FINAL CLINICAL STUDY REPORT

Protocol #: MP- 2

IND #: 63,384

September 15, 2011

First Subject First Visit: July 18, 2006

Last Subject Last Visit: January 10, 2011

Phase Two Pilot Study:
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in Patients with Treatment-resistant Posttraumatic Stress Disorder (PTSD)

A randomized, single-center, active placebo-controlled, double-blind, partial crossover study comparing response to psychotherapy assisted by 25mg or 125 mg MDMA.

A study performed in accordance with the principles of Good Clinical Practice as described in International Conference of Harmonization guidelines, including the archiving of essential documents.

SPONSOR

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1.0 SYNOPSIS

Name of Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Name of Investigational Product: 3,4-methylenedioxymethamphetamine (MDMA)
Name of Active Ingredient: 3,4-methylenedioxymethamphetamine (MDMA)
Title of Study: MDMA-Assisted Psychotherapy in Patients with Treatment-resistant Posttraumatic Stress Disorder (PTSD)
Protocol Number: MP-2
Investigators: Dr. med. Peter Oehen (Principal Investigator), Verena Widmer (Co-investigator), Dr. med. Rafael Traber (Independent Rater)
Study Center: Ulmenweg 24a, 4562 Biberist, Switzerland
Publication (reference): In preparation

Study Period: First Subject First Visit: July 18, 2006 Last Subject Last Visit: January 10, 2011	**Phase of Development:** Phase 2

Objectives:

The primary objective of this study was to evaluate changes in PTSD symptoms via CAPS scores gathered at baseline, three weeks after the second experimental session, and three weeks after the third experimental session.

The following main questions were explored in this study:

- Can MDMA, in the doses to be used in this study, be safely administered in the population of treatment-resistant PTSD subjects without any serious adverse events?
- Will subjects receiving the larger, full dose of MDMA, in combination with non-drug assisted psychotherapy, demonstrate greater symptomatic improvement than subjects given an active placebo dose of MDMA in combination with non-drug psychotherapy?
- Will subjects receiving three MDMA sessions, in combination with non-drug psychotherapy, demonstrate an additional improvement compared to subjects receiving only two sessions?
- Can treatment effects of MDMA-assisted psychotherapy be maintained beyond end of treatment?

Secondary Objectives:

- To evaluate changes in PTSD symptoms as assessed via PDS at baseline, the day after each experimental session, and three weeks after the third experimental session.
- To evaluate PTSD symptoms measured by CAPS and PDS scores three weeks after the second Stage 2 experimental session, three weeks after the third Stage 2 experimental session and two months after the third Stage 2 experimental session.
- To formally or informally evaluate CAPS scores in participants who underwent an optional open label continuation for treatment non-responders (Stage 3).
- To evaluate changes in PTSD symptoms assessed via CAPS and PDS scores obtained two, six and twelve months after the third experimental session.

Safety Objectives:

- To assess blood pressure and pulse during experimental sessions using automated blood pressure and pulse monitoring equipment.
- To assess body temperature at regular intervals during experimental sessions.
- To assess experience of degree of psychological distress by repeated administration of the SUD during experimental sessions.

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Name of Active Ingredient:
3,4-methylenedioxymethamphetamine (MDMA)

Methodology:
The study followed a randomized, active placebo-controlled, double-blind design, with subjects, psychotherapists, and independent raters blinded to participant condition. Twelve subjects with treatment-resistant PTSD were randomly assigned after baseline assessment to receive either a full dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2 to 2.5 hours later, or to receive an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2 to 2.5 hours later. Subjects underwent three sessions of MDMA-assisted psychotherapy scheduled to occur three to five weeks apart, one non-drug-psychotherapy session twenty four hours after each MDMA session, and two to four weekly integrative psychotherapy sessions after each MDMA session. PTSD symptoms were assessed by an independent rater once prior to MDMA-assisted psychotherapy, then three weeks after the second MDMA-assisted session and three weeks after the third experimental session. After unblinding, active placebo subjects had the opportunity to take part in an open-label continuation of the study, referred to as Stage 2. Outcome measures were administered three weeks after the second and third experimental session. Outcome measures were also scheduled two, six, and twelve months after the final experimental session as a follow-up. Subjects receiving the full dose in either Stage 1 or Stage 2 who did not show significant improvement in PTSD symptoms were offered the opportunity to take part in an open-label continuation of the study, Stage 3, consisting of two additional MDMA sessions with either 125 or 150mg MDMA.

Number of Subjects (planned and analyzed):
12 subjects planned; 14 subjects enrolled; 2 subjects dropped; 12 subjects completed and analyzed

Diagnosis and Main Criteria for Inclusion and Exclusion:
Participants who meet the following criteria would be considered for inclusion in this study:

1. Participants must meet DSM IV criteria for current PTSD (within the past 6 months) in response to a traumatic experience. An individual would not be excluded if she or he experienced more than one traumatic event. Participants must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must have had at least one unsuccessful attempt at treatment for PTSD. Treatments include psychotherapy and pharmacotherapy. Pharmacotherapies may include selective serotonin uptake inhibitors (SSRIs). Psychotherapeutic treatments may include, but are not limited to cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy. Treatment would be deemed unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.
3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of people with other mood and anxiety disorders is essential because recent literature indicates the marked frequency of the co-existence of other psychiatric disorders among patients with PTSD.
4. Participants must be at least 18 years old.
5. Participants must be willing to commit to medication dosing, therapy sessions, and follow-up sessions and to complete evaluation instruments.
6. Participants must be willing to refrain from taking any psychotropic medication from the outset of the study until follow-up evaluation at T3 (2 months after MDMA session 3), with the exception of gabapentin prescribed for pain control. The scheduled outcome measures at 6 and 12 months after the third experimental session will still be conducted regardless of whether additional psychotropic medication was used. If they are being treated with psychoactive drugs at the time they are recruited

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into the study, agreement to suspend treatment must be obtained in writing from their outside treating physician. The drugs would be tapered in an appropriate fashion to avoid withdrawal effects. They would be discontinued long enough before the first experimental (MDMA or placebo) session to avoid the possibility of any drug-drug interaction (the interval would be at least 5 times the particular drug's half-life).

7. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. If they desire that the investigators communicate directly with the therapist, participants must sign a release for the investigators to communicate directly with their therapist. They may not change therapists, increase the length and frequency of treatments, or commence any new type of therapy until after the administration of outcome measures at T3 (2 months after MDMA session 3). The scheduled outcome measures at 6 and 12 months after the third experimental session would still be conducted regardless of whether additional treatments were obtained.
8. Participants must agree that, for one week preceding each experimental session:
   They will refrain from taking any herbal supplement (except with prior approval of the research team). They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team). Without the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
9. Participants must agree to take nothing by mouth except alcohol-free liquids after 24.00 hours (midnight) the evening before each experimental session. Patients must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA-assisted therapy session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of MDMA.
10. Participants must be willing to remain overnight at Dr. Oehen's office after each experimental session until the non-drug session occurring the next morning**.**
11. Participants will be asked to locate an individual willing to drive them home the after the non-drug therapy session occurring the morning after the experimental sessions. If a participant is unable to locate someone to transport him or herself home, the investigators will assist the participant in obtaining transport from the office to the participant's home or any other location where he or she is staying temporarily.
12. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
13. Participants who do not adhere to the usual progression of scheduled visits, as may occur when a session is delayed, the participant must maintain weekly telephone contact with the investigators, and must agree to speak with the investigators if there is a significant increase in symptoms for which they were previously medicated, if there is any unanticipated need to contact their treating therapist, or if there are any changes in medication.
14. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
15. Participants must have sufficient proficiency in the German language to participate in MDMA-assisted psychotherapy. Participants must be able to read documents in German.
16. Subjects from the researchers' patient pool must have an interview with another psychiatrist not involved in the design or administration of the study before engaging in the informed consent process.

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The researchers will be careful when discussing the study with these individuals to ensure that the pre-existing patient-physician relationship does not unduly influence their decision concerning study participation.

Exclusion Criteria:

Prospective participants with the following conditions would be excluded:

1. Participants who appear at imminent risk for trauma and victimization as assessed by information gathered during the screening will not be eligible for study participation.
2. Women who are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control.
3. Participants with a history of or current primary psychotic disorder or bipolar affective disorder type 1.
4. Participants with dissociative identity disorder, or an eating disorder with active purging or borderline personality disorder.
5. Participants with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (People with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
6. Participants with uncontrolled hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
7. Participants weighing less than 50 kg or more than 105 kg.
8. Patients reporting prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months.
9. Participants who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
10. Participants requiring ongoing concomitant therapy with a psychotropic drug.
11. Participants meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
12. Any participant who is not able to give adequate informed consent. Participants in need of special protection such as minors; participants without the legal ability to act; participants who lack sufficient understanding or capacity to make or communicate responsible decisions concerning themselves by reason of mental illness, mental deficiency, physical illness or disability, advanced age or other cause (incapacitated persons).

Test Product, Dose, Mode of Administration, Lot Number:

Full dose of MDMA 125mg followed by optional supplement of 62.5mg on three occasions administered during psychotherapy; oral capsules; Lipomed AG Batch Number 94.1B5.51

Reference Therapy, Dose, Mode of Administration, Lot Number:

Active placebo dose of MDMA 25mg followed by optional supplement of 12.5mg on three occasions administered during psychotherapy; oral capsules; Lipomed AG Batch Number 94.1B5.51

Duration of Study:

Subjects participating in Stage 1 and the follow-up outcome measures completed the study in approximately 16 months. Subjects participating in Stage 2 completed the study in approximately 18 months. Subjects participating in Stage 3 completed the study in approximately 20 months.

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Criteria for Evaluation:
Efficacy: Primary outcome measures involve comparing Global CAPS scores at baseline, three weeks after the second experimental session, and three weeks after the third experimental session. Secondary outcome measures involve comparing PDS scores at baseline, three weeks after the second experimental session, and three weeks after the third experimental session.
Safety: Blood pressure, pulse, and body temperature were taken every thirty minutes four hours and hourly afterwards up to eight hours, or as needed. Abnormal lab values were collected after treatments were completed. Adverse events were collected throughout the study and spontaneously reported reactions were collected for eight days after each experimental session. Psychological distress during experimental sessions was collected every 60-90 minutes using the SUD and general wellbeing was assessed at every face-to-face visit, during and after each experimental session.

Statistical Methods:
[Planned] Results of outcome measure assessments were to be analyzed by nonparametric ANOVA using the F1_LD_F1 model. The results of two vs. three experimental sessions were to be analyzed using a Wilcoxon-Signed-Rank test. Follow-up, Stage 2 and Stage 3 data were to be informally analyzed. No statistical corrections were planned for multiplicity of data, and significance was set at $p < 0.05$.
[Actual] In addition to nonparametric ANOVA conducted at the site, the sponsor conducted repeated measures ANOVA comparing active placebo and full dose MDMA scores in Stage 1 and the follow-up. To assess whether three experimental sessions were more effective than two experimental sessions, the sponsor used a Student's paired T-test. Peak and average post-drug values in vital signs and psychological distress between active placebo and full dose MDMA subjects were compared.

Summary and Conclusions:
Efficacy results: CAPS scores showed a trend towards decreasing in the 8 subjects receiving full dose MDMA in comparison to 4 receiving active placebo. Average CAPS scores decreased 15.6 points (23.5%) in full dose subjects. PDS scores mirrored the results from the CAPS. Both CAPS and PDS scores decreased significantly over time in the follow-up period. Three experimental sessions were significantly more effective than two.
Efficacy conclusions: MDMA-assisted psychotherapy with full dose MDMA generated a clinically significant response in this small subject sample. Results failed to demonstrate statistical significance, but do suggest a trend toward significance. Future studies with larger sample size are warranted.
Safety results: There were no drug-related Serious Adverse Events. Two subjects withdrew from the study due to adverse events involving exacerbation of anxiety after completing a single experimental session. Five subjects exhibited elevation in systolic blood pressure above the predetermined cutoff of 160 mm Hg during 14 experimental sessions, and 2 subjects experienced diastolic blood pressure above 110 mm Hg during 3 experimental sessions for 6 hours or less. Body temperature was elevated above 1^{o}C in eight cases. Eight subjects experienced pulse greater than 110 after drug administration. However, no interventions were needed in any of these cases. One-way ANOVA performed upon peak change scores and post-drug average scores failed to detect any main effect of condition for diastolic blood pressure, heart rate, or body temperature during experimental sessions, whereas systolic blood pressure increased significantly. Spontaneously reported reactions occurred but generally resolved by the end of the 7-day window after each experimental session, and 13 possibly or probably related adverse events were collected.
Safety conclusions: MDMA-assisted psychotherapy did not cause any drug-related Serious Adverse Events. Cardiovascular effects and spontaneously reported reactions were similar to those reported in the literature, were self-limiting and did not require intervention. Data suggest that MDMA-assisted psychotherapy does not cause undue harm in this subject population.
Date of the report: September 15, 2011

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2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EC	Ethics Committee
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPCL	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IES	Impact of Events Scale
IND	Investigational New Drug
LSD	d-Lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NK	Natural Killer
OTC	Over the Counter (Non-Prescription)
PDS	Posttraumatic Diagnostic Scale
PI	Principal Investigator
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI-C	Post Traumatic Growth Inventory-Current State
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RCT	Randomized Clinical Trial
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)

SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

25 mg	Active placebo of MDMA
125 mg	Full dose of MDMA
150 mg	20% Larger Active Dose
Stage 1	Randomized Study Arm
Stage 2	Open-Label Partial Crossover Study Arm
Stage 3	Open-Label Arm with 20% Larger Active Dose for Nonresponders

3.0 ETHICS

3.1 Ethics Committee (EC)

The study and any amendments were reviewed and approved by the EC of the Canton of Aargau and Solothurn in Switzerland. See Appendix 14.1.3 Ethics Committee Approvals and Information for Subjects.

3.2 Ethical Conduct of the Study

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and U.S. FDA regulations that have their origins in the Declaration of Helsinki.

3.3 Subject Information and Consent

The informed consent forms (ICF) were reviewed and approved by the EC. After a brief interview with the investigator conducted over the telephone or in person, prospective participants met with the investigator to discuss the study and to give written informed consent to take part in the study if they chose to participate. Only after giving this consent were initial psychiatric and medical evaluations conducted. These activities were completed prior to enrollment. Subjects completed an ICF quiz to assess their understanding of the ICF. See representative ICFs for the study attached as Appendix 14.1.3.

4.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Dr. med. Peter Oehen was the Principal Investigator (PI) for this study. Dr. med. Oehen worked with co-investigator Verena Widmer. Both conducted psychotherapy and Dr. med. Oehen administered study drug during experimental sessions. The study took place at the offices of Dr. med. Oehen in Biberist, Switzerland. The study was developed by Dr. med. Oehen and the sponsor. Administration of screening and outcome measures was performed by Dr. med. Rafael Traber. The study was monitored by the sponsor.

Principal Investigator: Dr. med. Peter Oehen
Co-Investigator: Verena Widmer
Independent Rater: Dr. med. Rafael Traber
Randomization Monitor: Prof. Dr. pharm. Rudolf Brenneisen
Medical Monitor: Michael Mithoefer, M.D.
Biostatistician: Ilsa Jerome, Ph.D. and Christoph Kopp
Please see Appendix 14.1.5 for signatures of the PI and sponsor's Medical Monitor and Appendix 14.1.4 for CVs of investigators.

5.0 INTRODUCTION

This report describes a pilot study of MDMA-assisted therapy in people with chronic, treatment-resistant PTSD. This study was sponsored by MAPS, a non-profit organization focused on clinical research and public education. The protocol was developed based on findings from Phase I studies conducted in the U.S. and Europe and a Phase 2 study in Spain [1].

This study was part of the sponsor's clinical development plan evaluating the safety and efficacy of MDMA as an adjunct to psychotherapy for people with chronic, treatment-resistant PTSD. This study was also intended to provide the research team headed by the investigator with training and experience in MDMA-assisted psychotherapy, and to develop and standardize this potential treatment.

PTSD symptoms were assessed before and after treatment by an objective primary endpoint, where a blinded independent rater administered the Clinician-Administered PTSD Scale (CAPS), developed by the National Center for PTSD in the U.S [2, 3]. Early clinical experience with MDMA combined with psychotherapy suggests therapeutic potential for treating PTSD subjects, based on psychotherapy treatments conducted prior to the criminalization of MDMA in 1985. The qualities that have been associated with MDMA in anecdotal reports, including decreased defensiveness and enhanced therapeutic alliance, have the potential to be particularly useful as an adjunct to psychotherapy. The methodology for MDMA-assisted psychotherapy sessions was adapted from principles developed by Stanislav Grof, M.D. for LSD psychotherapy [4] and for Holotropic Breathwork [5-7]. These procedures are described in the sponsor's treatment manual for MDMA-assisted psychotherapy in people with PTSD [8]. Recent research suggests that MDMA may act in part via changing facets of emotion perception and reactivity to motion, and perhaps through elevation of the neuropeptide oxytocin [9-11].

Initial human trials of MDMA demonstrated that the drug can be administered safely under controlled conditions, with no evidence of significant or lasting toxicity in Phase I studies (see for example: [1, 9, 12-21]. No drug-related Serious Adverse Events have been reported during the course of MAPS' Phase 2 MDMA/PTSD studies.

6.0 STUDY OBJECTIVES

The following main questions were explored in this study:

- Can MDMA, in the doses to be used in this study, be safely administered in the population of treatment-resistant PTSD subjects without any serious adverse events?
- Will subjects receiving the full dose of MDMA, in combination with non-drug assisted psychotherapy, demonstrate greater symptomatic improvement than subjects given an active placebo dose of MDMA in combination with non-drug psychotherapy?
- Will subjects receiving three MDMA sessions, in combination with non-drug psychotherapy, demonstrate an additional improvement compared to patients receiving only two sessions?
- Can treatment effects of MDMA-assisted psychotherapy be maintained beyond end of treatment?

6.1 Primary Objective

- To evaluate changes in PTSD symptoms via CAPS scores gathered at baseline, three weeks after the second experimental session, and three weeks after the third experimental session.

6.2 Secondary Objectives

- To evaluate changes in PTSD symptoms as assessed via PDS at baseline, the day after each experimental session, and three weeks after the third experimental session.
- To evaluate PTSD symptoms measured by CAPS and PDS scores three weeks after the second Stage 2 experimental session, three weeks after the third Stage 2 experimental session, and two months after the third Stage 2 experimental session.
- To formally or informally evaluate CAPS scores in participants who underwent an optional open label continuation for treatment non-responders (Stage 3).
- To evaluate changes in PTSD symptoms assessed via CAPS and PDS scores obtained two, six, and twelve months after the third experimental session.

6.3 Safety Objectives

The safety objective presented in the protocol is item 1 in the Study Objectives listed above and has been formulated as individual objectives below:

- To assess blood pressure and pulse during experimental sessions using automated blood pressure and pulse monitoring equipment.
- To assess body temperature at regular intervals during experimental sessions.
- To assess experience of degree of psychological distress by repeated administration of the Subjective Units of Distress (SUD) during experimental sessions.

7.0 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan Description

The study followed a randomized, active placebo-controlled, double-blind design, with subjects, psychotherapists, and independent raters blinded to participant condition. Twelve subjects with treatment-resistant PTSD were randomly assigned after baseline assessment to receive either a full dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2 to 2.5 hours later, or to receive an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2 to 2.5 hours later. Subjects underwent three sessions of MDMA-assisted psychotherapy scheduled to occur three to five weeks apart, one non-drug-psychotherapy session twenty four hours after each MDMA-session, and two to four weekly integrative psychotherapy sessions after each MDMA session. PTSD symptoms were assessed by an independent rater prior to MDMA-assisted psychotherapy, three weeks after the second MDMA-assisted session, and three weeks after the third experimental session. After unblinding, active placebo subjects had the opportunity to take part in an open-label continuation of the study, referred to as Stage 2. Data gathered three weeks after the third experimental session was treated as the baseline for Stage 2, and outcome measures were administered three weeks after the second and third experimental session. Outcome measures would also be given two, six, and twelve months after the third experimental session. Subjects receiving the full dose in either Stage 1 or Stage 2 who did not show significant improvement in PTSD symptoms were offered the opportunity to take part in an open-label continuation of the study, Stage 3, consisting of two additional MDMA sessions. During these sessions, they could receive 125 mg followed 2 to 2.5 hours later by 62.5 mg MDMA or a 20% larger dose of 150 mg MDMA, followed by a supplemental dose of 75 mg administered 2 to 2.5 hours later, unless contraindicated by safety parameters. Participation in Stage 3 was offered after the follow-up outcome measures were completed.

7.2 Discussion of Study Design Including Control Groups

Subjects in this study received one of two treatments: a low, or active placebo, or a full dose of the study drug. The active placebo consisted of 25 mg MDMA possibly followed 2 to 2.5 hours later by 12.5 mg MDMA and the full dose consisted of 125 mg MDMA possibly followed 2 to 2.5 hours later by 62.5 mg MDMA. The full dose was chosen on the basis of use prior to scheduling of MDMA and use in the first study of MDMA-assisted psychotherapy [18]. Because of its psychoactivity, the study used an active placebo to maintain the study blind for the investigators conducting psychotherapy. A low dose of MDMA was chosen as a credible placebo that would not possess the therapeutic effects of the full dose. See 7.4.4 Selection of Doses in Study.

Use of an inactive placebo permits a clear determination of effects due to the study drug at the cost of difficulty maintaining the blind. In the sponsor's first clinical trial of MDMA-assisted psychotherapy, which employed an inactive placebo, the investigators correctly guessed condition assignment in every

case, and all but one subject also correctly guessed condition assignment. There is not yet enough information to establish what dose or material will make the best active placebo. The sponsor is currently investigating several active placebo doses of the study drug, and other studies have used the psychostimulants d-amphetamine, methamphetamine, methylphenidate, and the serotonin releaser and direct agonist mCPP as comparators [15, 22, 23].

The study followed a between-group partial crossover design. All participants were assigned to either active placebo or full dose MDMA in a blinded manner, meaning subjects, the investigators performing psychotherapy, and the independent rater were unaware of condition assignment, with dropouts replaced until twelve participants had completed the study. The first 12 participants who met inclusion criteria without meeting exclusion criteria were admitted to the study. The study was designed to enroll 8 participants in the full dose condition and four in the active placebo condition, with randomization designed accordingly to maintain this ratio while also maintaining the study blind. After completing the study, all active placebo subjects had the option of enrolling in Stage 2, an open-label crossover arm of the study. The goal of this arm was to investigate how subjects respond to full dose MDMA-assisted psychotherapy when compared to active placebo as a within-subject control group. Long-term follow-up evaluation was conducted two, six and twelve months after the final experimental session. Use of the partial crossover meant that the investigators were unable to compare subjects who received active placebo to those who received full dose MDMA at the time of the long-term follow up. However, the follow-up data was useful for an exploratory observation of changes in PTSD symptoms over 12 months since full dose MDMA treatment.

For a limited time, the study also permitted the investigators to enroll participants whose CAPS scores did not decline significantly after the follow-up in a third arm, Stage 3, wherein they could receive full dose MDMA or a larger 150 and 75 mg MDMA dose. This arm was removed from the protocol in a subsequent amendment to the protocol after no further changes in PTSD symptoms were observed. Since participation in Stage 3 was offered after the 12-month follow-up for full dose subjects who were deemed to be non-responders, this arm did not substantially interfere with long-term observations for these subjects.

7.3 Selection of Study Population

The first twelve participants who met all inclusion criteria without meeting any exclusion criteria were admitted to the study. Participants were recruited for the study by call for referral from specialized institutions such as trauma advice and counseling centers (outpatient clinics for psychotraumatology), as well as psychiatrists and psychotherapists in private practice.

7.3.1 Inclusion Criteria

Participants who meet the following criteria would be considered for inclusion in this study:

1. Participants must meet DSM IV criteria for current PTSD (within the past 6 months) in response to a traumatic experience. An individual would not be excluded if she or he experienced more than one traumatic event. Participants must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must have had at least one unsuccessful attempt at treatment for PTSD. Treatments include psychotherapy and pharmacotherapy. Pharmacotherapies may include selective serotonin uptake inhibitors (SSRIs). Psychotherapeutic treatments may include, but are not limited to cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy. Treatment would be deemed unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of people with other mood and anxiety disorders is essential because recent literature indicates the marked frequency of the co-existence of other psychiatric disorders among patients with PTSD.
4. Participants must be at least 18 years old.
5. Participants must be willing to commit to medication dosing, therapy sessions, and follow-up sessions and to complete evaluation instruments.
6. Participants must be willing to refrain from taking any psychotropic medication from the outset of the study until follow-up evaluation at T3 (2 months after MDMA session 3), with the exception of gabapentin prescribed for pain control. The scheduled outcome measures at 6 and 12 months after the third experimental session will still be conducted regardless of whether additional psychotropic medication was used. If they are being treated with psychoactive drugs at the time they are recruited into the study, agreement to suspend treatment must be obtained in writing from their outside treating physician. The drugs would be tapered in an appropriate fashion to avoid withdrawal effects. They would be discontinued long enough before the first experimental (MDMA or placebo) session to avoid the possibility of any drug-drug interaction (the interval would be at least 5 times the particular drug's half-life).
7. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. If they desire that the investigators communicate directly with the therapist, participants must sign a release for the investigators to communicate directly with their therapist. They may not change therapists, increase the length and frequency of treatments, or commence any new type of therapy until after the administration of outcome measures at T3 (2 months after MDMA session 3). The scheduled outcome measures at 6 and 12 months after the third experimental session would still be conducted regardless of whether additional treatments were obtained.
8. Participants must agree that, for one week preceding each experimental session:
They will refrain from taking any herbal supplement (except with prior approval of the research team). They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team). Without the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
9. Participants must agree to take nothing by mouth except alcohol-free liquids after 24.00 hours (midnight) the evening before each experimental session. Patients must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA-assisted therapy session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of MDMA.
10. Participants must be willing to remain overnight at Dr. Oehen's office after each experimental session until the non-drug session occurring the next morning**.**
11. Participants will be asked to locate an individual willing to drive them home the after the non-drug therapy session occurring the morning after the experimental sessions. If a participant is unable to locate someone to transport him or herself home, the investigators will assist the participant in obtaining transport from the office to the participant's home or any other location where he or she is staying temporarily.
12. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
13. Participants who do not adhere to the usual progression of scheduled visits, as may occur when a session is delayed, the participant must maintain weekly telephone contact with the investigators, and must agree to speak with the investigators if there is a significant increase in symptoms for which they were previously medicated, if there is any unanticipated need to contact their treating therapist, or if there are any changes in medication.

14. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
15. Participants must have sufficient proficiency in the German language to participate in MDMA-assisted psychotherapy. Participants must be able to read documents in German.
16. Subjects from the researchers' patient pool must have an interview with another psychiatrist not involved in the design or administration of the study before engaging in the informed consent process. The researchers would be careful when discussing the study with these individuals to ensure that the pre-existing patient-physician relationship does not unduly influence their decision concerning study participation.

7.3.2 Exclusion Criteria

Prospective participants with the following conditions would be excluded:
1. Participants who appear at imminent risk for trauma and victimization as assessed by information gathered during the screening would not be eligible for study participation.
2. Women who are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control.
3. Participants with a history of or current primary psychotic disorder or bipolar affective disorder type 1.
4. Participants with dissociative identity disorder, or an eating disorder with active purging or borderline personality disorder.
5. Participants with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (People with hypothyroidism who are on adequate and stable thyroid replacement would not be excluded).
6. Participants with uncontrolled hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
7. Participants weighing less than 50 kg or more than 105 kg.
8. Patients reporting prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months.
9. Participants who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
10. Participants requiring ongoing concomitant therapy with a psychotropic drug.
11. Participants meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
12. Any participant who is not able to give adequate informed consent. Participants in need of special protection such as minors; participants without the legal ability to act; participants who lack sufficient understanding or capacity to make or communicate responsible decisions concerning themselves by reason of mental illness, mental deficiency, physical illness or disability, advanced age or other cause (incapacitated persons).

7.3.3 Removal of Subjects from Therapy or Assessment

Subjects could withdraw consent at any time without prejudice. The investigator could withdraw a subject from the study if, in his or her clinical judgment, it was in the best interest of the subject or if the subject could not comply with elements of the protocol that were critical for safety or necessary for the scientific integrity of the study. If the investigator withdrew a subject from the study, the investigators explained the reason for withdrawing the participant. Subjects enrolled in the study who withdrew after the first experimental session or who the researchers decided for any reason should not continue in the study ("dropouts") could be replaced.

Subjects who withdrew were to be clinically monitored after withdrawal with the cause of withdrawal noted. Whenever possible, the tests and evaluations listed for the termination and outcome visits were carried out. Efforts were made to obtain information about adverse event (AE) resolutions, if applicable.

7.4 Treatments

7.4.1 Treatments Administered

Each dose consisted of the specified amount of racemic MDMA mixed with an inactive substance, lactose, to prevent the investigators from distinguishing doses through weight or appearance of the capsules. Each dose of MDMA was administered along with 250 to 300 mL electrolyte-containing fluid. MDMA was administered during each of the three experimental sessions, with the second and third session scheduled three to five weeks after the previous experimental session.

Subjects received an initial dose of 25mg or 125mg MDMA approximately 1 to 1.5 hours after they arrived at the study site for each experimental session. If the investigators believed the subject was able to tolerate a supplemental dose, then a supplemental dose was offered 2-2.5 hours later. Initial doses were distinguished from supplemental doses through labeling them “Dose 1” and “Dose 2” to ensure that the correct dose was administered at the scheduled time. The investigators did not administer the supplemental dose if the subject was exhibiting contraindicated signs or symptoms.

7.4.2 Identity of Investigational Product

The investigational product is d,l(3,4)-methylenedioxymethamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$ (HCl). The drug is a white, crystalline powder. The drug was administered orally in capsules. The product used in this study was synthesized by Lipomed AG, Switzerland in December 1998 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Appendix 14.1.10). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. Dr. pharm. Rudolf Brenneisen, Department of Clinical Research, University of Bern, Switzerland. This analysis reconfirmed identity, purity, and content of MDMA HCI Lipomed Batch no.94.1B5.5, with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually by Prof. Dr. Brenneisen. (see Appendix 14.1.10)

The encapsulation was performed by the Laboratory Bichsel in Interlaken, Switzerland. The MDMA was weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, an inactive compound, to ensure that all capsules had similar weights. The lowest dose contained in one capsule was 12.5 mg, which is the supplemental dose offered to participants in the active placebo condition, and the highest dose contained in one capsule was 125 mg, which is the initial dose offered to participants in the full dose condition. Capsules were prepared in such a way as to prevent investigators and participants from distinguishing contents of an active placebo capsule from a full dose capsule. MDMA was handled in accordance with all Swiss regulations and forms pertaining to the use of scheduled substances were maintained by the investigators. The MDMA was stored in a bank vault and only the investigators had access to the investigational product.

7.4.3 Method of Assigning Patients to Treatment Groups

Upon enrollment in the study, subjects were randomly assigned to the active placebo or full dose condition. Eight of 12 subjects, or 66.6%, were assigned to the full dose condition, and 4 of 12, or 33.3%,

were assigned to the active placebo condition. Condition assignments were performed with a table of random numbers generated by M. Collenberg at the Institute for Mathematical Statistics, University of Bern, who sent it to the randomization monitor. The randomization monitor created unblinding envelopes and packaged the drug with blinded labels. All investigators, subjects and independent raters remained blind to condition assignment until after Stage 1, per protocol. If there was an adverse event or other emergency requiring knowledge of subject's condition assignment, the blind could be broken for an individual subject using the unblinding envelopes.

7.4.4 Selection of Doses in Study

The lowest dose contained in one capsule was 12.5 mg, which was the supplemental dose offered to subjects in the active placebo condition, and the highest dose contained in one capsule was 150 mg, a dose potentially available for Stage 3 subjects. The dose of MDMA chosen for the active placebo condition has been selected on the basis of its ability to produce minimal but detectable subjective effects [24, 25]. The cumulative dose of 37.5 mg MDMA was not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose could produce slight alterations in consciousness, such as increased relaxation or tension [25].

The initial 125 mg dose of MDMA selected for the full dose condition was chosen on the basis of case reports of MDMA-assisted psychotherapy conducted in the U.S. prior to scheduling [26], as well as on data obtained from the first MAPS-sponsored MDMA/PTSD pilot study [18]. This dose was expected to reduce fear in response to emotionally upsetting thoughts, feelings, or memories and to increase access to emotionally intense material, constituting therapeutic activity. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [12, 24, 27-33].

With subjects carefully monitored for any indicators of adverse events, the initial dose of 150 mg, and the cumulative dose of 225 mg administered in Stage 3 was expected to be tolerable and pose no more than minimal risk based on previous studies. This dose was selected in order to test the idea that subjects may not respond to full dose if they are subject to factors that influence metabolism of the drug or are psychologically resistant. A slightly higher dose of drug may enable them to cross the threshold for therapeutic activity. Higher doses of up to 187.5 mg MDMA in a single administration have been used prior to the scheduling of MDMA in therapeutic contexts [34]. Charles Grob, M.D. administered single doses over 150 mg on eight occasions to four participants in his FDA-approved Phase 1 MDMA safety study without any Serious Adverse Events (SAEs) [24].

Table 1. Dose Regimen

Condition	Initial Dose	Supplemental Dose	Cumulative Dose
Active Placebo Dose	25 mg	12.5 mg	37.5 mg
Full Dose	125 mg	62.5 mg	187.5 mg
20% Larger Active Dose	150 mg	75 mg	225 mg

Source: Appendix 14.2.5.2

Both the active placebo and the full dose conditions use supplemental doses that are half of the initial dose, to make the dosing schedule equivalent across the conditions. The dosage and schedule of dosing was chosen on the basis of case reports describing the use of MDMA in psychotherapy [5, 30, 34]. Supplemental dosing performed 2 to 2.5 hours after the initial dose was intended to extend the course of drug effects without increasing their intensity.

7.4.5 Selection and Timing of Dose for Each Subject

Experimental sessions were allowed to proceed after subjects completed a urinary drug test and pregnancy test (if applicable) prior to each experimental session and obtained a negative result. Subjects received the initial dose of study drug approximately 1 to 1.5 hours after arriving at the study site. Supplemental dosing was generally completed if the investigators believed the subject was able to tolerate a supplemental dose, unless contraindicated for safety reasons. The supplemental dose was scheduled to occur when drug effects were expected to start waning, on the basis of previous therapeutic use of MDMA.

The investigators used clinical judgment as the basis for determining initial and supplemental dose for each of the two Stage 3 sessions, and they used their judgment when applicable to employ a different dose during the second session on the basis of their experience during the first Stage 3 session.

7.4.6 Blinding

All investigators, independent rater, and subjects were blind to condition assignment until the end of Stage 1 (3 weeks after the third experimental session) and outcome measures were completed by the independent rater. The randomization monitor and the statistician at the University of Bern were the only unblinded personnel for this study. The randomization monitor created sealed unblinding envelopes for each individual subject. If there was a SAE or other emergency requiring knowledge of subject's condition assignment, the blind could have been broken for that subject. This did not occur during the trial and all envelopes were sealed until the subject had completed Stage 1. According to the protocol, the blind was broken for all study staff and each individual subject at the end of Stage 1. If the subject had received the active placebo dose, they were offered enrollment in Stage 2.

MDMA is psychoactive and produces cardiovascular effects, including transient elevation in blood pressure, which required periodic monitoring by the investigators [25, 29, 31]. In order to maintain the integrity of the data, the blinded independent rater did not observe any of the safety data, including vital signs collected during experimental sessions. The independent rater administered the primary outcome measure. The independent rater did not have access to subject records other than outcome measure data.

7.4.7 Prior and Concomitant Therapy

Subjects eligible for this study were required to have tried either psychotherapy or pharmacotherapy to treat their PTSD symptoms without achieving remission. Subjects may have tried either of the two FDA approved SSRIs for PTSD, sertraline or paroxetine. At baseline, subjects were asked to provide the names and dates of any pre-study medications. These medications were recorded in the source records and collected on CRFs.

If subjects were taking psychotropic medications at enrollment, agreement to suspend treatment was to be obtained in writing from their treating physician. Prior to drug administration, subjects were required to taper off psychotropic medications with the exception of gabapentin prescribed for pain control. The medications were tapered in an appropriate fashion to avoid withdrawal effects. Medications were discontinued for a period of at least five times the particular drug's half-life. The goal of this restriction was to avoid any drug interactions and to provide a clear interpretation of the outcome for each subject. Subjects were allowed to resume taking medications after the follow-up evaluation two months after the final experimental session.

Subjects requiring ongoing concomitant therapy with a psychotropic drug, those meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days, and those reporting prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months were excluded from the study.

Subjects were permitted to continue seeing a psychotherapist during the course of the study, but they could not change therapists, increase the length and frequency of treatments, or commence any new type of therapy until after the administration of outcome measures two months after the third experimental session. Subjects from the investigator's patient pool were required to have an interview with another psychiatrist not involved in the design or administration of the study before engaging in the informed consent process to avoid undue influence on study participation.

Dietary and concomitant medication restrictions were recommended to subjects in preparation for experimental sessions. For one week preceding each experimental session, subjects were instructed to refrain from taking any herbal supplement, nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen), and prescription medications, with the exception of birth control pills, thyroid hormones or other medications approved by the research team. Subjects were asked to take nothing by mouth except alcohol-free liquids after midnight the evening before each experimental session, and to refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA-assisted therapy session. The investigators withheld caffeine and nicotine for 2 hours before and 6 hours after each dose of MDMA to avoid effects on vital signs.

7.4.8 Treatment Compliance

The PI was responsible for adequate and accurate accounting of investigational product usage. The PI administered all investigational product only to subjects included in the study following the procedures set out in the study protocol, within the context of an MDMA-assisted psychotherapy session. Subjects did not receive take-home doses. The date, dosage and time of dosing were recorded. The PI tracked capsules received and used and retained all unused capsules and containers thereof in the bank vault used for storage of the investigational product, until the sponsor was satisfied that the drug accountability records were correct. At the end of the study, all unused investigational product was returned to the randomization monitor and destroyed.

Information on concomitant medications was collected throughout the study to ensure treatment compliance. Urinary drug screens were performed once at baseline, prior to each MDMA administration and once at random during the study to ensure no use of commonly used illicit substances. Urinary drug screens specific to MDMA were administered at the follow-up visits completed two, six, and twelve months after the final experimental session as well. These tests demonstrated that all the subjects remained compliant and did not use MDMA during the follow-up period of the study.

7.5 Efficacy and Safety Variables

7.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Figure 1. Points of Administration of Measures in Stage 1

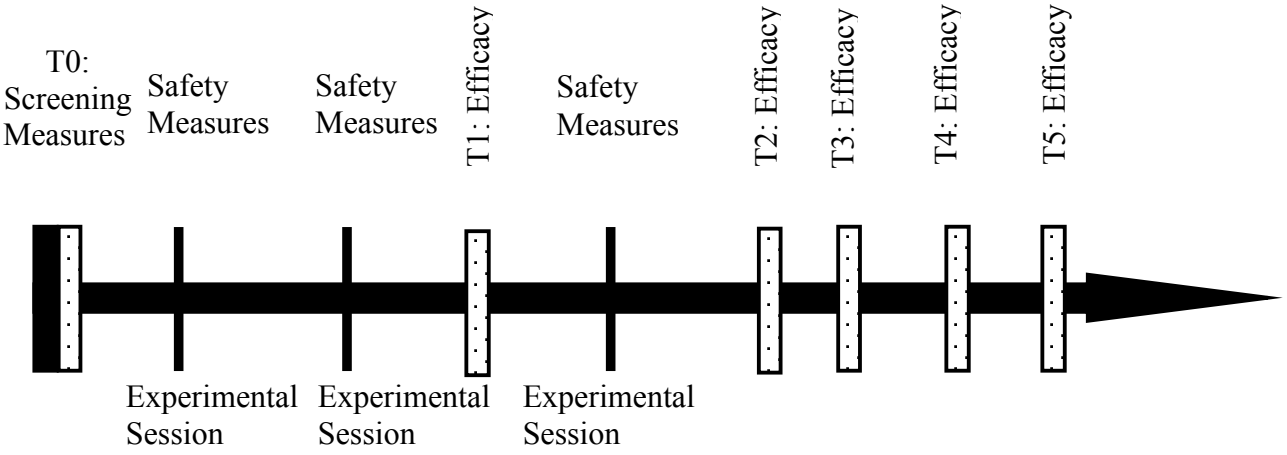


Table 2. Study Measures Assessed

Type of Measure	Name of Measure	Administered by
Screening	Structured Clinical Interview for Diagnoses according to DSM-IV criteria (SCID-IV)	Independent Rater
Medical Screening	Medical history and physical examination	Physician other than PI
Medical Screening	Electrocardiogram (ECG)	Physician other than PI
Medical Screening	HIV test	Clinical lab
Screening, Safety	Urine tests: drugs, pregnancy (if applicable)	Investigators
Screening, Safety	Liver panel, serum electrolytes, thyroid hormones in blood	Clinical lab
Screening, Efficacy	Clinician-Administered PTSD Scale (CAPS)	Independent Rater
Efficacy	PTSD Diagnostic Scale (PDS)	Self-report
Safety	Subjective Units of Distress (SUD)	Investigators
Safety	Vital signs	Investigators
Safety	Spontaneously reported reactions	Investigators
Safety	Adverse events	Investigators
Safety	General well-being	Investigators
Process	Belief of Condition Assignment	Investigators
Process	Reactions to Research Participation Questionnaire (RRPQ)	Investigators

7.5.2 Appropriateness of Measurements

7.5.2.1 Screening Measures

Screening measures conducted prior to enrollment constitute a standard battery of tests designed to thoroughly examine the potential subject for any medical issues. Psychological assessments consisted of the Structured Clinical Interview for Diagnoses according to DSM-IV criteria (SCID-IV) to determine whether an individual satisfied eligibility criteria [35]. The SCID is a semi-structured interview that permits accurate diagnosis of lifetime and current psychiatric disorders.

7.5.2.2 Efficacy Measures

Efficacy measures were established measures of PTSD symptoms known to be reliable and valid. All outcome measures were administered by an independent rater to provide an objective endpoint for evaluation of clinical outcome. The independent rater was blind to subject condition and was not present during psychotherapy sessions. All outcome measures were conducted at baseline, three weeks after the second experimental session, three weeks after the third experimental session, and at two, six and twelve months after the third Stage 1 or Stage 2 experimental session. One self-report outcome measure was also administered one day after each experimental session.

The CAPS is a structured clinical interview designed to assess the seventeen symptoms of PTSD along with five associated features [3]. The CAPS provides a means to evaluate the frequency and intensity dimensions of each symptom, the impact of symptoms on the patient's social and occupational functioning, the overall severity of the symptom complex, global improvement since baseline, and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [2, 36]. PTSD medications previously approved by the FDA used the CAPS as a measure of symptom severity and it is considered the gold standard in PTSD research. In this study, the German translation of the CAPS was used to ensure that subjects were interviewed in a language they could understand well. The German translation of the CAPS was previously validated in a small study [37]. The CAPS was administered at baseline and outcome measure assessments.

The Posttraumatic Diagnostic Scale (PDS) is a 49-item self-report measure assessing presence of PTSD symptoms as described in DSM-IV, including type of traumatic event, length since the event occurred, degree of distress, and presence of intrusive thoughts, avoidance, and hypervigilance [38, 39]. The PDS also assesses duration of symptoms and degree of impairment. The Cronbach alpha coefficient for the scale is reported to be 0.91 and test-retest reliability is 0.74. The PDS was administered one day after each experimental session as well as during outcome measure assessments.

7.5.2.3 Safety Measures

The measures of safety used in this study were routine clinical procedures. They were chosen to capture known effects of MDMA from the literature (as elevated blood pressure, heart rate, and body temperature). Safety measures were conducted by the investigators. These included close vigilance for and stringent reporting of selected reactions on the day of and 8 days after drug administration, AEs, and SAEs, as well as frequent measurement of vital signs and psychological distress during and after experimental sessions.

Mild anxiety and depressed mood are occasionally reported 1–3 days after MDMA administration as described in the Investigator's Brochure. Psychological distress related to drug administration could arise during the session or after as a result of subjects having difficulty integrating their experience after the drug effect had subsided. Subjects had the intention of confronting and working

through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions were expected and were considered an element of the psychotherapeutic process. The Subjective Units of Distress (SUD) was used to assess the degree of psychological distress during the course of each experimental session with a simple, one-item visual analog scale. This is a standardized subjective rating scale by which a participant can quickly rate comfort level throughout the session (l-7 scale). This measure provided an easy way to monitor safety during experimental sessions and was conducted every sixty to ninety minutes. General Wellbeing was collected at every face to face visit and for 7 days after each experimental session. This measure consists of two components. The letter component indicates how likely a subject is to deteriorate and the number component indicates the demeanor and state of mind of the subject, ranging from very stable to very distressed. This measure is easy to administer and indicates the general mental status of a subject.

Blood pressure and pulse were measured frequently during experimental sessions to ensure cardiovascular parameters were within acceptable limits. Blood pressure was measured every 30 minutes for the first 4 hours after drug administration and every 60 minutes for up to 8 hours afterwards. Body temperature was measured every 60-90 minutes. If parameters exceeded pre-determined cut-off values, these were specifically tracked to ensure return to baseline in parallel with subjective effects of the drug.

An AE is defined as any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

Adverse Events commonly reported in the literature on MDMA taken by healthy volunteers were compiled under the name “spontaneously reported reactions” and will be considered *expected AEs*. The investigators recorded these if the subject spontaneously volunteered this information on the day of and during the 8 days following each experimental session. Duration and severity of spontaneously reported reactions were collected during the day of the experimental session, and severity only was collected on the 8 days after the session. Spontaneously reported reactions were followed until resolution.

An *unexpected AE* is one that is not listed in the current Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event. If the subjects volunteered information on AEs other than the reactions described above, they were recorded throughout the study by the investigators. AEs were followed until resolution. The PI judged AEs for relatedness and severity according to the following criteria:

Severity:

- Mild: No limitation in normal daily activity
- Moderate: Some limitation in normal daily activity
- Severe: Unable to perform normal daily activity

Relatedness:

- Not Related: If exposure to the investigational product has not occurred, the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product.
- Possibly Related: The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.
- Probably Related: Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

All SAEs were followed with the most stringent reporting requirements and rapidly assessed by the PI and sponsor's Medical Monitor for relatedness, duration, and severity. A severe AE need not be serious in nature and an SAE need not be severe. An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

In addition, pre-existing events or conditions resulting in hospitalization were recorded on the medical history CRF. The hospitalization would not result in the event or condition being reported as a study-related SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition, since the onset of the event occurred before the subject entered the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion did not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

7.5.2.3 Process Measures

Process measures were administered by the investigators. Response to study participation and perceived degree of choice in taking part in the study was assessed with the Reactions to Research Participation Questionnaire (RRPQ), administered twelve months after the final experimental session [40]. This is a twenty four-item assessment of participants' experience of study participation, reasons for participation, and perceived costs and benefits of participation. This measure was administered to ensure lack of coercion in study participation and to report on the effectiveness of the informed consent process.

All subjects were asked the next day during the integrative session to indicate whether they believe they received active placebo or full dose MDMA during the experimental sessions for the Belief on Condition Assignment. This exploratory measure served as a means of measuring the success of study blinding for subjects and investigators. The investigators also maintained a record of beliefs concerning condition assignment. This was not collected as part of the CRFs but was provided upon study closure in the form of a spreadsheet.

7.5.3 Primary Efficacy Variables

The primary efficacy variable for this study was the CAPS. Change in CAPS Global Severity scores from baseline to three weeks after the third experimental session of Stage 1 was used to judge efficacy of treatment within the subject group enrolled in the study. Drugs previously approved by the FDA for PTSD used a CAPS score of 50 as a diagnostic cut-off [41-44]. For the purpose of this study, response was considered clinically significant if CAPS Global severity scores dropped below 50. Given the exploratory nature of this small pilot study in 12 subjects, results of hypothesis testing are reported, but larger subject populations will be necessary to draw definitive conclusions on efficacy.

7.5.4 Drug Concentration Measurements

Not applicable.

7.6 Data Quality Assurance

7.6.1 Clinical Procedures

MAPS personnel visited the study site prior to initiation of the study to review information about the investigational product, protocol requirements, randomization procedures, CRFs, monitoring requirements, and reporting of AEs and SAEs with the investigators.

7.6.2 Monitoring

At visits during and after the study, the site was monitored by a study monitor for compliance, including accurate and complete recording of data on CRFs, source documents and drug accountability records. The sponsor monitored the study at a rate that was appropriate for enrollment to ensure the study was conducted according to the principles of GCP.

7.6.3 Data Handling

Data management was conducted according to sponsor SOPs. Data recorded on CRFs were verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy. The PI ensured that CRFs and source documents of subjects enrolled in the study were available for inspection by MAPS representatives at the time of each monitoring visit.

Medical records, score sheets of study measures, and source documents were the primary source of data. The PI completed source documents upon consultation with the subjects and after reviewing medical records and score sheets. Study monitors reviewed the source documents in the presence of the PI to validate the recorded data in terms of correctness, completeness, legibility and accuracy. In case of obvious mistakes, those were discussed with the PI and corrected, initialed and dated by the PI accordingly. Entries to source and CRFs were made by the investigators only. If needed, the PI provided additional information by adding it to the subject's source documents. The validated CRFs were then collected from the study site.

Data entry personnel entered data from CRFs into a Microsoft Access database. Sponsor staff then reviewed the data and generated queries to the study site concerning any potential errors, omissions, or unlikely values in the data. After query resolution, the data was reviewed by sponsor staff and the PI. Once it was determined that the data had met quality assurance standards, a series of locked Excel files were generated and sent to the biostatistician. The biostatistician transferred data directly from Excel to SPSS Version 20.0 and additional restructuring was performed when necessary through SPSS. Analyses conducted by the site used SAS 9.1 for fitting the F1_LD_F1 model and R 2.7.1 for all other analyses. AEs were coded using MedDRA Version 14.

7.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

7.7.1 Statistical and Analytical Plans

Statistical evaluation was planned to be conducted by statisticians at the University of Bern in the Institute for Mathematical Statistics. The investigators planned to analyze results of outcome measure assessments by nonparametric analysis of variance (ANOVA) for all 12 study participants [45, 46]. The nonparametric framework was chosen for two reasons, that of the sample size being too small to assess the assumptions that underlie a parametric model, and because the primary outcome measure, CAPS score, is only measured on an ordinal scale. In order to compare the time courses of the control group and the treatment group, the investigators planned to apply an F1_LD_F1 model (cf. [45, 46]) with experimental intervention condition (MDMA versus active placebo) serving as a between-group factor and time of measurement serving as a within-subjects factor. The investigators were mainly interested in testing an interaction between experimental intervention condition and time. The effectiveness of three experimental sessions were planned to be compared to two experimental sessions by the Wilcoxon's Signed-Rank-Test for paired data. Statistical significance was set at 0.05. Because the sample size was small, the study had sufficient power only to detect large effects. Therefore, no statistical corrections were planned for multiple testing; p-values and confidence intervals would be reported instead.

Main analyses compared outcome measures collected at baseline with outcome measures during and at the end of Stage 1. While observations have been made of outcome measures in Stage 2 and Stage 3, they were not intended for formal analysis owing to the very small number of subjects who underwent these study arms. Whenever possible, comparisons were to be made between outcome measures during Stage 1, Stage 2 and Stage 3. Outcome measures at the end of Stage 1 and Stage 2 were compared to the follow-up, but they were not to be formally analyzed.

All subjects who received at least one experimental session and provided some safety data were considered evaluable for safety analysis in order to maximize information gained about MDMA-assisted psychotherapy in a clinical setting. Demographics were also calculated for all enrolled subjects, including dropouts.

Statistical tables and analyses were generated using SPSS Version 20.0. Missing values (e.g. from dropouts) were left out from inferential analyses because they were regarded as non-informative.

7.7.2 Determination of Sample Size

The sample size for this study was dictated by its exploratory nature. This small pilot study was conducted to test different variables in study design in preparation for large-scale studies in the future. There was no effect size available for calculation at the time the protocol was written, as the first sponsor-supported study of MDMA-assisted psychotherapy was still underway at the time. This study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with chronic, treatment-resistant PTSD. The sponsor intends to pool data across studies or perform meta-analyses of CAPS scores across all pilot studies.

7.8 Changes in the Conduct of the Study or Planned Analyses

Changes to the conduct of the study were made in five separate study amendments. Due to the exploratory nature of this pilot study, changes to the protocol were not considered to effect how the data would be analyzed. For a comprehensive list of changes to the protocol, see Appendix 14.1.1. Below is a brief summary of changes:

Protocol Amendment 1, dated August 16, 2006: Addition of description of an optional related brain imaging study that subjects could choose to participate in.

Protocol Amendment 2, dated May 28, 2007: Addition of audio recording and video recording of conventional (non-drug) and MDMA-assisted psychotherapy sessions to permit the sponsor to develop a standardized form of MDMA-assisted psychotherapy.

Protocol Amendment 3, dated February 19, 2008: Addition of Stage 3 for non-responders to examine whether offering an additional session and a higher dose of the investigational product could lead to improvement in PTSD symptoms.

Protocol Amendment 4, dated May 25, 2008: The protocol was amended to explicitly state that subjects who dropped out of the study would be replaced and that the study would end when twelve subjects completed the study.

Protocol Amendment 5, dated January 20, 2010: Cancellation of Stage 3 and the six-month follow-up.

In addition to the nonparametric analyses conducted at the site, the sponsor chose to conduct additional parametric analyses in order to ensure that the nonparametric statistical model was not leading to overinterpretation of the data. In order to assess whether three experimental sessions were more effective than two experimental sessions, the sponsor chose a student's T-test to conduct a comparison of paired data as opposed to the Wilcoxon-Signed-Rank Test. An additional exploratory analysis was added retroactively to the plan using a independent student's T-test to compare baseline scores to after third experimental session scores by condition. This comparison is used in the sponsor's current and future studies. A data analysis plan was prepared to describe the main efficacy and safety analyses, as well as additional and subsidiary analyses. See Appendix 14.1.9 for the analysis plan. All inferential statistics performed by the sponsor used SPSS Version 12.0 with data from the sponsor's locked database. The same database was used for the nonparametric analyses conducted at the site.

8.0 STUDY SUBJECTS

8.1 Disposition of Subjects

The investigators screened 30 potential participants and enrolled 14 subjects in this study. The primary reasons for screen failures are summarized in Figure 2. Two subjects (105 and 106) withdrew from the study after the first experimental session due to AEs. The blind was broken for these subjects at discontinuation. The disposition of subjects in this study is summarized in Figure 3.

Figure 2. Reasons for Screen Failures

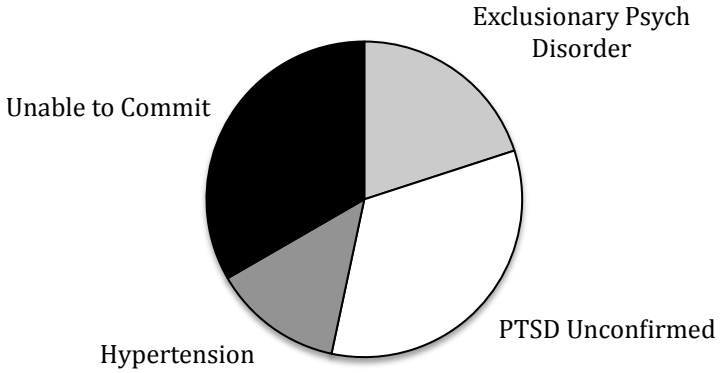
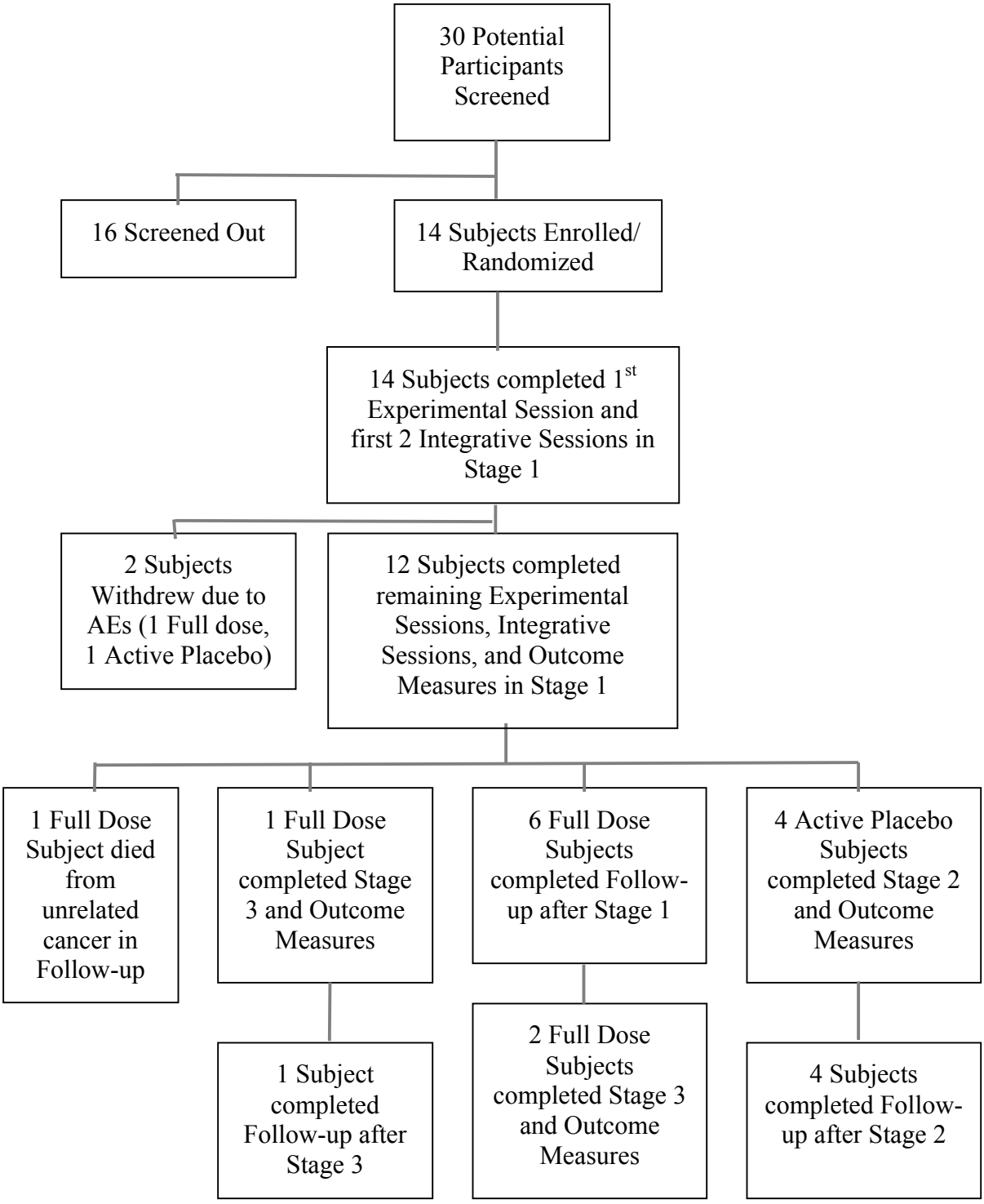


Figure 3. Disposition Summary of Subjects



8.2 Protocol Deviations

All protocol deviations are included as a categorized listing in Appendix 14.2.2.1. Overall, more deviations were observed in the full dose condition, most likely caused by the higher number of subjects in this group. Deviations from the protocol are summarized by category in Table 3. No subject was excluded from efficacy or safety analyses due to deviations. There were no systematic deviations. One subject was enrolled who did not meet criteria, with mild systolic hypertension noted at screening. This subject (112, full dose) was further monitored over 24 hours and the average blood pressure decreased. After discussion with the medical monitor the subject was enrolled. There were 3 subjects that met enrollment criteria but developed an exclusion criterion and were not withdrawn based on the judgment of the investigator. Subject 102 (full dose) consumed Ecstasy, an illicit preparation of unknown quality and dose that could contain MDMA, during the preparatory period of the protocol after enrollment but prior to the first experimental session. The PI discussed the subjective effects of this incident with the subject and concluded that it correlated with a subthreshold dose that was not clinically significant. Subject 103 (full dose) changed therapists after enrolling in the study and subject 107 (active placebo) displayed evidence of mild self harm on one occasion after receiving study drug; the behavior ceased after the single incident and was noted as an AE.

The most common deviations were visits performed outside of the window specified in the protocol. There were 86 visits out of window none of which created a safety risk and no data was excluded from analyses. Thirty-two of these were non-drug therapy sessions, 29 were outcome measures, 16 were experimental sessions, 7 were screening and enrollment visits and 2 were enrollments in Stage 3 that were out of window.

There were 19 incidents of informed consent procedures not performed per protocol. All subjects did sign the informed consent and most deviations were related to new versions of informed consents not being signed by all subjects. Versions of the informed consent were created multiple times throughout the study based on requests from regulatory agencies, the EC and the Sponsor, to comply with ICH-GCP guidance and to ensure use of certified translations. However, the RRPQ results in Appendix 14.2.11.2 demonstrate that the subjects did not perceive coercion in deciding to participate in the study. Commonly ranked reasons for participation were “To help myself”, “To help others”, “I was curious” and “I thought I would get better access to healthcare.”

Table 3. Number of Subjects with Protocol Deviations

	Total (N=14)	Full Dose (N=9)	Active Placebo (N=5)
Number of Protocol Deviations	111	64	47
Entered study but did not meet entry criteria	1	1	0
Developed withdrawal criteria during study but not withdrawn	3	2	1
Protocol procedure not performed per protocol	2	2	0
Procedure or visit out of window	86	47	39
Informed consent performed not per protocol	19	12	7

Source: Appendix 14.2.2.1

9.0 EFFICACY EVALUATION

9.1 Data Sets Analyzed

All subjects who completed Stage 1 were included in main efficacy analyses. Completion of Stage 1 was defined as completion of three blinded experimental sessions with associated integrative sessions and two

outcome measure assessments. These assessments were conducted three weeks after the second and third experimental sessions prior to unblinding for each subject. Criteria for inclusion in analyses were developed prior to the start of the study.

The two subjects who withdrew from the study due to AEs were replaced in order to obtain data from 12 subjects. The two subjects each completed a single experimental session and were excluded from efficacy analyses. (See Appendix 14.2.3)

9.2 Demographic and Other Baseline Characteristics

Table 4. Subject Demographics Summary

Demographic	Total (N=14)	MDMA (N=9)	Active Placebo (N=5)
Percent of Subjects by Gender			
Female (N)	78.6% (11)	50.0% (7)	28.6% (4)
Male (N)	21.4% (3)	14.3% (2)	7.1% (1)
Average Age in years (SD)	41.8 (10.9)	42.4 (13.0)	40.9 (6.9)
Percent of Subjects by Ethnicity			
African (N)	7.1% (1)	0.0% (0)	7.1% (1)
European (N)	85.7% (12)	57.1% (8)	26.6% (4)
Middle Eastern (N)	7.1% (1)	7.1% (1)	0.0% (0)
*Percent of Subjects by Trauma Etiology**			
Accident (N)	21.4% (3)	14.3% (2)	7.1% (1)
Life-threatening Illness (N)	7.1% (1)	7.1% (1)	0.0% (0)
Medical Treatment (N)	21.4% (3)	14.3% (2)	7.1% (1)
Rape/Sexual Assault (N)	14.3% (2)	7.1% (1)	7.1% (1)
Sexual Abuse (N)	50.0% (7)	28.6% (4)	21.4% (3)
Average Duration of PTSD in Years(SD)	17.8 (11.8)	15.5 (12.3)	21.8 (11.0)
Percent of Subjects with History of Substance Abuse			
Drug Abuse (N)	14.3% (2)	11.1% (1)	20.0% (1)
Alcohol Abuse (N)	7.1% (1)	11.1% (1)	0% (0)
Percent of Subjects with Comorbid Disorder			
Unipolar Depression (N)	85.7% (12)	88.9% (8)	80.0% (4)
Panic Disorder (N)	7.1% (1)	0% (0)	20.0% (1)
Eating Disorder (N)	7.1% (1)	11.1% (1)	0% (0)
Seasonal Affective Disorder (N)	7.1% (1)	0% (0)	20.0% (1)
Specific Phobia (N)	7.1% (1)	0% (0)	20.0% (1)
Dysthymia (N)	7.1% (1)	11.1% (1)	0% (0)
Average Duration of Past Psychotherapy in Months (SD)	52.7 (66.7)	30.8 (31.0)	101.9 (102.9)
Percent Subjects with Past Medication Use for PTSD (N)	57% (8)	55.5% (5)	60.0% (3)
Average Duration of Medication Use for PTSD in Months (SD)	30.5 (32.5)	36.4 (41.3)	20.7 (32.5)
Subjects Reporting Prior Ecstasy Use (Number of Incidences)	1 (3)	0 (0)	1 (3)

Source: Appendix 14.2.4.1, 14.2.4.2, 14.2.4.5, 14.2.4.6, 14.2.4.7, 14.2.4.8
* When more than one index trauma was listed, all were included in frequency calculations.

There were 14 subjects enrolled in this study with an average age of 41.84 years old (range = 23-68). The subjects were primarily female (78.5%) leading to the gender distribution being fairly equal across conditions. Twelve of the subjects were European. Due to the small sample size of this study, it was not feasible to sample a diverse subject population. The subject sample was highly comorbid, as is commonly observed with the general PTSD patient population. Unipolar depression was the most frequently observed comorbid disorder. A single subject assigned to the active placebo condition reported prior "Ecstasy" use on three occasions five to ten years before enrolling in the study. Two subjects reported prior drug abuse and one subject reported prior alcohol abuse prior to 60 days before enrollment.

9.3 Measurements of Treatment Compliance

The study drug was always administered under the supervision of the PI and the co-therapist during the experimental sessions. The PI was responsible for recording dosing on the CRF and completing accountability logs.

9.4 Efficacy Results and Tabulations of Individual Subject Results

9.4.1 Analysis of Treatment Efficacy

This study was designed to explore the efficacy of full dose MDMA (125mg +/- 62.5 mg) in comparison to active placebo MDMA (25mg +/- 12.5 mg) for the treatment of chronic, treatment-resistant PTSD. CAPS Global scores were found to decline in the full dose condition from 66.4 +/- 13.6 at baseline to 50.7 +/- 19.7 (N = 8) after the third experimental session. On average, CAPS scores declined 23.5%, or 15.6 points, in the full dose condition, which is comparable to a clinically significant response [43, 47]. In contrast, CAPS scores in the active placebo condition increased 5.2% from 63.2 +/- 7.9 at baseline to 66.5 +/- 7.5 (N=4) after the third experimental session. The average CAPS score of 50 was used as a diagnostic cut-off in this study, and full dose subjects dropped to only 0.6 points above this cut-off on average at the end of Stage 1. For an assessment of clinical significance based on a self-report measure, please see results of the secondary outcome measure, the PDS, below. See Table 5 for average CAPS scores in total and by condition assignment in Stage 1.

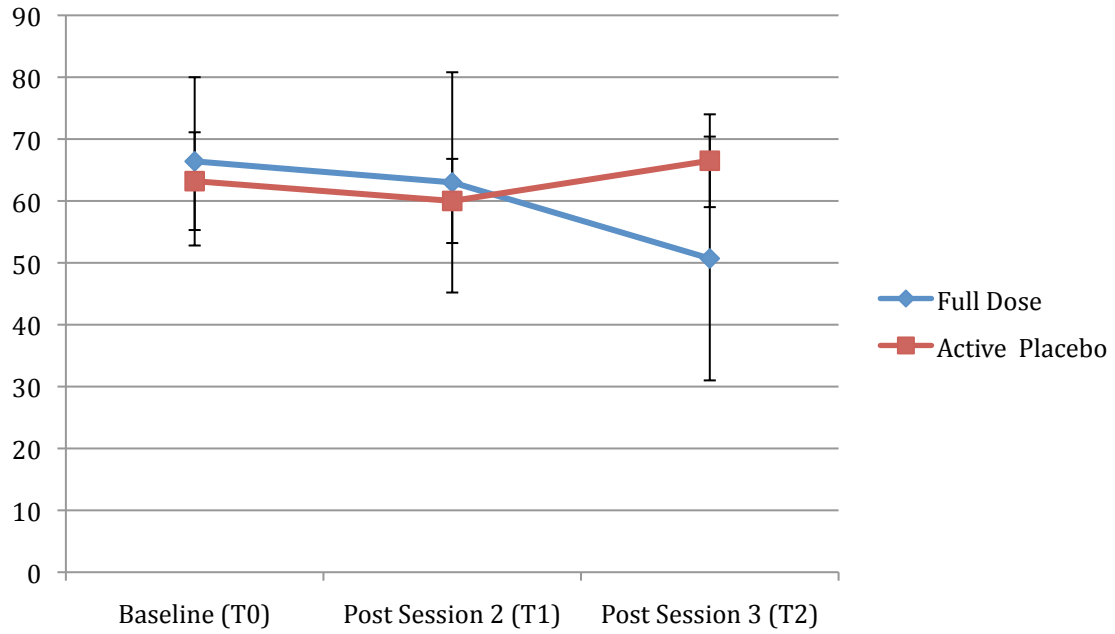
Table 5. Condition Assignment in Stage 1 vs. CAPS Global Scores

	Baseline (T0)	Post Session 2 (T1)	Post Session 3 (T2)	2-Month Follow-up (T3)*	6-Month Follow-up (T4)*	12-Month Follow-up (T5)*
Active Placebo						
N	4	4	4	4	1	4
Mean	63.2	60.0	66.5	36.7	21.0	31.5
SD	7.9	6.8	7.5	13.6	0.0	19.2
Full Dose						
N	8	8	8	8	2	6
Mean	66.4	63.0	50.7	49.1	63.5	35.5
SD	13.6	17.8	19.7	16.8	3.5	16.8
Total						
N	12	12	12	12	3	10
Mean	65.3	62.0	56.0	45.0	49.3	33.9
SD	11.7	14.7	17.9	16.4	24.7	16.8

Source: Appendix 14.2.6.1
* Follow-up visits were conducted after Stage 2 for active placebo subjects.

The main analysis for hypothesis testing conducted by the sponsor consisted of parametric repeated measures ANOVA using CAPS Global scores collected at baseline (T0), three weeks after the second experimental session (T1) and three weeks after the third experimental session (T2) of Stage 1, with time of administration as a within-subject factor and condition as a between-group factor. Data across time of administration did not meet assumptions of sphericity (Mauchly's Test = 8.87, df = 2, p = 0.01), so comparisons used the Greenhouse-Geisser Adjustment. No main effects were found for time or condition. There was also no significant interaction between time of administration and condition ($F = 3.7$, df = (1.3, 10), $p > 0.05$), but there was a trend for an interaction, with $p = 0.07$. The main analysis conducted at the site with nonparametric repeated measures ANOVA using the same time points found a significant simple time effect ($p < 0.05$) in the full dose condition ($p = 0.002$), but not the active placebo condition ($p = 0.475$). The interaction of time with condition was found to show a distinct decrease that also failed to prove significant ($p = 0.066$). The similarity of the p values between the two types of analysis demonstrate that the conclusions based on these data are consistent between the sponsor and the site.

Figure 4. Change in CAPS Global Scores of Stage 1 Subjects



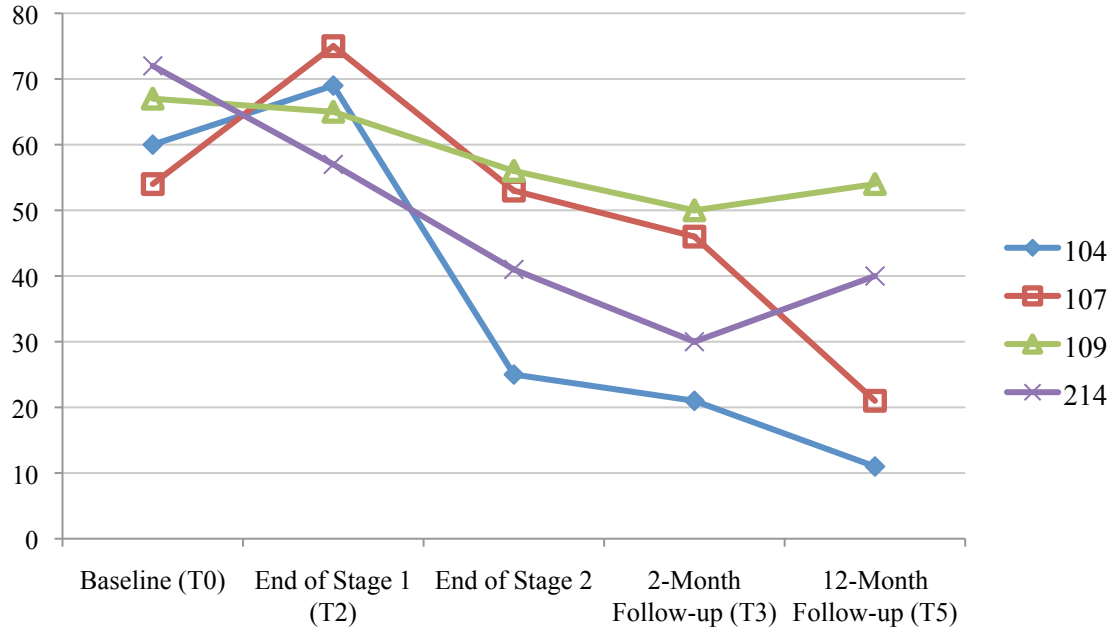
In addition to the main analysis comparing three time points in Stage 1, the sponsor conducted an independent student's T-test on the decrease in CAPS Global scores collected at baseline (T0) and three weeks after the third experimental session (T2) of Stage 1. CAPS scores of full dose subjects did not decrease significantly in this interval ($T=-1.782$, df=10, $p =0.105$). The mean difference score was 15.6, with a 95% confidence interval of 0.5 to 30.7. The sponsor notes that the underlying variation in the subject sample may have influenced the ability of the statistical analyses to detect significance in the changes experienced by full dose subjects.

The sponsor analyzed the time course of the downward trend in CAPS Global scores using a student's paired T-test comparing scores at T1 to T2. A significant decrease ($p < 0.05$) was found between T1 and T2 in the full dose condition ($p = 0.004$) but not in the active placebo condition ($p = 0.298$). The site conducted a Wilcoxon-Signed-Rank test for paired data to analyze the difference between T1 and T2, and also found a significant decrease in the full dose condition ($p = 0.016$). Although the p values are not as close, the conclusions of both the sponsor and the site are in agreement that 3 experimental sessions appear to be more effective than 2 experimental sessions in this subject group.

CAPS sub-scale scores were analyzed using parametric repeated measures ANOVA by the sponsor. No significant effects of time or interactions with condition were found for re-experiencing (CAPS sub-scale B), avoidance (CAPS sub-scale C), hyper-vigilance (CAPS sub-scale D), or degree of distress (CAPS sub-scale F). In the site's nonparametric ANOVA analysis, a significant time effect was found, with T1 having lower cluster C scores than T0 ($p = 0.042$), whereas the interaction of time with condition was not significant. The T0 comparison to T2 showed no significant interactions although a simple time effect was found with the full dose condition ($p = 0.0007$). In addition, a trend to a simple time effect was noted with cluster B scores ($p = 0.072$), suggesting changes occurring in the full dose group only. This discrepancy in conclusions is discussed under Section 9.4.2 Statistical and Analytical Issues.

All four active placebo subjects continued to Stage 2 and received open-label full dose MDMA. Due to the small sample size, a formal analysis of the results of Stage 2 were not possible. However, these subjects experienced a distinct decrease in PTSD symptom severity with average CAPS Global scores dropping from 66.5 +/- 7.5 (N=4) at the end of Stage 1 to 43.7 +/- 14.1 (N=4) at the end of Stage 2. See Figure 4 for a by-subject display of changes in CAPS scores in Stage 2 and the subsequent follow-up period. This decrease provides an important within-subject control, demonstrating that these subjects were not fundamentally different than subjects assigned to the full dose condition with respect to treatment resistance.

Figure 5. Change in CAPS Global Scores of Active Placebo Subjects Continuing to Stage 2



Ten of 12 subjects were assessed 12 months after their final Stage 1 or Stage 2 experimental session (T5). Subjects excluded from analysis were subjects 101, who died from cancer unrelated to drug administration prior to reaching this point, and 108, who underwent Stage 3 without receiving a long-term follow up assessment first. The 12-month follow-up visit took place one year after the third Stage 1 or Stage 2 session, as appropriate, and all subjects had received three sessions with full dose MDMA, either during Stage 1 or Stage 2. From the 2-month follow-up (T3) after receiving full dose MDMA in either Stage 1 or Stage 2, CAPS Global scores had dropped from an average of 45.0 +/- 16.4 (N=12) at T3 to 33.9 +/- 16.8 (N=10) at T5. Hypothesis testing was conducted using CAPS Global scores in total and comparisons were made across time from Baseline, T3, and T5. There was a significant effect of time, $F = 23.4$, $df = (2, 8)$, $p < 0.000$. Subjects with missing data were excluded from this analysis (N=10).

When T5 scores of subjects who were originally assigned to the active placebo condition and full dose subjects were compared, on average both were below the diagnostic cut-off of 50. These data suggest that these subjects may retain the benefits they experienced three weeks after their third full dose MDMA session, and that they may even continue to improve after finishing the treatment portion of the study.

The PDS was used to estimate self-reported PTSD symptoms and degree of impairment as a secondary measure in this study. Average PDS scores were found to decline in the full dose condition from 31.0 +/- 6.3 at baseline to 21.4 +/- 11.8 (N = 8) at T2. In contrast, PDS scores in the active placebo condition increased slightly from 23.5 +/- 1.9 at baseline to 30.7 +/- 6.2 (N=4) at T2. The PDS scores were in good agreement with results of the primary efficacy measure, the CAPS. See Table 6 for average PDS severity scores in total and by condition assignment in Stage 1.

The analysis for hypothesis testing conducted by the sponsor consisted of repeated measures ANOVA using PDS severity scores collected at baseline (T0), one day after each experimental session, and three weeks after the third experimental session (T2) of Stage 1, with time of administration as a within-subject factor and condition as a between-group factor. Data across time of administration did not meet assumptions of sphericity (Mauchly's Test = 18.8, df = 9, p = 0.03), so comparisons used the Greenhouse-Geisser Adjustment. No main effects were found for time or condition. There was also no significant interaction between time of administration and condition ($F = 3.4$, df = (1.9, 10), $p > 0.05$), but there was a strong trend for an interaction, with $p = 0.054$. The nonparametric analysis conducted at the site found a significant interaction between time and condition with $p = 0.014$. This discrepancy in conclusions is discussed under Section 9.4.2 Statistical and Analytical Issues.

In addition to the planned analyses, the sponsor conducted an independent student's T-test on the decrease in PDS scores collected at baseline (T0) and three weeks after the third experimental session (T2) of Stage 1. PDS scores of full dose subjects decreased significantly in this interval ($T=-3.047$, df=9.993, $p =0.012$). The mean difference score was -16.9, with a 95% confidence interval of -29.2 to -4.5. The PDS scores were strongly interacting in the main analysis, suggesting that according to self-report measures subjects may have experienced reduction in PTSD symptoms in this interval.

Table 6. Condition Assignment in Stage 1 vs. PDS Severity Scores

	Baseline (T0)	1 Day Post Session 1	1 Day Post Session 2	1 Day Post Session 3	3 Weeks Post Session 3 (T2)	2-Month Follow-up (T3)*	12-Month Follow-up (T5)*
Active Placebo							
N	4	4	4	4	4	4	4
Mean	23.5	26.0	28.7	28.5	30.7	15.5	10.5
SD	1.9	3.5	8.3	8.9	6.2	6.4	8.6
Full Dose							
N	8	8	8	8	8	8	6
Mean	31.0	30.6	22.5	20.7	21.4	19.6	14.8
SD	6.3	10.0	12.8	9.4	11.8	11.9	12.2
Total							
N	12	12	12	12	12	12	10
Mean	28.5	29.1	24.6	23.3	24.5	18.2	13.1
SD	6.3	8.5	11.5	9.6	11.0	10.3	10.6

Source: Appendix 14.2.6.2
* Follow-up visits were conducted after Stage 2 for active placebo subjects.

As was done with long-term follow up CAPS scores, PDS symptom severity scores of all subjects were combined in analysis at T3 and T5, since all subjects had received full dose MDMA at that point in the study. From the 2-month follow-up (T3) after receiving full dose MDMA in either Stage 1 or Stage 2, PDS severity scores had dropped from an average of 18.2 +/- 10.3 (N=12) at T3 to 13.1 +/- 10.6 (N=10) at T5. Hypothesis testing was conducted using PDS severity scores in total and comparisons were made with time of administration as a within-subjects factor at baseline, T3, and T5. Subjects with missing data were excluded from this analysis (N=10). Data across time of administration did not meet assumptions of sphericity (Mauchly's Test = 6.6, df = 2, p = 0.037), so comparisons used the Greenhouse-Geisser Adjustment. There was a significant effect of time, F = 15.1, df = (1.3, 18), p =0.001. Since change from baseline to T2 only showed trends toward significance, it appears that a greater decline in PTSD symptoms occurred during the 12-month follow-up. However, as only ten participants have usable scores at T5, the sample is small and some subjects received additional treatment with other medications and/or psychotherapy.

9.4.2 Statistical/Analytical Issues

The general statistical approach planned for this trial has been described in Section 7.7. This section is to address statistical issues specifically as they relate to data from this clinical study. These issues will be discussed briefly here and the reader is referred to the statistical Appendix 14.1.9 for further details. Any departures from preplanned analyses were noted in Section 7.8.

The sponsor conducted parametric repeated measures ANOVA that was different than the nonparametric ANOVA analyses originally planned and conducted at the site for this study. The primary difference between the two analyses was in the approach to handling non-normal data. . The F1_LD_F1 model assumes that such a small subject sample can be expected to have a non-normal distribution and attempts to address this through the use of medians instead of means. In contrast, the sponsor assessed sample data sphericity by performing Mauchly's test prior to conducting each repeated measures ANOVA as a means of addressing distribution, which reports the Mauchly's W. When this statistic indicated a failure to meet assumption of sphericity, the sponsor reports results adjusted for lack of sphericity via Greenhouse-Geisser adjustment.

Due to the difference in methods, the sponsor's analysis did not reproduce findings of simple time effects, but were in agreement on the lack of a significant interaction between time and condition for CAPS sub-scale scores. Furthermore, the sponsor's analysis was not in agreement with conclusions reached by the site on the interaction of time and condition in PDS severity scores. Given that the CAPS sub-scale scores and PDS severity scores are not part of a main analysis, this discrepancy has been duly noted but does not effect the sponsor's efficacy conclusions from this study. The analyses from the site have been provided in Appendix 14.1.9.

9.4.2.1 Adjustments for Covariates

The sample size was small and homogenous, and no adjustments for covariates were made.

9.4.2.2 Handling of Dropouts or Missing Data

Two subjects, 105 and 106, withdrew from the study due to AEs after the first experimental session. Data from these subjects were used in examining safety data but not efficacy data. The withdrawal of these subjects was prior to the outcome measure assessments 3 weeks after the second and third experimental sessions, so their data is omitted from main analyses. (See Appendix 14.2.3)

9.4.2.3 Interim Analyses and Data Monitoring

Although the possibility of an interim analysis was added to the protocol with Amendment 5, it was not conducted.

9.4.2.4 Multicenter Studies

This was a single center study conducted in Switzerland.

9.4.2.5 Multiple Comparisons/Multiplicity

The Bonferroni method was used to adjust for multiplicity in comparison of the PDS sub-scale scores, since these scores provide different ways of measuring the same impairment from PTSD symptoms. Descriptive statistics are presented alongside each comparison. The PDS consists of a global scale and two sub-scales, making for three comparisons of symptom severity via PDS. The significance level (2-sided) of 0.05 was divided by 3 to give a (2-sided) multiplicity-adjusted significance level of 0.05/3 = 0.01.

CAPS sub-scale scores were not adjusted, due to current thought in the PTSD field based on confirmatory factor analyses that the symptom clusters measured by CAPS sub-scales can vary independently and measure different symptom clusters [47-49]. The global CAPS score and PDS global score were not corrected, as each observation differs in administration time (T0, T1, T2, T3, T4, T5).

9.4.2.6 Use of an "Efficacy Subset" of Patients

The sample size was too small for the use of "efficacy subsets." All available data was included from subjects who completed outcome measure assessments in Stage 1.

9.4.2.7 Active-Control Studies Intended to Show Equivalence

This was an exploratory study of safety, tolerability and efficacy, not designed to show equivalence.

9.4.2.8 Examination of Subgroups

Not applicable.

9.4.3 Tabulation of Individual Response Data

In addition to a continuous assessment of PTSD severity through the CAPS Global score and sub-scales B-D, the CAPS also provides a dichotomous measure of subjects meeting diagnostic criteria for PTSD. Selected results of subjects meeting diagnostic criteria throughout the study are presented in Table 7. These results lend additional support to the within-subject comparison of the effect of full dose MDMA on subjects who received active placebo in Stage 1, as 75% of subjects who received full dose MDMA satisfied diagnostic criteria for PTSD either at the end of Stage 1 or Stage 2. Interestingly, both groups of subjects who received full dose MDMA continued to improve during the follow-up period, with a reduction to 60% of total subjects satisfying diagnostic criteria for PTSD after one year.

Table 7. Condition Assignment in Stage 1 vs. Subjects Meeting Diagnostic Criteria for PTSD in the CAPS

Condition in Stage 1	Baseline (T0)	End of Stage 1 (T2)	End of Stage 2	2-Month Follow-up (T3)*	12-Month Follow-up (T5)*
Active Placebo (N/Total)	100% (4/4)	100% (4/4)	75% (3/4)	50% (2/4)	25% (1/4)
Full Dose (N/Total)	100% (8/8)	75% (6/8)	N/A	100% (8/8)	83% (5/6)
Total (N/Total)	100% (12/12)	83% (10/12)	75% (3/4)	83% (10/12)	60% (6/10)

Source: Appendix 14.4.21
* Follow-up visits were conducted after receiving full dose MDMA in Stage 2 for active placebo subjects.

9.4.4 Drug Dose, Drug Concentration, and Relationships to Response

This study compared the effect of two different doses (25mg and 125mg) of MDMA on PTSD symptom severity. In addition, a few subjects received an initial dose of 150 mg MDMA in Stage 3 for exploratory purposes. These initial doses were followed by a supplemental dose equivalent to half the initial dose approximately 2 hours later unless contraindicated. Based on the small sample size, a formal analysis of dose response was not possible in this study. The sponsor intends to pool these data with other pilot studies supported by the sponsor in order to conduct a meta-analysis of dose response of PTSD symptoms. Please see Section 10.1 Extent of Exposure for individual subject data on MDMA doses received in this study.

9.4.5 Drug-Drug and Drug-Disease Interactions

Subjects who were taking psychotropic medications at enrollment were required to taper off psychotropic medications upon enrollment with the exception of gabapentin prescribed for pain control to avoid any drug interactions and to provide a clear interpretation of the outcome for each subject. Subjects were allowed to resume taking medications after the follow-up evaluation two months after the final experimental session (T3).

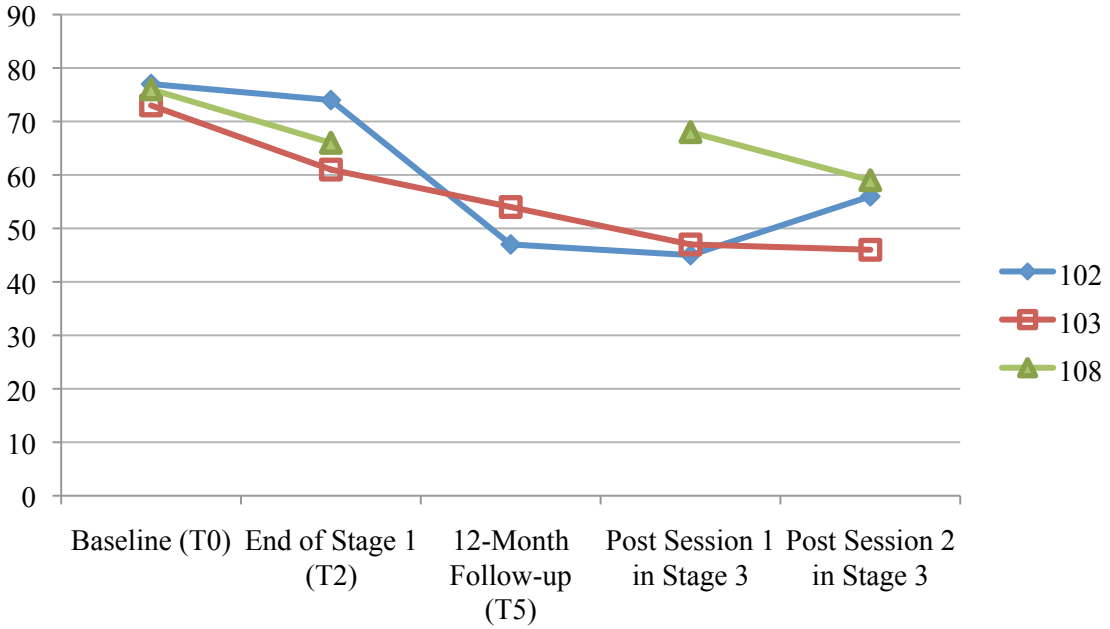
In this small subject population, based on the safety profile of the drug discussed in Section 10.0, drug-disease interactions were not observed.

9.4.6 By-Subject Displays

Three subjects (102, 103, 108) underwent a third study arm with two additional sessions of MDMA-assisted psychotherapy during Stage 3 if the investigators believed they had not responded to treatment with full dose MDMA during Stage 1. Subjects selected for this arm of the study were included if they had received full dose MDMA in three experimental sessions and still had severe PTSD symptoms based on CAPS scores. As described earlier, Stage 3 was later discontinued in a protocol amendment, and subjects 110, 111, 112, 213 and 214 were not offered participation in this arm. Please see Section 10.1 Extent of Exposure for individual subject data on MDMA doses received in Stage 3. PTSD symptoms were assessed at the 12-Month follow-up (T5) prior to Stage 3 and after each experimental session as shown in Figure 5. An informal examination of CAPS scores in this population does not suggest that

taking part in Stage 3 reduced CAPS scores, although scores were lower for subjects 102 and 103 during Stage 3 assessments. Rather, it appears that the CAPS scores of these subjects continued to decrease during the follow-up period prior to Stage 3. The 12-month follow-up data of subject 108 was collected after Stage 3, unlike 102 and 103. This subject's score had in fact continued to decrease to 38. Based on these informal observations, these data suggest that the follow-up period after MDMA-assisted psychotherapy may be more effective than additional sessions assisted by slightly higher doses of MDMA for reduction of PTSD symptom severity in these individuals.

Figure 6. Change in CAPS Global Scores of Non-Responder Subjects Continuing to Stage 3



9.4.7 Efficacy Conclusions

Overall, while encouraging, the results of this small exploratory pilot study have demonstrated clinically significant improvement but are not sufficient to demonstrate statistically significant treatment efficacy. Taking a conservative approach in hypothesis testing, the sponsor observed trends in CAPS and PDS scores suggesting three psychotherapy sessions assisted by 125 mg MDMA may cause some study subjects to experience fewer PTSD symptoms than subjects given 25 mg MDMA. However, larger studies with more subjects are necessary to make formal conclusions about efficacy of this treatment.

To support the results of the CAPS, which was administered by a blinded independent rater, this study employed the PDS to collect self-report data from subjects about the severity of their PTSD symptoms. The PDS results demonstrated a strong trend in this study, suggesting a response to full dose MDMA that was close to clinical significance. Taken together, the CAPS and PDS data from this study make a strong argument that future clinical trials of MDMA-assisted psychotherapy could produce clinically and statistically significant reductions in PTSD symptoms with larger subject samples.

Using a student's T-test, the sponsor found significance in the decrease of CAPS scores when comparing results after two experimental sessions to those after three experimental sessions. Given that this was an exploratory study, the sponsor also conducted an unplanned analysis using an independent T-test to compare the decrease from baseline scores to after the third experimental session and found significant reduction in self-reported PTSD symptoms according to the PDS in the full dose group. While obtaining

information about the time course of drug response was important, the repeated measures ANOVA results were not statistically significant. Using this information, the sponsor intends to directly compare results after three experimental sessions to baseline in future studies.

Results from Stage 2 demonstrate that subjects who were originally given active placebo MDMA were not necessarily less responsive to treatment, as they showed evidence of improvement after Stage 2. Alternately, results may be interpreted as demonstrating that more psychotherapy sessions cause PTSD symptom severity to decrease further. However, based on Stage 3 results the sponsor postulates that the follow-up period after the end of the treatment period was more effective than additional MDMA sessions at decreasing PTSD symptom severity in this study.

A significant decrease in CAPS and PDS scores was observed in the 12-month follow-up, suggesting that if benefits are gained from MDMA-assisted psychotherapy, they are retained and may grow over time. However, caution should be used in interpreting these results due to the lack of a control group, as all subjects had received full dose MDMA prior to the follow-up, because the Stage 2 arm was conducted open-label after breaking the blind, and many subjects resumed concomitant therapy during the follow-up.

Overall, these results suggest that three sessions of MDMA-assisted psychotherapy with full dose MDMA may be responsible for clinically significant reduction in PTSD symptoms as evidenced by a trend towards improvement in comparison to active placebo. The sponsor cautiously interprets these data as justification for larger clinical trials in Phase 3.

10.0 SAFETY EVALUATIONS

10.1 Extent of Exposure

Both conditions assessed in this study received investigational product that differed in the dose they received. Each exposure to investigational product consisted of an initial dose, administered orally in a capsule with water, and a supplement capsule administered two hours later, unless contraindicated. In all Stage 1 and Stage 2 experimental sessions and four of six Stage 3 sessions, the supplement was half the size of the initial dose. In two of the Stage 3 sessions (subject 102 and 103), the supplemental dose administered was less than half of the original dose based on the clinical judgment of the investigator. Study drug was not administered outside of experimental sessions.

Table 8. Extent of Exposure to Investigational Product by Subject

Subject	Condition in Stage 1	Gender	Ethnicity	Age	Cumulative Exposure (mg)	Number of Exposures
101	Full Dose	Female	European	39	562.5	3
102	Full Dose	Male	European	31	1000	5
103	Full Dose	Female	European	39	962.5	5
104	Active Placebo	Male	European	46	675	6
105	Full Dose	Male	Middle Eastern	40	125	1
106	Active Placebo	Female	African	42	37.5	1
107	Active Placebo	Female	European	40	675	6
108	Full Dose	Female	European	23	975	5
109	Active Placebo	Female	European	29	675	6
110	Full Dose	Female	European	41	562.5	3
111	Full Dose	Female	European	56	437.5	3
112	Full Dose	Female	European	68	562.5	3
213	Full Dose	Female	European	42	562.5	3
214	Active Placebo	Female	European	45	675	6

Source: Appendix 14.2.5.2

Table 9. Maximum Dose of Investigational Product Received by Subject

Subject	Condition in Stage 1	Maximum Dose Received in Study		
		Initial Dose (mg)	Supplemental Dose (mg)	Cumulative Dose (mg)
101	Full Dose	125	62.5	187.5
102	Full Dose	150	75	225
103	Full Dose	150	62.5	212.5
104	Active Placebo	125	62.5	187.5
105	Full Dose	125	62.5	187.5
106	Active Placebo	25	12.5	37.5
107	Active Placebo	125	62.5	187.5
108	Full Dose	150	75	225
109	Active Placebo	125	62.5	187.5
110	Full Dose	125	62.5	187.5
111	Full Dose	125	62.5	187.5
112	Full Dose	125	62.5	187.5
213	Full Dose	125	62.5	187.5
214	Active Placebo	125	62.5	187.5

Source: Appendix 14.2.5.2

10.2 Adverse Events

10.2.1 Brief Summary of Adverse Events

10.2.1.1 Spontaneously Reported Reactions

Spontaneously reported reactions were considered expected AEs and were collected for a total of 8 days after each experimental session. Reactions that continued beyond this window were recorded as unexpected AEs for the full duration. All subjects enrolled and treated experienced at least one reaction on the day of the experimental session as well as at least once during the 8 days after each experimental session.

10.2.1.2 Unexpected Adverse Events

Sixty-one unexpected AEs occurred during the course of study, 2 of which were serious. Both of the SAEs were unrelated to drug administration. One SAE took place prior to drug administration and the other was the death of a subject due to cancer. Thirteen AEs were deemed possibly or probably related by the PI.

Table 10. Overview of Unexpected Adverse Events by Condition in Stage 1

	Full Dose (N)	Active Placebo (N)	Total (N)
Any AEs	77.0% (47)	23.0% (14)	100% (61)
At Least Possibly Related AEs	14.8% (9)	6.5% (4)	21.3% (13)
Serious AEs	100% (2)	0.0% (0)	3.3% (2)
At Least Possibly Related SAEs	0.0% (0)	0.0% (0)	0.0% (0)

Source: Appendix 14.4.17

10.2.2 Display of Adverse Events

An overview of subjects experiencing unexpected adverse events is presented in Table 12. Summaries of spontaneously reported reactions on the day of and 8 days after drug administration are presented in Appendices 14.2.7.6 and 14.2.7.7.

A detailed summary of adverse events possibly or probably related to drug administration is presented in Appendix 14.2.7.2. Eight of the thirteen treatment-emergent AEs (61.5%) occurred after the subjects received full dose MDMA either in Stage 1 or Stage 2. Detailed listings for unexpected severe adverse events are presented in Appendix 14.2.7.3. Severe treatment-emergent AEs were evenly distributed between doses (N=2, 50% in each). There was one death, unrelated to drug administration from brain metastasis of a tumor, listed as one of the SAEs in Appendix 14.2.7.4. There were 2 AEs leading to withdrawal listed in Appendix 14.2.7.5.

10.2.3 Analysis of Adverse Events

10.2.3.1 Spontaneously Reported Reactions

All subjects in both conditions experienced at least one spontaneously reported reaction on the day of or during 8 days after drug administration. The number of reactions reported in the full dose group were also more, as expected, since more subjects were assigned to this group. See Table 11 for total reactions reported on the day of experimental sessions and their mean severity and duration by condition. See Table 12 for total reactions reported on the 8 days after experimental sessions and their mean severity and duration by condition. Stage 2 data was pooled with full dose subjects in Stage 1 since they both received full dose MDMA. Subjects participating in Stage 3 were a subset of Stage 1 full dose subjects and mean severity and mean duration data for reactions reported in Stage 3 are presented in Table 12.1.1 and 12.1.2.

Table 10. Spontaneously Reported Reactions In MP-2 On Day Of Experimental Session

	Total Reports		Mean Severity** (1=mild, 3=severe)		Mean Duration** (hours)	
	125mg	25mg	125mg	25mg	125mg	25mg
Insomnia	16	4	2.1 (1-3)	1.8 (1-3)	2.5 (1-7)	3.2 (2-7)
Loss of appetite	15	4	1.9 (1-3)	2.0 (1-3)	9.4 (1-24)	16.8 (1-24)
Restless	15	0	1.2 (1-2)	0	1.4 (0.5-6)	0
Tight jaw	14	1	1.4 (1-3)	1.0 (1-1)	2.4 (0.5-4)	3.0 (3-3)
Fatigue	13	2	1.5 (1-2)	1.0 (1-1)	2.9 (0.5-4)	1.0 (1-1)
Thirsty	13	0	1.3 (1-2)	0	2.6 (1-6)	0
Headache	11	5	1.6 (1-2)	1.8 (1-2)	2.2 (1-4)	5.7 (1-24)
Impaired gait/balance	12	3	1.0 (1-1)	1.0 (1-1)	0.8 (0.5-3)	0.9 (0.5-2)
Feeling cold	11	1	1.1 (1-2)	1.0 (1-1)	2.4 (1-8)	2.0 (2-2)
Anxiety	10	2	1.6 (1-3)	1.5 (1-2)	3.6 (0.5-24)	1.0 (1-1)
Nausea	6	2	1.8 (1-3)	1.0 (1-1)	1.0 (0.5-4)	0.7 (0.5-1)
Dizzy	8	3	1.0 (1-1)	1.0 (1-1)	1.3 (0.5-4)	2.2 (0.5-4)
Dry mouth	7	0	1.1 (1-2)	0	2.0 (1-4)	0
Perspiration	6	0	1.5 (1-2)	0	2.3 (1-6)	0
Difficulty concentrating	6	0	1.1 (1-2)	0	2.4 (0.5-24)	0
Low mood	4	1	1.3 (1-2)	2.0 (2-2)	3.5 (1-6)	2.0 (2-2)
Nystagmus	3	0	1.0 (1-1)	0	0.9 (0.5-1)	0
Feeling weak	3	0	1.8 (1-2)	0	2.5 (2-3)	0
Private Worries	3	0	1.5 (1-2)	0	0.7 (0.5-1)	0
Drowsy	2	0	1.0 (1-1)	0	2.2 (0.5-4)	0
Parasthesias	2	0	1.0 (1-1)	0	1.7 (0.5-3)	0
Heavy legs	1	0	1.0 (1-1)	0	2.0 (2-2)	0
Need More sleep	1	0	2.0 (2-2)	0	2.0 (2-2)	0
Irritable	0	0	0 (0-0)	0	0	0

Source: Appendix 14.2.7.6

* Mean percentage for full dose sessions included: All available data for Stage 1 sessions of full dose subjects (N = 9) and Stage 2 sessions of subjects originally assigned to active placebo (N = 4).

** Mean duration/severity (Minimum reported– Maximum reported)

The most commonly reported reactions on the day of the experimental session were insomnia, loss of appetite and restlessness in subjects receiving full dose, and headache, insomnia and loss of appetite in subjects receiving active placebo. Insomnia and loss of appetite were the most commonly reported reactions in both conditions. Total reports of reactions were lower in the active placebo group due to more subjects receiving the full dose in Stage 1 and Stage 2, which were combined in safety analyses. Restlessness, tight jaw, feeling cold and thirst were commonly reported reactions in the full dose group that were minimally reported in the active placebo group. Dizziness, headache and impaired gait/balance were also frequently reported in both groups. Severe insomnia (107, 109, 110), loss of appetite (107), tight jaw (108), anxiety (105), and nausea (108) were reported by subjects receiving full dose during Stage 1 or 2 on the day of the experimental session. Severe insomnia (107) and loss of appetite (107) were reported by one subject receiving active placebo on the day of the experimental session. It should be

noted that subject 107 experienced severe insomnia and loss of appetite both in Stage 1 when receiving active placebo and Stage 2 when receiving full dose. Duration was collected up to the closest half hour on the day of the experimental session. Most reactions resolved when drug effects diminished. Loss of appetite, difficulty concentrating, anxiety, and headache persisted beyond this window to 24 hours, but was self-limiting. Acetaminophen (Paracetamol) and ibuprofen were used as rescue medications to manage these reactions when appropriate.

Table 11. Spontaneously Reported Reactions In MP-2 During 8 Days After Experimental Session

	Total Reports (#reports/N)* **		**Mean Severity** (1=mild, 3=severe)**		**Mean Duration** (Days)**	
	125mg	25mg	125mg	25mg	125mg	25mg
Fatigue	19/61	6/24	1.5 (1-3)	1.4 (1-3)	3.0 (1-7)	3.5 (1-7)
Insomnia	19/52	6/31	1.9 (1-3)	1.6 (1-3)	2.9 (1-8)	5.7 (3-8)
Low mood	19/53	6/24	1.4 (1-3)	1.4 (1-2)	2.6 (1-8)	3.2 (2-5)
Anxiety	11/34	1/4	1.6 (1-3)	1.0 (1-1)	3.0 (1-8)	1.0 (1-1)
Difficulty concentrating	11/29	0/0	1.5 (1-3)	0 (0-0)	2.9 (1-8)	0 (0-0)
Private Worries	9/24	2/7	1.4 (1-3)	1.1 (1-2)	2.4 (1-5)	2.0 (1-3)
Dizzy	9/19	5/7	1.6 (1-2)	1.3 (1-2)	2.1 (1-5)	1.3 (1-4)
Irritable	9/19	1/2	1.3 (1-2)	1.0 (1-1)	2.1 (1-5)	2.0 (2-2)
Loss of appetite	8/39	5/15	1.5 (1-3)	1.5 (1-3)	5.0 (1-8)	4.0 (1-7)
Tight jaw	7/14	0	1.2 (1-2)	0 (0-0)	1.6 (1-5)	0 (0-0)
Headache	7/12	4/26	1.9 (1-3)	1.5 (1-2)	2.6 (1-6)	6.7 (4-8)
Feeling cold	7/11	1/2	1.2 (1-2)	1.0 (1-1)	2.1 (1-5)	2.0 (2-2)
Restless	6/19	0	1.4 (1-3)	0 (0-0)	3.2 (1-7)	0 (0-0)
Feeling weak	5/7	0	1.1 (1-2)	0 (0-0)	1.4 (1-2)	0 (0-0)
Dry mouth	4/9	0	1.0 (1-1)	0 (0-0)	2.3 (1-4)	0 (0-0)
Nausea	4/6	3/7	1.0 (1-1)	1.2 (1-2)	1.2 (1-2)	4.7 (1-6)
Need More sleep	3/11	2/10	1.1 (1-2)	1.2 (1-2)	3.3 (1-7)	3.5 (1-6)
Impaired gait/balance	3/6	0	1.4 (1-2)	0 (0-0)	2.0 (1-4)	0 (0-0)
Drowsy	2/2	1/3	1.0 (1-1)	1.0 (1-1)	1.0 (1-1)	3.0 (3-3)
Thirsty	1/4	0	1.2 (1-2)	0 (0-0)	4.0 (4-4)	0 (0-0)
Nystagmus	1/1	0	1.0 (1-1)	0 (0-0)	1.0 (1-1)	0 (0-0)
Perspiration	1/1	0	1.0 (1-1)	0 (0-0)	1.0 (1-1)	0 (0-0)
Parasthesias	0/0	0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Heavy legs	0/0	1/1	0 (0-0)	1.0 (1-1)	0 (0-0)	1.0 (1-1)

Source: Appendix 14.2.7.7

* Mean percentage for full dose sessions included: All available data for Stage 1 sessions of full dose subjects (N = 9) and Stage 2 sessions of subjects originally assigned to active placebo (N = 4).

** Mean duration/severity (Minimum reported– Maximum reported)

*** Total Reports include (total number of times a reaction was reported / N observations over 8 days after each experimental session)

During the 8 days following each experimental session, severity was collected on each day and duration was computed across 8 days. The most commonly reported reactions during this time were fatigue, insomnia, and low mood in both groups. The second most common reactions were anxiety and difficulty concentrating in subjects receiving full dose, and loss of appetite and needing more sleep in subjects receiving active placebo. Total reports of reactions were lower in the active placebo group due to more subjects receiving the full dose in Stage 1 and Stage 2, which were combined in safety analyses. Anxiety, difficulty concentrating, restlessness, tight jaw, and feeling weak were commonly reported reactions in the full dose group that were minimally reported in the active placebo group. Dizziness, increased private worries and loss of appetite were also frequently reported in both groups. Insomnia and headache were the reactions with the highest mean severity 8 days after the experimental session in both groups. Overall, the active placebo group experienced less severe reactions on average. Subjects receiving full dose in Stage 1 or 2 reported severe fatigue (101, 108, 109), insomnia (101, 109, 107, 108), low mood (101, 105, 110), anxiety (105, 107, 101), difficulty concentrating (101), increased private worries (101), loss of appetite (108), headache (109), and restlessness (101). Active placebo subjects reported severe fatigue (107), insomnia (107, 214) and loss of appetite (107). Severe reactions either resolved within 7 days after the experimental session or if persisting beyond this window were diminished in severity.

Three subjects received higher initial doses of 150 mg MDMA in Stage 3 as described in section 10.1 Extent of Exposure. For 2 of these subjects, the investigator chose not to administer the supplemental dose at half the initial dose due to reactions reported during the experimental session. This reaction was severe tight jaw, reported on 4 of the 6 Stage 3 sessions by 2 of 3 subjects. The other severe reaction reported on the day of the experimental session was insomnia. During 8 days after the experimental session, fatigue was the most commonly reported reaction that was reported as severe for 4 days after the first session and 2 days after the second session by subject 108.

Most reactions were self-limiting and resolved by the seventh day after the experimental session. Insomnia, low mood, anxiety, difficulty concentrating and loss of appetite persisted in full dose subjects and insomnia and headache persisted in active placebo subjects beyond this window. All reactions continuing beyond the eighth day were tracked as AEs until resolution. Over the counter medications, including Acetaminophen (Paracetamol) and ibuprofen, were used as rescue medications to manage these reactions when appropriate.

10.2.3.2 Unexpected Adverse Events

A total of 61 AEs were reported in 11 subjects. Three subjects, one in the full dose condition, did not report any unexpected AEs. The incidence of AEs by condition was 77.0% (47) in subjects receiving full dose and 22.9% (14) in subjects receiving active placebo. The most commonly reported AEs were psychiatric disorders (44.3%). Many of these were included among spontaneously reported reactions but they were tracked as AEs since they persisted beyond the 7-day window after experimental sessions. (See Appendix 14.2.7.1) Subjects all had the intention of confronting and working through traumatic experiences in this study. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. AEs defined as expected were originally compiled from literature on healthy volunteers. It is worth investigating which AEs should be expected, given that the subject population enrolled in this study had multiple PTSD symptoms present at baseline that would be classified as psychiatric disorders.

Thirteen AEs (in 7 subjects) were considered possibly or probably related to drug administration. Nine of these were included in the spontaneously reported reactions but were found to persist beyond the 7-day window after experimental sessions and were tracked as AEs for the full duration. The most noteworthy

Table 12. All Adverse Events Grouped by Body System

Adverse Event	Mild		Moderate		Severe		Total	
	PR	NR	PR	NR	PR	NR	PR	NR
Psychiatric								
Increased Private Worries	111	110					1	1
Panic Attack			101		101		2	0
Suicidal Behavior		103					0	1
Anxiety		213(2)		110(3)	105,106		2	5
Difficulty Concentrating		105,111					0	2
Insomnia		107(2)		110,105 107(2)		107 (2)	0	8
Low mood		111		105			0	2
Sleepy		105					0	1
Self Harm		107					0	1
Somatoform disorder				110			0	1
Nervous System								
Headache			105 109	106	109		3	1
Decrease in Vision		213					0	1
Dizziness		213					0	1
Gastrointestinal								
Vomiting	108						1	0
Abdominal Cramps/Pain		112				108	0	2
Nausea		111					0	1
Diarrhea		213					0	1
General								
Body Pain						106	0	1
Fatigue	109(2)	108	109	107			3	2
Respiratory, Thoracic, and Mediastinal								
Bronchial Disorder				106			0	1
Dyspnea		112					0	1
Pneumonia				213(2)			0	2
Metabolism and Nutrition								
Lack of appetite		108					0	1
Anemia/iron deficiency		109					0	1
Hypothyreosis				110			0	1
Musculoskeletal & Connective Tissue								
Leg cramps		109					0	1
Neck pain				109			0	1
Ear and Labyrinth								
Otitis media		109					0	1
Infections and Infestations								
Urinary Infection			107				1	0
Angina Tonsillaris				108			0	1
Injury, Poisonings and Procedural								
Injury to left arm				101			0	1

Investigations Elevated ESR				101			0	1
Neoplasms Brain metastasis						101	0	1
Skin and Subcutaneous Tissue Psoriasis petit-plaque		111					0	1
Vascular Hypertension		111					0	1

Source: Appendix 14.2.7.1

Table 13. Frequency of Unexpected Adverse Events by Body System and by Condition

Body System	Full Dose (N)	Active Placebo (N)	Total (N)
No AE (N subjects)	1	2	3
Ear and Labyrinth Disorders	0.0%	0.7% (1)	1.6% (1)
Gastrointestinal Disorders	10.6% (5)	0.0% (0)	8.2% (5)
General Disorders and Administration Site Conditions	4.3% (2)	28.6% (4)	9.8% (6)
Infections and Infestations	4.3% (2)	0.0%(0)	3.3% (2)
Injury, Poisonings and Procedural Complications	2.1% (1)	0.0% (0)	1.6% (1)
Investigations	2.1% (1)	0.0% (0)	1.6% (1)
Metabolism and Nutrition Disorders	6.4% (3)	0.0% (0)	4.9% (3)
Musculoskeletal and Connective Tissue Disorders	4.3% (2)	0.0% (0)	3.3% (2)
Neoplasms: Benign, Malignant and Unspecified	2.1% (1)	0.0% (0)	1.6% (1)
Nervous System Disorders	8.5% (4)	14.3% (2)	9.8% (6)
Psychiatric Disorders	44.7% (21)	42.9% (6)	44.3% (27)
Respiratory, Thoracic, and Mediastinal Disorders	6.3% (3)	7.1% (1)	6.5% (4)
Skin and Subcutaneous Tissue Disorders	2.1% (1)	0.0% (0)	1.6% (1)
Vascular Disorders	2.1% (1)	0.0% (0)	1.6% (1)
Total	48	16	64

Source: Appendix 14.2.7.1

were two panic attacks experienced by subject 101, one moderate and the other severe, both 2 days after drug administration, which resolved the same day. The Investigator's Brochure lists panic and psychological distress as a possibility as a result of subjects having difficulty integrating their experience after the drug effect has subsided. This subject was also experiencing an unrelated brain metastasis that was undiagnosed at the time, which later caused the death of the subject. Subject 108 experienced mild vomiting after drug administration, which resolved the same day. Subject 107 contracted a moderate urinary infection after drug administration that lasted 8 days. The Investigator's Brochure lists transient immunosuppression as a possible AE for a few days after drug administration, so the PI considered this a possibly related event.

Table 14. Frequency of Unexpected Adverse Events by Relatedness and by Condition

Relatedness	Full Dose (N)	Active Placebo (N)	Total (N)
Unrelated	80.9% (38)	71.4% (10)	78.7% (48)
Possibly Related	17.0% (8)	28.6% (4)	19.7% (12)
Probably Related	2.1% (1)	0.0% (0)	1.6% (1)

Source: Appendix 14.2.7.2

There were nine severe unexpected AEs. The majority of AEs were not severe. Severe AEs were experienced in equivalent frequency between conditions, with 5 after full dose and 4 after active placebo. Subject 105 and 106 both experienced severe exacerbation of anxiety, in the form of an increase of their PTSD symptoms, upon drug administration. In the opinion of the investigator, the remaining severe AEs were generally considered to be related to the underlying trauma and PTSD symptoms these subjects were experiencing. Subject 106 experienced general body pain. Subject 107 suffered from chronic insomnia, reported as severe on two occasions. Subject 108 suffered from severe lower abdominal pain and subject 109 had a severe headache also related to a comorbid condition after whiplash injury that persisted for 15 days despite taking prescription concomitant medication (ibuprofen). See Appendix 14.2.7.3.

Table 15. Frequency of Unexpected Adverse Events by Severity and by Condition

Severity	Full Dose (N)	Active Placebo (N)	Total (N)
Mild	48.9% (23)	28.6% (4)	44.3% (27)
Moderate	42.5% (20)	35.7% (5)	41.0% (25)
Severe	8.5% (4)	35.7% (5)	14.8% (9)

Source: Appendix 14.2.7.3

AEs in this study were self-limiting and often resolved with full recovery or return to baseline (85.2%). Of the remaining AEs, 6 persisted at the end of the study but were diminishing. Subject 213 experienced a decrease in vision unrelated to drug administration that persisted at the same level upon completion of the study. Subject 101 had an abnormal, clinically significant lab value of elevated erythrocyte sedimentation rate (ESR) that persisted and worsened. This abnormal lab finding lead to the diagnosis of brain metastasis of a breast tumor, which ultimately caused the subject's death.

Table 16. Frequency of Unexpected Adverse Events by Outcome and by Condition

Outcome	Full Dose (N)	Active Placebo (N)	Total (N)
Full Recovery	85.1% (40)	85.7% (12)	85.2% (52)
Persists, Diminishing	8.5% (4)	14.3% (2)	9.8% (6)
Persists, the Same	2.1% (1)	0.0% (0)	1.6% (1)
Persists, Worsening	2.1% (1)	0.0% (0)	1.6% (1)
Death	2.1% (1)	0.0% (0)	1.6% (1)

Source: Appendix 14.2.7.1

10.2.4 Listing of Adverse Events by Subjects

Adverse events are listed by subject in Appendix 14.4.17.

10.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

10.3.1 Listing of Death, other Serious Adverse Events, and other Significant Adverse Events

10.3.1.1 Deaths

Table 17. Listing of Deaths

Dose (mg)	Subject	Adverse Event (Preferred Term)	Date of Last Drug Admin	Onset date	Resolution date	Severity	Action taken for Study	Action taken-treatment	Outcome
125	101	Brain metastasis	4-Jan-07	31-May-07	18-Jul-07	Severe	Removed from study	Hospitalization	Death

Source: Appendix 14.2.7.4

10.3.1.2 Other Serious Adverse Events

Table 18. Listing of Other Serious Adverse Events

Dose (mg)	Subject	Adverse Event (Preferred Term)	Date of Last Drug Admin	Onset date	Resolution date	Severity	Action taken-treatment	Outcome
Before dosing	103	Suicidal Behavior	None	20-Feb-07	21-Feb-07	Mild	None	Full recovery/ return to baseline

Source: Appendix 14.2.7.4

10.3.1.3 Other Significant Adverse Events

Table 19. Listing of Other Significant Adverse Events

Dose (mg)	Sub-ject	Adverse Event (Preferred Term)	Date of Last Drug Admin	Onset date	Resolu-tion date	Action taken-treatment	Severity	Outcome	Relatedness
125	101	Panic attack	24-Nov-06	26-Nov-06	26-Nov-06	Prescription Med	Moderate	Full recovery/ return to baseline	Possibly related
125	101	Panic attack	4-Jan-07	6-Jan-07	6-Jan-07	Prescription Med	Severe	Full recovery/ return to baseline	Possibly related
125	105	Exacerba-tion of Anxiety	6-Sep-07	6-Sep-07	19-Sep-07	Withdrawn from study due to AE, Prescription Med	Severe	Persists, diminishing	Probably related
25	106	Anxiety Reaction	13-Mar-08	13-Mar-08	UNK-Apr-08	Prescription Med, Therapy	Severe	Full recovery	Possibly related

Source: Appendix 14.2.7.5

10.3.2 Narratives of Deaths, other Serious Adverse Events, and Certain Other Significant Adverse Events

10.3.2.1 Deaths

Subject 101 (female, age 39, PTSD duration 20 years, trauma: life threatening illness and sexual abuse) died from metastasis of a tumor in the brain during the post-treatment follow-up period of the study. The subject had a diagnosis of breast cancer in 1997 that relapsed in 1999 and was treated with chemotherapy prior to admission into the study, which was part of the trauma that caused her PTSD. During the follow-up period of the study, the subject began behaving recklessly and exhibiting signs of frontal lobe syndrome. The subject was admitted to the hospital on 31-May-07 and the tumor was detected in the brain, as well as multiple metastases in the skeletal system, pelvis and lymphatic system. According to the oncologists the brain tumor was at least one year old. The subject died on 18-Jul-07. The subject's death arose from a previous condition and was determined to be unrelated to the study drug.

10.3.2.2 Other Serious Adverse Events

Subject 103 (female, age 39, PTSD duration 3 years, trauma: sexual abuse) allegedly exhibited suicidal behavior after conflict with her ex-husband, and was detained in a psychiatric hospital two weeks prior to administration of the study drug. The subject was able to leave the hospital the next day. The subject had not exhibited suicidal or violent tendencies or a mental condition requiring hospitalization prior to or after this event. Since the subject had not yet received the study drug, the event was determined to be unrelated to the study drug.

10.3.2.3 Other Significant Adverse Events

Subject 101 (female, age 39, PTSD duration 20 years, trauma: life threatening illness and sexual abuse) experienced two panic attacks during the study, one moderate and the other severe. The subject received 125mg + 62.5mg MDMA on 19-Oct-06, 24-Nov-06 and 04-Jan-07. The panic attacks occurred 2 days after the last two experimental sessions. The second panic attack was more severe. The subject had discovered a lump under her breast and suspected relapse of breast cancer in February 2007. During the months following the panic attack, the investigator reports that the subject's mental condition was rapidly deteriorating, with increasingly reckless behavior indicative of frontal lobe syndrome. Three months after the final experimental session, the subject was diagnosed with an abnormal, clinically significant elevated Erythrocyte Sedimentation Rate during clinical lab analyses conducted on-study. Five months after the final experimental session in May 2007, during the follow-up period, the subject received concomitant therapy of 75mg Venlafaxin for 11 days followed by 10mg Escitalopram for 13 days after which she stopped due to side effects. The subject experienced recurrent dissociative states until her death from a brain tumor described under Section 10.3.2.1.

Subject 105 (male, age 40, PTSD duration 9 years, trauma: accident) experienced severe exacerbation of anxiety, which was a part of PTSD symptoms present at baseline, during the first experimental session that was probably related to drug administration. This event interrupted the experimental session and was treated with additional support during therapy until the drug effects dissipated. This event lead to a change in planned dose, as the investigator used clinical judgment to decide not to administer the supplemental dose. After the session the subject was treated with 4mg Lorazepam (Ativan) per day and 30mg Mirtazapine (Remeron) per day for 5 days as rescue medications. Seven days after the experimental session the subject chose to withdraw from the study due to the AE and increase in PTSD symptoms experienced during and after the experimental session. The blind was broken at that time and revealed that the subject had received 125mg MDMA. The subject was prescribed 10mg Olanzapine (Zyprexa) in addition to the rescue medications listed above and stabilized post-study.

Subject 106 (female, age 42, PTSD duration 20 years, trauma: multiple types and occurrences of sexual assault) experienced severe anxiety in reaction to being confronted with traumatic memories during the first experimental session that was possibly related to drug administration. This event was treated with additional support in the form of therapy after the drug effects dissipated. The subject chose to withdraw

from the study after two integrative sessions due to the difficulty of facing the trauma. The blind was broken and the subject had received 25 + 12.5mg MDMA. A final exit CAPS assessment showed she still had severe PTSD symptoms with a Global CAPS score of 80. Starting 19 days after the experimental session the subject was treated with 75mg Venlafaxin (Effexor) per day and 10mg Zolpidem (Ambien) per day and stabilized post-study.

10.3.3 Analysis of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Significant AEs that were observed during or shortly after experimental sessions were panic attacks and exacerbation of anxiety. Subject 101 experienced two panic attacks 2 days after two experimental sessions, but this subject also exhibited improvement in PSTD symptoms, with benefits sufficient to offset the risk involved. The relapse of the subject's cancer immediately after experimental sessions and the size of the brain tumor suggest that the panic attacks may not have been entirely caused by the study drug. Subject 105 (full dose) experienced severe anxiety during and persisting after the experimental session, which lead to the subject's decision to withdraw from the study. This subject stabilized after withdrawing from the study on prescription medication. Subject 106 (active placebo) experienced severe anxiety as a reaction to traumatic memories during the experimental session, which lead to the subject's decision to withdraw from the study. This subject also stabilized on prescription medication after withdrawing from the study.

These significant AEs were treated with prescription medications and followed by additional phone contact and therapy 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 reactions to MDMA. The SAEs observed in this study were unrelated to drug administration as described under Section 10.3.2.

10.4 Clinical Laboratory Evaluation

10.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Measurement

Clinical laboratory tests were conducted for comprehensive metabolic profiling as a part of screening to establish medical eligibility for the study. Any abnormal findings were considered as baseline for that subject. A subset of tests, the liver panel and serum electrolytes, were repeated at termination prior to the follow-up period to test for any physiological changes that could be related to drug administration. Results of clinical laboratory tests are available upon request. Abnormal values after completion of Stage 1 or Stage 2 were collected from the site and are presented below.

Table 20. Listing of Abnormal Laboratory Values

Subject	Condition	Abnormal Test Date	Abnormal Test Value	Evaluation	Test value at Baseline	Normal Range
101	Full dose	15-Mar-07	ESR: 32	CS	ESR: 2.4	<10 mm
108	Full dose	18-Mar-09	Bilirubin: 28	CS	Bilirubin: 22	< 25 mg/dl

Source: Appendix 14.2.9.1

10.4.2 Evaluation of Individual Clinically Significant Abnormal Values

Only two abnormal lab values were found at the end of Stage 1 in two full dose subjects.

Subject 101, who had a medical history of breast cancer, exhibited elevated ESR levels at the end of Stage 1. The ESR is a non-specific indicator of inflammation in the body. The subject was hospitalized for an unrelated SAE on 31-May-07 and diagnosed with brain metastasis of primary breast carcinoma, which was the probable cause of elevated ESR levels. This abnormal clinically significant finding was noted approximately 3 months after the last experimental session and was recorded as an AE that was unrelated to study drug.

Subject 108, who had a medical history of hereditary elevation of bilirubin (Morbus Meulengracht), exhibited elevated levels of bilirubin at the end of Stage 3. Bilirubin levels can be indicative of decreased liver function, but the other liver enzymes were normal at that time, supporting the interpretation that the bilirubin levels were slightly elevated compared to baseline due to hereditary factors. This abnormal clinically significant finding was noted approximately 3 months after the last experimental session and was recorded as an AE that was unrelated to study drug.

10.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

10.5.1 Vital Signs

Pre-drug, peak and post-drug average systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, and body temperature were assessed during each experimental session for all subjects. Safety analyses included all available data. Overall, subjects receiving full dose MDMA experienced higher blood pressure than subjects receiving active placebo. None of the cases of elevated blood pressure, pulse, or body temperature required clinical intervention or transfer of the subject to an emergency department.

Table 21. Pooled Average Blood Pressure Values Across Stage 1 Sessions By Condition

Condition		SBP			DBP		
		Pre-Drug	Peak	Post-Drug	Pre-Drug	Peak	Post-Drug
Full Dose	N*	9	9	9	9	9	9
	Mean	133.7	159.5	138.2	82.5	93.9	82.7
	Min	106	124	111	65	73	65
	Max	177	200	168	101	121	102
Active Placebo	N*	5	5	5	5	5	5
	Mean	119.5	131.3	115.8	76.3	84.8	74.5
	Min	110	117	107	72	76	69
	Max	126	144	127	84	92	81

Source: Appendix 14.2.9.2
* All available data was used for safety analyses. Means were weighted by the N of each session.

One-way ANOVA confirmed that there were no differences in vitals between groups at baseline during Stage 1. One-way ANOVA performed upon peak change scores and post-drug average scores failed to detect any main effect of condition for DBP, heart rate, or body temperature during Stage 1. However, there was a main effect of condition for peak and post-drug SBP values, with peak and post-drug average SBP higher after full dose MDMA than after active placebo (F (peak) = 6.4, df = (1, 12), $p = 0.03$ and F (post-drug) = 5.8, df = (1, 2), $p = 0.03$). Mean peak SBP values for subjects receiving full dose MDMA were 159.5 versus 131.3 in active placebo. Mean post-drug SBP was 138.1 versus 115.8 in active placebo. These values represent averages across three experimental sessions. Two subjects in the full dose

group had a medical history of mild or intermittent hypertension. One subject experienced severe exacerbation of anxiety, and high levels of stress are known to influence blood pressure. These factors most likely influenced the significance of hypothesis testing differences by condition in SBP.

As an added safety measure in this study, vital signs above pre-determined limits were monitored more frequently in order to increase vigilance for any possible hypertensive crises, hyponatremia or hyperthermia. Individual subjects experiencing SBP above 160 or DBP above 110 are listed in Table 22 and 23. All five of these subjects experienced blood pressure values above cutoff when they received at least a full dose of MDMA, either in Stage 1, Stage 2 or Stage 3. Only one incidence was noted in Stage 3 with an initial dose of 150mg, and the same subject experienced values above cutoff with an initial dose of 125mg as well, suggesting that the 20% higher dose was not responsible for increased blood pressure. The investigators exercised clinical judgment when electing to administer the supplemental dose for subjects 105 and 111 based on medical history and observations during the experimental sessions. All subjects who experienced blood pressure levels above cutoff had PTSD from either medical malpractice or accidents.

Table 22. Subjects Experiencing Systolic Blood Pressure over Cutoff (SBP > 160)

Subject	Trauma etiology	Relevant Medical History	Stage / Session	Dose (mg)	Pre-drug SBP	Peak SBP	Duration Exceeding Cutoff	Post-drug SBP
102	Accident	N/A	Stage 1 / Session 1	125+62.5	142	173	4 hours	150
			Stage 1 / Session 2	125+62.5	147	166	4 hours	155
			Stage 1 / Session 3	125+62.5	150	169	4 hours	156
			Stage 3 / Session 1	150+62.5	144	185	2 hours	161
104	Medical Treatment	N/A	Stage 2 / Session 1	125+62.5	127	176	1 hours	153
			Stage 2 / Session 2	125+62.5	127	179	3 hours	159
			Stage 2 / Session 3	125+62.5	143	183	1.5 hours	153
105	Accident	N/A	Stage 1 / Session 1	125	147	164	5 hours	142
111	Medical Treatment	Unstable BP elevation under stress	Stage 1 / Session 1	125	128	193	1.5 hours	160
			Stage 1 / Session 2	125	151	187	1.5 hours	164
			Stage 1 / Session 3	125+62.5	149	172	6 hours	159
112	Medical Treatment/ Malpractice	Mild systolic hypertension	Stage 1 / Session 1	125+62.5	176.5	191	5 hours	167
			Stage 1 / Session 2	125+62.5	166	200	4 hours	167
			Stage 1 / Session 3	125+62.5	153.5	198	5 hours	168

Source: Appendix 14.4.13

Blood pressure levels were above cutoff for 1.5 to 6 hours, depending on the session. No signs of cardiovascular crises were observed and none of these subjects required clinical intervention. These data suggest that if these subjects had not been monitored more frequently, an equivalent outcome would have been obtained and blood pressure levels would have still decreased back to baseline.

Subjects who experienced DBP above cutoff were a subset of subjects who experienced SBP above cutoff. DBP values remained above cutoff for 2 to 5 hours, depending on the subject. All instances of DBP levels above cutoff were observed when subjects received full dose MDMA. The two subjects who experienced elevated DBP both had a history of mild hypertension or unstable blood pressure and had PTSD from medical trauma. Both subjects went back to normal after drug effects wore off and had no sign of cardiovascular symptoms.

Table 23. Subjects Experiencing Diastolic Blood Pressure over Cutoff (DBP > 110)

Subject Number	Trauma etiology	Relevant Medical History	Stage / Session	Dose (mg)	Pre-drug DBP	Peak DBP	Duration Exceeding Cutoff	Post-drug DBP
111	Medical Treatment	Unstable BP elevation under stress	Stage 1 / Session 2	125	98	121	2 hours	102
112	Medical Treatment/ Malpractice	Mild systolic hypertension	Stage 1 / Session 1	125 +62.5	95.5	114	5 hours	98
			Stage 1 / Session 3	125 +62.5	96	111	5 hours	100

Source: Appendix 14.4.13

Elevated body temperature was most likely to occur two to three hours post-drug. Two of four cases of elevated blood pressure occurred prior to two hours post-drug and two occurred after three hours post-drug. Body temperature was higher in subjects who received active placebo MDMA, albeit not by a great deal (e.g. peak of 38.3 degrees C after active placebo versus 37.6 degrees C after full-dose MDMA). There were eight instances of body temperature rising more than 1 degree C. Four instances of elevated body temperature occurred in two subjects in the active placebo condition and two in the full dose condition. Four of five low-dose participants and three of nine full dose subjects had elevated body temperature.

Table 24. Pooled Average Vitals Across Stage 1 Sessions By Condition

Condition		Pulse			Body Temperature		
		Pre-Drug	Peak	Post-Drug	Pre-Drug	Peak	Post-Drug
Full Dose	N*	9	9	9	9	9	9
	Mean	80.0	99.6	85.8	36.6	37.6	37.2
	Min	62	71	65	35.8	36.7	36.6
	Max	109	121	108	37.6	38.6	37.9
Active Placebo	N*	5	5	5	5	5	5
	Mean	89.1	113.1	89.6	36.8	38.3	37.7
	Min	60	69	61	36.3	36.9	36.6
	Max	94	124	90	37.1	38.5	38.0

Source: Appendix 14.2.9.2

* All available data was used for safety analyses. Means were weighted by the N of each session.

In summary, full dose MDMA correlated with significantly elevated SBP. All other vital signs did not vary significantly by condition. Despite higher levels of exposure, there was no need for clinical

intervention during either Stage 3 experimental session. It appears that increasing MDMA dosage increases likelihood of greater cardiovascular effects, but that elevation in body temperature may not be as strongly related with dosage as blood pressure.

10.5.2 Other Observations Related to Safety

In this study, psychological distress was considered a part of the therapeutic process. In order to maintain a high standard of vigilance for possible repercussions of psychological distress, the study design incorporated two measures. Psychological distress of subjects was assessed periodically throughout experimental sessions with a single-item, seven-point measure known as the SUD. The investigators also assessed general wellbeing before and after experimental sessions to determine whether subjects needed additional support during the 8-day window after drug administration when AEs were expected to occur. Hypothesis testing using one-way ANOVA found no difference in peak levels of distress by condition using the SUD. The SUD scores did exhibit a characteristic rise as drug effects peaked, but were found to return to baseline or lower after drug effects diminished. Likewise, general wellbeing scores also did not vary by condition, and were primarily used by the investigators to gage whether additional support was needed in the form of psychotherapy or closer monitoring by phone.

Thirteen subjects provided guesses concerning their condition assignment after each experimental session. One of the subjects who dropped out of the study failed to provide a guess of their condition assignment. Five subjects were accurate in guessing their condition after each of three sessions, three made an accurate guess on at least one occasion, and one subject who completed a single experimental session accurately guessed condition assignment. Four of 13 failed to correctly guess their condition assignment after any of the three experimental sessions. Two of the 4 who incorrectly guessed their condition were in the active placebo condition and 2 were in the full dose condition. Four of the 6 who correctly guessed their condition were in the full dose condition, and 2 were in the active placebo condition. The investigators correctly guessed the condition for 7 of 9 full dose subjects and 1 of 4 active placebo subjects. Overall, they were accurate in guessing condition assignment in 8 of 13 subjects and not accurate in 5 cases. These data suggest that the blind was somewhat successful, particularly in making it more difficult for participants and investigators to identify active placebo dose MDMA.

10.6 Safety Conclusions

Administration of an initial dose of 25 or 125 mg and a supplement of 12.5 or 62.5 mg MDMA produced expected and unexpected AEs, but none of the SAEs were related to the study drug. Receiving an initial dose of 150 mg MDMA followed either by 62.5 or 75 mg did not produce any alarming adverse events. A greater number of mild, moderate and severe adverse events were associated with receiving the full dose of MDMA. Participants receiving 125 mg MDMA were more likely to report expected AEs such as loss of appetite, insomnia or tight jaw. In some subjects these reactions were severe on the day of the experimental session and during the 7-day window after the session. However, some active placebo subjects experienced severe insomnia and loss of appetite as well. Severity of expected AEs was generally higher in participants receiving the full dose. The greater number of subjects receiving full dose may have contributed to this effect. Most expected adverse events subsided after drug effects waned, while others lasted beyond this interval but were self-limiting, and there was full recovery after 85% of the unexpected AEs. AEs deemed at least possibly related to the study drug occurred in both groups, but to a greater extent in the full dose group. As expected, 125 mg MDMA produced greater cardiovascular effects than 25 mg, including elevations above clinical cut-off. None of these instances of elevation required medical intervention. Elevated body temperature was seen in participants in both conditions, suggesting lack of a dose-related affect of MDMA upon body temperature.

A single death due to brain metastasis occurred in a subject assigned to full dose MDMA. The death arose from cancer progression, with cancer predating enrollment in the study.

Administering either a full or active placebo dose of MDMA to subjects with chronic PTSD did not produce deleterious effects and appears to have acceptable safety. Commonly reported adverse events were transient.

11.0 DISCUSSION AND OVERALL CONCLUSIONS

This study was designed to explore the safety, tolerability, and efficacy of full dose MDMA compared to a low dose of MDMA as an active placebo, administered during three experimental sessions as an adjunct to psychotherapy for the treatment of chronic, treatment-resistant PTSD.

Fourteen adult subjects were enrolled and treated for at least one experimental session. Two subjects withdrew from the study due to AEs, and the remaining twelve subjects completed outcome measure assessments. The results of the main analysis suggest that full dose subjects experienced clinically but not statistically significant reduction in PTSD symptom severity using the CAPS as the primary outcome measure. Based on the sponsor's analysis, both the primary and secondary outcome measures were in agreement on a trend toward statistical significance. CAPS scores after three experimental sessions were significantly lower than scores after two experimental sessions in full dose subjects but not active placebo subjects. CAPS and PDS scores continued to decrease during the follow-up period after all subjects received full dose MDMA in either Stage 1 or Stage 2. In order to make definitive statements on the efficacy of MDMA-assisted psychotherapy for PTSD treatment, the sponsor would like to conduct larger studies.

A survey of pharmacologic studies for the treatment of PTSD yields a range of 10-63% drop (median 33%) in the CAPS Global scores as indication of clinically significant change in PTSD symptom severity [50]. A majority of the studies have used statistical significance, agreement with secondary measures, and the opinion of clinicians as evidence of clinical significance. In this study, full dose MDMA subjects experienced a 23.5% drop in PTSD symptom severity. Previous clinical trials of two drugs approved by the FDA for PTSD, sertraline and paroxetine, used 50 points as a diagnostic cut-off CAPS score for enrollment and a >30% decrease in CAPS score as the cut-off to demonstrate clinically significant response [41-44]. In this study, subjects receiving full dose MDMA dropped to 50.7 +/- 19.7 on average, which constitutes a 15.6 point decrease in CAPS scores. A 15 point decrease has been used in previous studies and is cited in the CAPS Interviewer's Guide as evidence of a clinically significant drug response [43, 47].

Interestingly, the active placebo subjects in this study did not appear to experience a placebo effect, as has been previously noted in other PTSD pharmacotherapy studies [41-44]. Generally previous studies have reported the difference in PTSD scores to account for the placebo effect. Some researchers have proposed that the frequent assessments of PTSD symptoms may be responsible for the placebo effect [51], however the results of this study do not support this interpretation. The sponsor plans to investigate the effects of the active placebo dose in future studies.

One full dose subject died during the 12-month follow-up period due to unrelated brain metastasis of a tumor 5 months after drug administration. One subject experienced an unrelated SAE of suicidal behavior resulting in psychiatric hospitalization prior to drug administration. One full dose and one active placebo subject withdrew from the study due to possibly or probably related AEs involving anxiety. There was no pattern of clinically relevant laboratory abnormalities in either study group. Both doses of MDMA were well tolerated with severe insomnia (N=3 in full dose vs. N=1 in active placebo) and loss of appetite (N=1 in full dose vs. N=1 in active placebo) reported by both groups, and severe tight jaw (N=1 in full dose and

N=2 in Stage 3) was reported in higher dose groups as the most common reactions on the day of the experimental session. Both groups reported severe fatigue (N=3 in full dose vs. N=1 in active placebo), insomnia (N=4 in full dose vs. N=2 in active placebo), and loss of appetite (N=1 in full dose vs. N=1 in active placebo) during the 8 days following the experimental session. Subjects receiving full dose also reported severe low mood (N=3), anxiety (N=3), difficulty concentrating (N=1), increased private worries (N=1), headache (N=1), and restlessness (N=1) during the 8 days following the experimental session. Spontaneously reported reactions were self-limiting and generally resolved by the end of the 8-day window after drug administration.

12.0 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

12.1 Safety Data

Table 12.1.1 Spontaneously Reported Reactions In MP-2 Stage 3 on Day of Experimental Sessions

	Total Reports (N/6 sessions)	Mean Severity* (1=mild, 3=severe)	Mean Duration* (Hours)
Tight Jaw	4	2.3 (1-3)	3.3 (2-5)
Impaired Gait/Balance	4	1.0 (1-1)	0.5 (0.5-0.5)
Insomnia	3	2.3 (1-3)	3.3 (2-4)
Dizziness	3	1.0 (1-1)	0.5 (0.5-0.5)
Loss of Appetite	2	2.0 (2-2)	24 (24-24)
Nausea	2	1.0 (1-1)	12.5 (1-24)
Dry Mouth	2	1.5 (1-2)	2.5 (1-4)
Thirsty	2	1.5 (1-2)	2.2 (0.5-4)
Headache	2	1.5 (1-2)	1.5 (1-2)
Perspiration	2	1.0 (1-1)	2.0 (1-3)
Restless	1	1.5 (1-2)	2.5 (2-3)
Fatigue	1	1.0 (1-1)	2.0 (2-2)
Feeling Weak	1	1.0 (1-1)	2.0 (2-2)
Anxiety	1	1.0 (1-1)	1.0 (1-1)
Parasthesias	1	1.0 (1-1)	1.0 (1-1)
Heavy Legs	1	1.0 (1-1)	0.5 (0.5-0.5)
Nystagmus	1	1.0 (1-1)	0.5 (0.5-0.5)
Difficulty Concentrating	0	0 (0-0)	0 (0-0)
Drowsiness	0	0 (0-0)	0 (0-0)
Irritable	0	0 (0-0)	0 (0-0)
Increased Private Worries	0	0 (0-0)	0 (0-0)
Low Mood	0	0 (0-0)	0 (0-0)
Need More Sleep	0	0 (0-0)	0 (0-0)
Feeling Cold	0	0 (0-0)	0 (0-0)

Source: Appendix 14.2.7.6

* Mean duration/severity (Minimum reported – Maximum reported)

Table 12.1.2 Spontaneously Reported Reactions In MP-2 Stage 3 During 8 Days After Experimental Sessions

	Total Reports (#reports/N)**	Mean Severity* (1=mild, 3=severe)	Mean Duration* (Days)
Fatigue	5/27	1.7 (1-3)	5.4 (1-7)
Low Mood	2/4	1.0 (1-1)	2.0 (1-3)
Need More Sleep	2/2	1.0 (1-1)	1.0 (1-1)
Anxiety	2/2	1.0 (1-1)	2.0 (2-2)
Dry Mouth	1/1	1.0 (1-1)	1.0 (1-1)
Irritable	1/1	1.0 (1-1)	1.0 (1-1)
Increased Private Worries	1/1	1.0 (1-1)	1.0 (1-1)
Difficulty Concentrating	0	0 (0-0)	0 (0-0)
Dizziness	0	0 (0-0)	0 (0-0)
Drowsiness	0	0 (0-0)	0 (0-0)
Headache	0	0 (0-0)	0 (0-0)
Heavy Legs	0	0 (0-0)	0 (0-0)
Impaired Gait/Balance	0	0 (0-0)	0 (0-0)
Insomnia	0	0 (0-0)	0 (0-0)
Tight Jaw	0	0 (0-0)	0 (0-0)
Loss of Appetite	0	0 (0-0)	0 (0-0)
Nausea	0	0 (0-0)	0 (0-0)
Nystagmus	0	0 (0-0)	0 (0-0)
Parasthesias	0	0 (0-0)	0 (0-0)
Perspiration	0	0 (0-0)	0 (0-0)
Restless	0	0 (0-0)	0 (0-0)
Feeling Cold	0	0 (0-0)	0 (0-0)
Thirsty	0	0 (0-0)	0 (0-0)
Feeling Weak	0	0 (0-0)	0 (0-0)

Source: Appendix 14.2.7.7

* Mean duration/severity (Minimum reported – Maximum reported)

** Total Reports include (total number of times a reaction was reported / N observations over 8 days after each experimental session)

Table 12.1.3. Subjective Units of Distress During Stage 1 Experimental Sessions

Experimental Session #	Condition	Pre-drug		Peak		Post-drug	
		Mean	SD	Mean	SD	Mean	SD
Session 1	Active Placebo (N = 5)	3.8	1.2	5.0	0.7	3.7	0.9
	Full Dose (N = 9)	4.2	1.6	5.0	1.9	2.7	1.7
Session 2	Active Placebo (N = 4)	4.1	1.2	6.0	1.4	3.1	0.6
	Full Dose (N = 8)	3.8	1.4	4.5	1.3	2.9	1.2
Session 3	Active Placebo (N = 4)	4.1	1.3	5.2	1.7	3.5	0.5
	Full Dose (N = 8)	3.7	1.9	4.6	1.5	2.6	1.2

Source: Appendix 14.2.10.1

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