approval for the prescription use of MDMA-assisted psychotherapy in patients with chronic, treatment-resistant PTSD. MAPS and investigators 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. 2012, Oehen et al. 2012). MAPS is currently sponsoring two US-based Phase 2 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 a study in Israel (MP-9) and a study in Vancouver, BC (MP-4) also treating individuals with chronic, treatment-resistant PTSD. 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. MAPS recently obtained FDA and IRB approval to sponsor 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 sizes 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	**Number of Subjects**		
Inactive placebo	8		
25mg MDMA	8		
30mg MDMA	5		
40mg MDMA	4		
75mg MDMA	6		
100mg MDMA	4		
125mg MDMA	53		
Unknown (still blinded)	7		
Total	95		
	Number of Subjects		
Age Range	Male	Female	Total
20-29	9	7	16
30-39	15	16	31
40-49	10	19	29
50-59	6	8	14
60-69	1	4	5
Racial Group	**Number of Subjects**		
Asian	0		
Black	0		
Caucasian	87		
Middle Eastern	3		
Hispanic/Latino	2		
Native American	1		
Other	2		
Total	95		

18.0 APPENDIX B: Serious Adverse Events

Table 5: All Studies Cumulative Serious Adverse Reactions
(Based on final data from completed studies and preliminary data from ongoing studies received from the sites)

Study	Subject Number	Country Gender Age	Adverse Event Preferred Term*	Onset Date Onset Time	Resolution Date	Severity	Outcome	Suspect Drug	Daily Dose Route Formulation	Dates of Treatment Duration of Treatment
MP-8	0811	U.S. MALE 46	Increase in Ventricular Extrasystoles	08-Mar-13 1 hr 17 min post-drug	09-Mar-13	Moderate	Full recovery/ return to baseline	125mg MDMA	30mg + 15mg 30mg + 15mg 30mg (no suppl) 125mg +62.5mg 125mg (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 final data from completed studies and preliminary data from ongoing studies received from the sites)

System Organ Class Preferred Term*	125mg MDMA	30mg MDMA	Before dosing
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		
Psychiatric Disorders			
Suicidal ideation	1	1	
Major depressive episode	1		
Cardiac Disorders			
Increase in Ventricular Extrasystoles	1		

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

19.0 APPENDIX C: Severe Adverse Events

Table 7: All Studies Severe Adverse Events Within the Reporting Period
(Based on preliminary data received from the sites)

Study	Dose	Subject Number	Adverse Event Preferred Term	Date Last MDMA Admin.	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-12	125mg	12003	Anxiety	4-Oct-13	05-Oct-13	11-Oct-13	No	Continuous	None	Therapy	None	Full recovery	Not related
MP-12	125mg	12003	Anxiety	13-Dec-13	16-Dec-13	17-Dec-13	No	Continuous	None	Prescription Medication	None	Full recovery	Not related
MP-12	UNK	12008	Low Mood	2-May-14	7-May-14	27-Jun-14	No	Continuous	None	Therapy	None	Resolved back to baseline	Probably related
MP-12	100mg	12012	Restlessness	6-Jul-14	8-Jul-14	16-Jul-14	No	Continuous	None	Therapy	None	Resolved back to baseline	Possibly related
MP-12	100mg	12012	Ruminations	6-Jul-14	8-Jul-14	16-Jul-14	No	Continuous	None	Therapy	None	Resolved back to baseline	Possibly related
MP-12	100mg	12012	Anxiety	25-Jul-14	28-Jul-14	21-Sep-14	No	Continuous	None	Therapy	None	Resolved back to baseline	Possibly related
MP-12	100mg	12012	Low Mood	25-Jul-14	28-Jul-14	21-Sep-14	No	Continuous	None	Therapy	None	Resolved back to baseline	Possibly related

20.0 APPENDIX D: Severe Adverse Events by Relatedness

Table 8: Cumulative Frequency of Severe Adverse Events by Relatedness

(Based on final CRFs collected from sites and analyzed from the sponsor database listings for completed studies, and preliminary data for ongoing studies)

Adverse Event	**MP-1**		**MP-2**		**MP-8**		**MP-9**		**MP-12**		**MP1-E2**		**Total**	
Number of Subjects	23		14		22		4		14		3		80**	
Number of Experimental Sessions	67		52		84		8		39		3		253	
Relatedness	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(3%)	0
Major depressive episode		1				1							0	2(3%)
Depressed mood									4				4(5%)	
Ruminative cognition									2				2(3%)	
Anxiety, distress			2		1				2	4			5(6%)	4(5%)
Insomnia				2									0	2(3%)
Agoraphobia		1											0	1(1%)
Suicidal thoughts						1						1	0	2(3%)
Nervous System														
Headache			1										1(1%)	0
Sciatica		1											0	1(1%)
Gastrointestinal				1										
Abdominal Cramps/Pain										1			0	2(3%)
General														
Benzodiazepine withdrawal		1											0	1(1%)
Restlessness									2				2(3%)	
Body Pain				1									0	1(1%)
Musculoskeletal & Connective Tissue														
Musculoskeletal chest pain	1												1(1%)	0
Infections and Infestations														
Sinusitis		1											0	1(1%)
Neoplasms				1										
Brain metastasis													0	1(1%)

** Note: PR = Possibly or Probably Related to drug, NR = Not Related to drug, in the opinion of the investigator prior to breaking blind.*
*** Note: Percentages were calculated based on number of subjects experiencing the AE. Each subject receives between 2 and 6 experimental sessions, depending on the study protocol and their condition assignment.*

21.0 APPENDIX E: Expected Adverse Events (Spontaneously Reported Reactions)

Table 9: Severe Spontaneously Reported Reactions Reported on the Day of the Experimental Session and 7 Days Post in MDMA-assisted Psychotherapy Studies by Dose During the Reporting Period
(Based on preliminary data for ongoing studies)

Study	Dose	Subject Number	Diagnosis	Date Last Drug Admin.	Onset Date	Date stopped being severe	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Outcome
MP-12	125mg	12003	Anxiety	4-Oct-13	05-Oct-13	9-Oct-13	11-Oct-13	No	Continuous	None	Therapy	Full recovery
MP-12	125mg	12003	Anxiety	13-Dec-13	16-Dec-13	16-Dec-13	17-Dec-13	No	Continuous	None	Prescription Medication	Full recovery
MP-12	UNK	12008	Low Mood	2-May-14	7-May-14	8-May-14	27-Jun-14	No	Continuous	None	Therapy	Resolved back to baseline
MP-12	100mg	12012	Restlessness	6-Jul-14	8-Jul-14	11-Jul-14	16-Jul-14	No	Continuous	None	Therapy	Resolved back to baseline
MP-12	100mg	12012	Ruminations	6-Jul-14	8-Jul-14	12-Jul-14	16-Jul-14	No	Continuous	None	Therapy	Resolved back to baseline
MP-12	100mg	12012	Anxiety	25-Jul-14	28-Jul-14	31-Jul-14	21-Sep-14	No	Continuous	None	Therapy	Resolved back to baseline
MP-12	100mg	12012	Low Mood	-Jul-14	28-Jul-14	31-Jul-14	21-Sep-14	No	Continuous	None	Therapy	Resolved back to baseline

Table 10: Cumulative Frequency of Severe Spontaneously Reported Reactions Reported During and 7 Days After Blinded and Open Label Experimental Sessions by Dose
(Based on final CRFs collected from sites and analyzed from the sponsor database listings for completed studies and preliminary data from ongoing studies)

MDMA Dose (mg)	**UNK**	**0**	**25**	**30**	**75**	**100**	**125**	**150**
Number of Subjects	**2**	**8**	**6**	**5**	**6**	**5**	**43**	**3**
Number of Experimental Sessions*	**2**	**16**	**15**	**12**	**12**	**13**	**168**	**4**
Psychiatric								
Anxiety	0	5(31%)	0	0	0	2 (15%)	15(9%)	0
Low Mood	1(50%)	0	0	0	0	1(8%)	4(2%)	0
Insomnia	0	0	3(20%)	0	0	0	9(5%)	2(50%)
Ruminations	0	0	0	0	0	1(8%)		
Restlessness	0	0	0	0	0	1(8%)	1(1%)	0
Nervous System								
Headache	0	0	0	0	0	0	2(1%)	0
Disturbance in attention	0	0	0	0	0	0	1(1%)	0
Gastrointestinal System								
Nausea	0	0	0	0	0	0	5(3%)	0
General								
Fatigue	0	1(6%)	1(7%)	0	0	0	12(7%)	1(25%)
Musculoskeletal & Connective Tissue								
Muscle tightness (jaw)	0	0	0	0	0	0	4(2%)	2(50%)
Metabolism and Nutrition								
Lack of appetite	0	0	1(7%)	0	0	0	4(2%)	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 Number	Adverse Event Diagnosis	Date Last MDMA Admin.	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-2	125mg MDMA	0101	Brain metastasis (frontal brain syndrome)	4-Jan-07	31-May-07	18-Jul-07	Y	Continuous	Removed from study	Hospital-ization	None	Death	None