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<th>Study Phase</th>
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<th>Experimental Session 1</th>
<th>Experimental Session 2</th>
<th>Experiment Analysis 1</th>
<th>Experiment Analysis 2</th>
<th>Post-Closet Follow-Up</th>
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*a - Time point is one day after experimental session 2 - Pre-Closet 1, 2 hours prior MDM = C - 1 hour beginning of session 1 - N = needed 2 - Immediate 30 minute 3 - Baseline collected for seven days prior experimental session 4 - Hours prior to experimental session 5 - Hours prior to Day 2 and Day 3, those only 10 - One month after the second experimental session has been the third experimental session 1 - On the day of the third experimental session 1 - Only in sessions with pre-closet follow-up; bottom row K - All measures listed except for the ACCPT*
9.3 Assessments and Measures

Screening and outcome measures were chosen to be well recognized in the literature and because of prior use in other sponsor-supported studies of MDMA-assisted psychotherapy in people with PTSD.

Eligibility for the study will be determined based on psychiatric diagnoses confirmed during screening through medical history, the Structured Clinical Interview for Diagnoses (SCID-I-RV) and the CAPS.

9.3.1 Outcome Measures

The primary outcome measure will be the CAPS, a clinician-administered measure for PTSD diagnosis and assessment of symptom intensity and frequency. A qualified, blinded IR will perform the CAPS at baseline and outcome measurement time points according to the Time and Events Table. The IR will not be present during the subject’s experimental sessions nor have any information regarding the experimental sessions. Subjects will be instructed not to inform the IR of any beliefs they or others have concerning their condition assignment during the evaluation session. The CAPS provides a standardized method to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the subject’s social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS interview takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [130, 131].

The secondary measure of PTSD symptoms will be the PDS, a self-report measure designed to follow DSM-IV criteria for assessing PTSD. The measure is derived from the Posttraumatic Symptom Scale – Self Report (PSS-SR), a measure also intended to tap into diagnostic criteria for PTSD. The PDS contains 49 items, with responses made on a four-point scale, ranging from 0 (“not at all”) to 3 (“five or more times a week”). The PDS consists of a list of 12 potential traumatic events, 12 items addressing elements of the traumatic event, of 17 symptom items, and nine items assessing impact on areas of life function [132]. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The 17 items are summed to create a symptom severity scale. Cronbach’s alpha for the symptom severity scale is 0.92. The PDS has test-retest reliability of 0.74 after a two-week and one-month interval, and subscales are inter-correlated, with correlations ranging from 0.73 to 0.82, and PDS scores have a moderate to good correlation with SCID-I-RV diagnosis, with kappa = 0.65 [132]. Subjects will complete the PDS questionnaire at baseline, after the first and third experimental sessions, at the primary endpoint, at the end of Stage 1, and equivalent time points in Stage 2 and at the Long Term Follow-up, as specified in the Time and Events Table.

The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the
self or others. The Independent Rater administering the CAPS will perform the GAF assessment. The GAF will serve as a measure of global functioning and will be performed at the same times the CAPS is administered.

The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [133, 134]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Subjects will complete the PTGI according to the Time and Events table.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [135, 136], that will serve as a measure of depression according to DSM-IV criteria [137]. The BDI-II has been validated, has high inter-rater consistency and good test-re-test reliability and is not overly sensitive to daily variations in mood. It takes five to 10 minutes to complete [137]. Score cutoffs indicate: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. Higher scores indicate more severe depressive symptoms. Subjects will complete the BDI-II according to the Time and Events table.

The NEO-PI will serve as a measurement of personality [138, 139]. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Subjects will complete the NEO-PI according to the Time and Events table.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. Possible responses range from 0 to 4 on a five-point scale [140]. The PSQI consists of seven sub-scales: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to 10 minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach’s alpha of 0.83[140, 141]. Global scores correlate with other measures of alertness and self-reported sleep quality [142]. Subjects will complete the PSQI according to the Time and Events table.

The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual’s thoughts, feelings, or experiences into the stream of consciousness or memory [143, 144]. It is an established measure of dissociative symptoms. The scale consists of statements describing facets of dissociation. Respondents indicate how often the specific experience happens to them, from “never” to “always.” Responses on the original scale were made via visual analog scales. The DES-II uses the same items but with responses made on a 10-point scale from “0%” to “100%.”
of the time. The scale is scored by treating percentages as single digits to produce a total score. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms [143]. Reliability of the DES-II is high (ranging from 0.79 to 0.96 in an early review), and a reported Cronbach’s alpha of 0.95 [144, 145]. There may be a relationship between experiencing dissociation and occurrence of chronic PTSD [144, 146]. Subjects will complete the DES-II according to the Time and Events table.

9.3.2 Safety Measures

Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions. The Clinical Investigators will be available via mobile phone or pager throughout the study to ensure subject safety.

Safety measures, including vital signs and a measurement of psychological distress, will be assessed during all experimental sessions. Subjects will rate their current degree of subjective distress with the SUD scale, which is a single-item self-report scale. The SUD will be completed repeatedly during the experimental sessions, with the degree of distress marked along seven points. Results of the SUD are intended to assist therapists in maintaining subject safety during experimental sessions.

The therapists will assess general wellbeing during each preparatory session, on each integrative session and during telephone calls for seven days. Results of this scale are intended to assist therapists in maintaining subject safety throughout the study.

During the course of each MDMA-assisted psychotherapy session, the Subjective Units of Distress (SUD) scale will be used to assess degree of psychological distress experienced at various points during the session. Subject and Clinical Investigator beliefs concerning subject condition assignment (either full dose or comparator) will be assessed during the non-drug psychotherapy session occurring on the day after each experimental session. Neither the SUD scale nor condition assignment beliefs measures are outcome measures.

The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [147]. It assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during face-to-face interview or over the telephone. C-SSRS scores are sensitive to changes in suicidal ideation or behavior over time, and the measure demonstrates good convergent validity with other measures of suicidality [148]. The C-SSRS will be performed by the PI at baseline, and repeated throughout the protocol to assess suicidality. See the Time and Events Table for a detailed schedule.
The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [149] is a relatively brief battery of assessments for cognitive function. It consists of 12 subtests that cover verbal and visual memory and attention and takes approximately 30 minutes to administer. Tasks include recall of lists, figures and stories, picture naming, semantic fluency, copying a figure, digit span and coding, and line orientation. Scores on the RBANS subtests can be used to obtain a total score and five index scores; attention, immediate memory, delayed memory, language and visuospatial/constructional scores. Factor analyses of the RBANS and samples of veterans and people with schizophrenia suggest that the RBANS possesses two factors rather than five [150, 151]. The RBANS has alternate forms, allowing repeated administration. Test performance by healthy controls were distinguishable from performance by people with probable Alzheimer’s disease or the neurodegenerative condition Huntington’s disease [152], and the test has high split-half reliability, with coefficients ranging from 0.80 to 0.88 [149]. Test-retest reliability is good for total RBANS scores in healthy controls and psychiatric patients [153]. The RBANS has been used in community-based and psychiatric samples [150, 154] and in a prospective investigation of the effects of chemotherapy upon cognitive function [155]. Each administration of the RBANS will use one of parallel forms of RBANS, and each participant will not complete the same form twice. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

The Paced Auditory Serial Addition Test (PASAT) is a measure of psychomotor speed, auditory information processing and computation ability [156]. The PASAT was originally designed to assess recovery after traumatic brain injury, and has been used subsequently to assess cognitive function in other populations [156, 157]. It takes approximately ten to 15 minutes to administer. The measure involves the addition of a series of digits presented at a three or two second interval, with responses made by adding each number to the prior digit. The PASAT consists of two alternate forms, permitting repeated administration. PASAT scoring includes collecting number of correct and incorrect responses, time to response (latency of response) and any failure to respond. There was a positive correlation between responses on the PASAT and a non-numerical paced measure. The measure is internally consistent (Cronbach’s alpha of 0.90), and it has high test-retest reliability, with reliability ranging from 0.90 to 0.97 [157-159]. The first administration of the PASAT will use one of the two alternate forms, and the second administration will use the other. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure and heart rate will be assessed periodically during each experimental session by an automatic blood pressure (BP) and pulse monitor. Blood pressure and pulse will be measured at the outset of the experimental session, and once approximately every 30 minutes for the first four hours of the experimental session, and once every hour, or as needed, thereafter. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic, or pulse of 110 are exceeded. Blood pressure will also be measured more frequently if there are symptoms, such as chest pain, shortness of breath or neurological symptoms that may be indicative of hypertension. The therapists will
Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ).

A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain [160-162]. The changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from “None” to “Worst Case Imaginable”. This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD [161, 163-165]. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response [161, 164, 165].

All AEs and spontaneously reported reactions will be collected, as described in Section 14.0. AEs and spontaneously reported reactions may be collected during face-to-face visits or over the telephone. Common reactions that are spontaneously reported are collected for seven days after each experimental session on a separate CRF page and will be categorized as mild, moderate, or severe.

9.3.3 Process Measures

All sessions after enrollment may be recorded to audio and video, including introductory, integrative, and experimental sessions for research and training purposes. These recordings will be used for further development of the manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental, and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor’s ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues [166, 167]. Subjects respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores: internal unity, external unity, transcendence of time and space, ineffability and paradoxicality, claim of difficulty in describing the experience in words, sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to complete. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ).
should be recorded on the Screening Log. A CRF will not be completed for subjects who
limit monitoring will not be done. It is the responsibility of the PI to file the Screening Log in the
Investigator Site File (ISF) to be readily available for on-site monitoring and/or
inspection by relevant authorities.

Questions regarding the belief of condition assignment and certainty of the belief will be
asked of the therapists and subjects at the integrative session on the day after each
blinded experimental session in Stage 1. Each therapist responsible for treating the
subject will indicate their belief of condition assignment and certainty based on the full
dose (125mg) and comparator dose (50mg) groups. In line with informed consent
obfuscation, where the comparator dose is not revealed, subjects will initially be asked if
they believe they received MDMA or not during this assessment. If they believe they
received MDMA, they will be asked about what dose they think they received. These
beliefs are collected as a part of the sponsor’s ongoing initiative to optimize the doubleblind as a part of dose response studies.

Perceptions of the experimental sessions will be collected from each full dose subject
during the primary endpoint visit after unblinding and from Stage 2 subjects during the
secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage
2. Perceptions will be collected again at the end of Stage 1/Stage 2 according to the Time
and Events Table. These perceptions are collected as a part of the sponsor’s ongoing
initiative to assess the therapeutic value of the third experimental session and information
on the optimal therapeutic dose of MDMA.

The long-term follow-up questionnaire has been developed internally by the Sponsor to
assess long-term benefits and harms of MDMA-assisted psychotherapy at the long-term
follow-up visit.

9.4 Visit Descriptions

9.4.1 Prescreening, Screening, and Baseline Evaluation (Pre-study)

Prospective subjects will be prescreened by telephone according to an IRB-approved
script to learn if they meet basic eligibility criteria. All individuals who are prescreened
should be assigned a screening number and recorded on the Subject Screening Log where
information on the selection of potential subjects in the trial should be collected.

Upon signing the IRB-approved informed consent form (ICF), the potential subject may
commence study-related screening activities. The screening number should also be
recorded on the signed ICF. If a subject is enrolled, the study staff should record the
enrollment date and assign a subject number. If a subject is not enrolled, an explanation
should be recorded on the Screening Log. A CRF will not be completed for subjects who
are not enrolled. These subjects will only be documented on the Screening Log and
source records. It is the responsibility of the PI to file the Screening Log in the
Investigator Site File (ISF) to be readily available for on-site monitoring and/or
inspection by relevant authorities.
Screening may take place over more than one day and should be complete by up to two months prior to enrollment. Screening may take up to two months, with the baseline CAPS being conducted no more than 8 weeks before the first experimental session, leaving room for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, plus one week for stabilization. If the CAPS is completed outside of this window for a subject, the PI should consult the Sponsor CRA and Medical Monitor to determine if the baseline CAPS should be repeated. The maximum window from the start of screening to the first experimental session is 13 weeks. If, after reviewing all information, the PI concludes that a subject is eligible, they will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

a. Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any tests or evaluations for the study.
b. Assign the subject a screening number. Complete the Screening Log.
c. Review the ability of females of childbearing potential to become pregnant and their commitment to practice appropriate birth control as determined by the PI for the treatment period of the study.
d. The PI will obtain medical and psychological history by interview.
e. The PI will collect information on pre-study and current medications.
f. Tinnitus and chronic pain symptom severity will be collected using a visual analog scale in subjects with a medical history of these conditions.
g. A physician will perform a general physical examination. The examination will involve the following procedures:

- Blood pressure.
- Pulse.
- Height.
- Weight.
- Body temperature.
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities.
- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function).
- Electrocardiogram (ECG).
- Serum electrolytes, metabolic profile, urinalysis and complete blood count
- Thyroid stimulating hormone (TSH), free T3, and free T4.
- Human Immunodeficiency Virus (HIV) serology.
- Urine-dip pregnancy test on females with childbearing potential.
- Urinary drug test.
- C-SSRS to assess past and current suicide risk.

Results of HIV serology will be kept confidential, and appropriate referral for counseling may be necessary in accordance with local law. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the subject's source record. Clinically significant abnormal values will be captured as medical history in the CRF. If, upon examination, there are questions raised about
possible medical problems, the PI will request a review of subject medical records and request additional tests or assessments as indicated.

A blinded Independent Rater who will not be present during any of the therapy sessions will administer:

- Structured Clinical Interview for Diagnoses I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms,
- CAPS to assess PTSD symptoms and eligibility, which may be recorded to video in as many instances as necessary to establish inter-rater reliability,
- GAF to assess general psychological function,
- PASAT to assess cognitive function,
- RBANS to assess cognitive function.

The subject will complete the following self-report measures:

- PTGI (in reference to time since the trauma)
- PDS to assess self-reported PTSD symptoms
- BDI-II to assess depression symptoms
- NEO-PI to assess changes in personality
- PSQI to assess changes in sleep quality
- DES-II to assess dissociation symptoms

9.4.2 Preparatory Psychotherapy Sessions - Visits 1, 2, 3 (Stage 1), 18 (Stage 2)

Subjects who do not complete all screening activities will not be enrolled. Eligibility may be discussed by phone after screening is complete and at the time Visit 1 is scheduled but the final confirmation will occur at Visit 1. If all inclusion criteria and no exclusion criteria are met, the subject will be enrolled and issued a subject number.

During Visit 1:

a. Complete a final review of Inclusion/exclusion criteria.
b. Assess general wellbeing.
c. Confirm eligibility and willingness to participate in study.
d. Assess general wellbeing.
e. Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications will be collected as described in Section 14.0 of the protocol.
f. Discuss medication tapering, if applicable. Upon confirmation of eligibility, the PI will consult the prescribing physician to initiate medication tapering for subjects who must refrain from taking a psychiatric medication for the study. Tapering will follow a time course appropriate for the medication as specified in the Medication Tapering Table in Section 14.4 of the protocol, with the first experimental session scheduled to occur one week after complete washout.

The subjects will undergo three preparatory sessions lasting 90 minutes with their therapist team, prior to their first experimental session. The first preparatory session will
take place at Visit 1 after enrollment confirmation. Preparatory sessions should be scheduled approximately one week apart, with the first experimental session taking place 3-5 weeks after enrollment, and no more than 8 weeks ± 1 week after the baseline CAPS. In Stage 2 (for comparator dose crossover subjects), only one preparatory session will take place prior to their first full dose open-label experimental session, as described in the Time and Events Table.

Adherence criteria for preparatory sessions should be completed as a part of one of the three sessions. These elements do not have to be accomplished in any specific order or in every preparatory session. Generally, adherence criteria for these sessions include that the therapists will work with the subject to prepare for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts, which is intended to develop therapeutic alliance.

During the preparatory sessions:

a. Therapists may record all sessions to audio and video. Subjects may review recordings from these sessions upon request.
b. Collect AEs and Medications as described in Section 14.0 of the protocol,
c. The therapists will inquire about any possible changes in the subject’s health to ensure that subject continues to meet eligibility criteria and if applicable, will confirm that the subject has appropriately tapered off of medications.
d. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
e. The subject and therapists will discuss goals for the experimental session and will review what will happen during the experimental session, following standard procedures and techniques discussed in the treatment manual.
f. Prior to the experimental session, the therapists will introduce the subject to the attendant that will remain with the subject during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress.
g. If a subject would like a companion present during or after the experimental session, a meeting between the therapists and that individual will be scheduled prior to the first experimental session. There must be mutual agreement between the subject and therapists concerning the presence of the companion.
h. The therapists will administer the C-SSRS just prior to beginning the second preparatory session, unless a subject is still undergoing medication washout. Subjects still undergoing medication washout will complete the C-SSRS during the second preparatory session or at a point after washout is complete prior to the first experimental session.
i. Assess general wellbeing at each preparatory session.
j. During the third and last preparatory session, give the Reminder of Study Rules to the subject, which includes instructions and restrictions for conduct prior to receiving the drug. Subjects must agree to:

- Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the experimental session.
- Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within twenty-four hours of each experimental session.
- Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so.

9.4.3 Experimental Sessions - Visits 4, 8 (Stage 1), 13, (Full Dose Group Stage 1), 19, 23, 28 (Stage 2)

Experimental sessions of MDMA-assisted psychotherapy should be scheduled approximately three to five weeks apart. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions. The dose of the drug and blinding procedures will vary based on the stage of the study.

Adherence criteria for experimental sessions should be completed as a part of each experimental session. These elements do not have to be accomplished in any specific order. Generally, adherence criteria for these sessions include that the therapists will create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids trauma-related material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

Pre-drug:

a. At least 24 hours prior to the first experimental session the subject will be randomized. The PI will obtain the container assignment using a web-based randomization program prior to the blinded sessions.

b. On the day of the experimental session, the subject will arrive approximately 60 to 90 minutes prior to drug administration.

c. Confirm continuing eligibility by reviewing inclusion/exclusion criteria.

d. Perform a urine drug screen. A positive drug screen will be reviewed by the PI and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the subject from the study.

e. If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.

f. If the subject continues to meet criteria and the subject reports that they followed appropriate rules and restrictions, the session will proceed.
g. Review procedures for the experimental session with the subject.
h. Record the entire session to video and audio if possible. Subjects may review audio or
video recordings of their experimental sessions upon request.
i. The session will last for approximately eight hours or longer, followed by an
overnight stay at the study site.
j. The therapists will administer the C-SSRS prior to drug administration.
k. Before drug administration, discuss and review the subject’s goals, intentions and
concerns and some of the commonly experienced effects of MDMA.
l. Instruct the subject not to use caffeine or nicotine two hours before or six hours after
the dose of drug.
m. Subject body temperature will be measured at baseline prior to initial dose
administration and approximately every hour after that. The therapists may make
more frequent measurements if body temperature exceeds more than 1°C above
baseline.
n. Subjects will complete the SUD at baseline prior to initial dose administration.
Subjects will complete the SUD every 60 to 90 minutes, until the session is over,
allowing a window of up to 30 minutes to fit into the psychotherapy process where a
natural break occurs. If necessary, the therapists can make a greater number of
measurements as their clinical judgment dictates.
o. Measure blood pressure and pulse at baseline prior to the experimental session, and
once every half-hour throughout the experimental session if the established thresholds
for normal blood pressure and pulse have not been exceeded for the duration of the
experimental session. More frequent measures will be taken if the established
thresholds of 160 systolic, 110 diastolic, or pulse 110 are exceeded. Measurements
should be taken more frequently until the values fall below these levels or until they
have been decreasing for 15 minutes or have stabilized at a level judged by the PI to
be safe. The therapists may also make more frequent measurements if a subject
exhibits symptoms indicative of hypertension.

During:

p. At approximately 10:00 in the morning, subjects will receive the initial dose of drug
along with a glass of water.
q. The subject will sit or recline on comfortable furnishings. Eyeshades and a program
of music will be provided if the subject wishes to use them. Subjects may speak to the
therapists whenever they wish, who will provide guidance and support as needed.
r. After the first hour, if the subject has not spoken spontaneously, check in with
him/her about the nature of the experience. For the rest of the experience, as
appropriate, the therapists will support and encourage the subject in emotional
processing and resolution of whatever psychological material is emerging as
described in the treatment manual.
s. Record any spontaneously reported reactions during the session.
t. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use
the visual analog scale to collect the changes in symptoms.
u. Provide water and electrolyte containing fluids throughout the session but not to
exceed 3L overall.
v. An optional supplemental dose half the size of the initial dose may be administered approximately 1.5 to 2.5 hours after the initial dose unless contraindicated.

w. Provide food during the latter part of the session.

x. If there is a companion who has previously been asked and has agreed to be present during part or all of the MDMA-assisted session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the therapists. Alternatively, the support person may arrive after the session has ended.

y. If it is appropriate to do so, initiate the first question of the C-SSRS at any point in the session if the subject is experiencing significant psychological distress that does not respond readily to processing with the therapists according to the methods described in the treatment manual. The C-SSRS is required at least once during the session. It is preferable to administer it towards the end of the session at about six hours after the initial dose.

z. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory, and emotionally stable.

**Table 5. Example Schedule of Procedures and Measures for Experimental Sessions**

<table>
<thead>
<tr>
<th>Approximate Time</th>
<th>Procedure or Action</th>
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<tbody>
<tr>
<td>9:00</td>
<td>Urine drug screen, pregnancy test, C-SSRS</td>
</tr>
<tr>
<td>9:45</td>
<td>Baseline BP, pulse, SUD</td>
</tr>
<tr>
<td>9:55</td>
<td>2nd Baseline BP, pulse, BT, SUD</td>
</tr>
<tr>
<td>10:00</td>
<td><strong>Drug Administration</strong>, begin recording to audio and video</td>
</tr>
<tr>
<td>10:30</td>
<td>BP, pulse</td>
</tr>
<tr>
<td>11:00</td>
<td>BP, pulse, SUD, BT</td>
</tr>
<tr>
<td>11:30</td>
<td>BP, pulse, <strong>May administer supplemental dose</strong></td>
</tr>
<tr>
<td>12:00</td>
<td>BP, pulse, BT</td>
</tr>
<tr>
<td>12:30</td>
<td>BP, pulse, SUD</td>
</tr>
<tr>
<td>13:00</td>
<td>BP, pulse</td>
</tr>
<tr>
<td>13:30</td>
<td>BP, pulse, BT</td>
</tr>
<tr>
<td>14:00</td>
<td>BP, pulse, SUD</td>
</tr>
<tr>
<td>Every hour, and as needed</td>
<td>BP, pulse</td>
</tr>
<tr>
<td>Every 60 to 90 minutes</td>
<td>SUD, temperature</td>
</tr>
<tr>
<td>Approximately six hours after administration</td>
<td>C-SSRS, General Wellbeing</td>
</tr>
</tbody>
</table>

Post-drug:

aa. Give the subject the SOCO to be completed after the end of the experimental session and prior to leaving the treatment facility the next day.

bb. The therapists will depart the site when they have concluded that the subject is emotionally and medically stable. Clinical Investigators shall remain available to subjects during the experimental session and for one week after via twenty-four-hour cellular phone for integration as needed.

cc. If the PI decides not to administer any optional supplemental or clinical titration doses, as described in Section 8.3, in a given experimental session, the unused...
capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the pharmacy safe.

dd. Spontaneously reported reactions, AEs, and Medications will be collected as described in Section 14.0 of the protocol.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a companion may accompany the subject during the overnight stay. An attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will monitor subject condition and will help subjects relax during the overnight stay. The attendant will be an individual with some training in managing psychological distress. If there is an emergency or the subject needs additional support, the attendant can contact the therapists. The subject and a companion will receive information that will allow them to contact the therapists during the overnight stay in the case of an emergency or request for additional support. Subjects will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

9.4.4 Integrative Sessions 24 Hours after Experimental Session - Visits 5, 9 (Stage 1), 14 (Full Dose Group Stage 1), 20, 24, 29 (Stage 2)

On the morning after each experimental session, both of the therapists from the subject’s team will meet with the subject during a 60 to 90-minute integrative therapy session.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include discussing material that emerged during experimental sessions and helping subjects integrate their experiences both internally and into daily life. Therapists will validate the choices of the subject about how much they wish to communicate their thoughts, feelings, and experiences at this time, but will elicit enough information to be able to assess the subject’s level of emotional stability and state of emotional and physical wellbeing. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone for additional meetings if needed. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative psychotherapy sessions:

a. The integrative psychotherapy session may be recorded to audio and video. Subjects may review these data upon request.

b. The therapists will administer the C-SSRS during each integrative session.

c. Prior to integrative psychotherapy, the subject and both therapists will indicate their beliefs concerning subject condition assignment.

d. Discuss and review events that occurred with the subject during the experimental session, including thoughts, feelings, and memories. If necessary, the therapists will
help the subject to reduce any residual psychological distress he or she is experiencing. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in experimental sessions to emotionally threatening everyday situations. The therapists will be supportive, validating the experience and facilitating understanding and emotional clearing.

e. The therapists will remain available any time the subject needs support outside the scheduled integration sessions.

f. Assess the subject’s mental health, general wellbeing and the presence of any remaining reactions during integrative psychotherapy immediately after each experimental session.

g. Integrative psychotherapy sessions can also serve as an opportunity for the therapists to gather information about the effects of the drug on the subject in an unstructured manner.

h. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.

i. After the integrative psychotherapy session following the experimental session, a person previously selected by the subject will provide a ride home to the subject. If the subject is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the subject due to unforeseen events, the therapists will assist the subject in finding an alternative means of returning home.

j. Spontaneously reported reactions, AEs, and Medications will be collected as described in 14.0 of the protocol.

k. Remind the subjects that they will have daily phone contact for the next seven days.

9.4.5 A Week of Daily Contact

During daily phone contact:

a. Clinical Investigators will follow the most recent version of the treatment manual in all matters relating to follow-up subsequent to the experimental psychotherapy sessions.

b. Starting on the day of the integrative psychotherapy session following each experimental session, one of the therapists will contact the subject via telephone or in person on a daily basis for one week. The goal of daily contact is assessment of changes in general wellbeing, safety of the subjects, and offering support for subjects.

c. The integrative phone contact will be for a brief check-in lasting five to 15 minutes, or as long as necessary to address any subject’s concerns and to assess subject’s wellbeing. Additional telephone contact can be initiated at the request of the therapists or subject.

d. On the second and seventh day of phone contact after the experimental session, the therapists will administer the C-SSRS.

e. General wellbeing will be assessed at each phone call.

f. Spontaneously reported reactions, AEs, and Medications will be collected as described in Section 14.0 of the protocol.
9.4.6 Integrative Psychotherapy Between Experimental Sessions - Visits 6, 7, 10, 11, (Stage 1), 15, 16, (Full Dose Group Stage 1), 21, 22, 25, 26, 30, 31 (Stage 2)

In addition to the session the morning after each experimental session, the subject will have two additional integrative psychotherapy sessions with the therapists between each experimental session and in the month following the last experimental session. The therapists may conduct more sessions if they and the subject deem it necessary.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or in each integrative session. Generally, adherence criteria for these sessions include integration of material that emerged as a part of experimental sessions and afterward into daily life. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative psychotherapy sessions:

a. Record each integrative session to audio and video if possible. Subjects may review these recordings upon request.
b. The C-SSRS will be administered just prior to beginning each integrative session.
c. General wellbeing will be assessed at each integrative session.
d. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
e. The subject will complete the PDS questionnaire on the third integrative session after the first and third experimental sessions, according to the Time and Events Table.
f. The subject and therapists will continue to work on supporting the subject as she or he considers his or her experiences during experimental sessions.
g. The therapists will use clinical judgment to assess the subject’s psychological wellbeing during this period of time. If there are any indications of continuing anxiety or distress, the therapists may arrange to work on reducing the distress at a specially scheduled integrative therapy session, through continuing contact, or at the next regularly scheduled integrative therapy session. The subject may also initiate contact with the therapists at any time throughout the study.
h. Collect AEs and medications as described in Section 14.0 of the protocol.
i. NOTE: If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all data normally collected during the telephone call will be completed in person.
9.4.7 Evaluation at Primary Endpoint and Unblinding - Visit 12 (Stage 1)

The primary endpoint evaluation in Stage 1 will occur one month (within a window of plus or minus two weeks) after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the Independent Rater and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point one month after their last experimental session.

At the primary endpoint:

a. Subjects will meet the Independent Rater for at least an hour and a half.

b. The blinded Independent Rater will administer:
   - CAPS to assess PTSD symptoms, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
   - GAF to assess general psychological function.
   - PASAT to assess cognitive function.
   - RBANS to assess cognitive function.

c. The subject will complete the following self-report measures:
   - PTGI to assess post-traumatic growth (in reference to start of the study)
   - PDS to assess PTSD symptoms.
   - BDII-II to assess depression symptoms.
   - NEO-PI to assess changes in personality.
   - PSQI to assess changes in sleep quality.
   - DES-II to assess dissociation symptoms.

d. After completing all assessments and measures, the subject will meet with the therapists for approximately 30 minutes.

e. The therapists will assess suicidality with the C-SSRS.

f. General wellbeing will be assessed.

g. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.

h. The blind will be broken for the subject’s condition assignment. Only the Independent Rater will remain blind to condition assignment at this time.

i. If the subject was assigned to receive the comparator dose, the therapists will discuss continuation to Stage 2. Comparator dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1.

j. Collect perceptions of experimental sessions from full dose subjects after unblinding.

k. Collect AEs and medications as described in Section 14.0 of the protocol.

l. If the subject was assigned to receive full dose MDMA, the subject will complete a third open-label experimental session, with associated daily phone calls and integrative sessions in Stage 1.
9.4.8 End of Stage 1 - Visit 17 (Full Dose Group Stage 1)

Full dose subjects will repeat outcome measures and meet with the therapists again two months (within a window of plus or minus two weeks) after their final open-label experimental session, which will be their final visit in Stage 1. This visit will consist of two meetings that may be completed on separate days, one with the Independent Rater and the other with the therapists.

At the end of Stage 1:

a. The Independent Rater will administer the CAPS, GAF, RBANS and PASAT.

b. Subjects will complete the PDS, BDI-II, DES-II and PSQI, PTGI (in reference to start of the study).

c. Full dose subjects who complete Stage 1 and comparator dose subjects who elect not to participate in Stage 2 will complete the RRPQ and continue on to the Long-term Follow-up.

d. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.

e. The therapists will assess suicidality with the C-SSRS.

f. Collect perceptions of experimental sessions.

g. Subjects who will continue on to the Long-term Follow-up may return to taking psychiatric medications after the End of Stage 1 if necessary.

h. Subjects who will continue on the Long-term Follow-up will receive a memory aid card for use between their End of Stage 1 visit and the 12-month follow-up. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the termination visit. Memory Aids will not be collected.

i. Collect AEs and medications as described in Section 14.0 of the protocol.

9.4.9 Open-label Stage 2 (Comparator Dose Subjects from Stage 1)

During Stage 2:

a. Subjects will be reminded that participation in Stage 2 is voluntary and optional.

b. Subjects who elect to cross over to Stage 2 will undergo the same course of therapy and evaluation as in Stage 1, with the exception that the subject will complete a single preparatory psychotherapy session instead of three (see Section 9.4.2), and varied active doses of MDMA will be administered in an open-label context to explore the optimal therapeutic dose (e.g. without unblinding). Visits will be scheduled consecutively according to the Time and Events Table.

c. Assessment of PTSD symptoms at the primary endpoint will serve as baseline assessments in Stage 2. If the start of Stage 2 is delayed for more than 8 weeks from the primary endpoint (Visit 12) to the first preparatory session in Stage 2 (Visit 18), the Independent Rater will re-administer the CAPS and GAF. The subjects will complete the PDS, BDI-II, PSQI, PTGI (in reference to start of the study), and the DES-II. These scores will be used as the baseline for comparison to assessment at the secondary endpoint and end of Stage 2.

d. Experimental sessions will be conducted according to procedures described in Section
9.4.3

1. During the first experimental session, subjects will receive a 100mg initial dose of MDMA and may receive a 50mg optional supplemental dose of MDMA.

2. At the beginning of the second and third experimental sessions, the co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg initial dose of MDMA. If a 100mg initial dose of MDMA is selected, an optional supplemental dose of 50mg MDMA may be administered. If a 125mg initial dose of MDMA is selected, an optional supplemental dose of 62.5mg MDMA may be administered.

3. If the PI decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the pharmacy safe.

c. Integrative sessions will be conducted according to procedures described in Sections 9.4.4 and 9.4.6.

d. Phone calls will be conducted according to procedures described in Section 9.4.5.

e. At the secondary endpoint based on procedures described in Section 9.4.7, the Independent Rater will administer the CAPS and GAF. Subjects will complete the PDS, BDI-II, PSQI, PTGI (in reference to start of the study), and DES-II as described in the Time and Events Table.

f. At the end of Stage 2 based on procedures described in Section 9.4.8, the Independent Rater will administer the CAPS, GAF, RBANS and PASAT. Subjects will complete the PDS, BDI-II, DES-II, PSQI, PTGI (in reference to start of the study), and NEO-PI as described in the Time and Events Table.

h. The End of Stage 2 will be completed in the same manner as the End of Stage 1 as described in Section 9.4.8.

i. Clinical Investigators will follow the most recent treatment manual in all matters relating to the psychotherapy sessions.

9.4.9 Long-term Follow-up

All subjects will be evaluated for long-term effects 12 months (within a visit window of plus or minus one month) after their last MDMA-assisted psychotherapy session. This visit will consist of two meetings, one with the Independent Rater and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point. This visit may be audio and video recorded.

At the Long-term Follow-up visit:

a. The Independent Rater will administer the CAPS and GAF.

b. Subjects will complete the PDS, BDI-II, NEO-PI, PSQI, PTGI (in reference to start of the study), and DES-II.

c. Subjects will have a final meeting with at least one of the therapists to review specified AEs and medications since the last visit. Subjects should bring the Memory
10.0 Removal of Subjects from Therapy or Assessment

Subjects can withdraw consent at any time without prejudice. The PI can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the protocol that are critical for safety and/or for the scientific integrity of the study. If the PI withdraws a subject from the study, the PI will explain the reason for withdrawing the subject. The reason for early termination will be recorded in the subject’s source records and CRF.

Subjects will be clinically monitored after withdrawal, the cause of which will be recorded in the subject’s source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI and/or sponsor.

If the subject develops any exclusion criteria, which in the opinion of the Medical Monitor, affects the safety of the subjects (including psychiatric diagnosis, pregnancy or excluded medications), the subject will discontinue treatment but remain in the study for follow-up purposes. Whenever possible, the tests and evaluations listed for the primary endpoint and 12-month follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI, Medical Monitor and/or Sponsor.

Subjects who discontinue treatment prior to the primary endpoint will be replaced. Individuals who replace these subjects will be assigned the next available subject number. Subjects who discontinue treatment after the primary endpoint in Stage 1 or after continuation to Stage 2 will not be replaced. If Stage 1 subjects discontinue treatment before the primary endpoint, the site should contact the randomization monitor for replacement instructions. Detailed instructions will be provided to the site in a separate document.
11.0 Premature Discontinuation of the Study

The sponsor or the PI (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the PI is to promptly inform the study subjects and will assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with national and provincial regulations.

12.0 Data Analysis

The sponsor will judge the clinical and statistical significance of the study based on a comparison of observer-blind data collected at baseline and the primary endpoint using the primary outcome measure, which is the CAPS. Descriptive statistics will be computed overall and within the two dose conditions for all available data from outcome measures, including minimum, maximum, average, and standard deviation. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Cohen’s techniques will be used to estimate effect sizes between conditions for all outcome measures for Stage 1, Stage 2, and 12-month follow-up.

The sponsor will examine full dose and comparator dose groups for homogeneity through comparing demographic characteristics. There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression. However, owing to small sample size, such variations may arise by chance.

The sponsor will examine CAPS scores for the primary outcome analysis at baseline and the primary endpoint in full dose and comparator dose conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05.

For exploratory purposes, the sponsor will examine PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, and DES-II scores at baseline and the primary endpoint in full dose and comparator dose conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05. Changes in outcome measures from the primary/secondary endpoint to the 2-month follow-up in Stage 1/Stage 2 will be compared for a within-subject analysis with p value set at 0.05 to see whether a third session produces further decline in symptoms.

An exploratory repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after each experimental session, at the primary endpoint, and at the end of Stage 1 with p value set at 0.05. Condition will serve as a between-subjects factor. Results of ANOVA analysis will be used to examine the effects of each experimental session on self-reported PTSD symptom severity. PDS and CAPS scores may be correlated via Pearson’s product moment correlation at baseline and the primary
The first US phase II trial with MDMA to be completed in September, 2008, was conducted in an outpatient setting with a "crash cart" of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately ten minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study MDMA was administered on 51 different occasions at a dose of either 125 mg. by mouth or 125 mg. followed in 2-2.5 hours by an additional 62.5 mg. Blood pressure, pulse and body temperature were closely monitored, but never reached levels that required intervention, nor were there any other medical problems requiring treatment during the MDMA sessions. Subsequently a similar study has been approved in Canada.

The sponsor will collect Changes in Tinnitus and/or Pain visual analog scale scores from any subject reporting tinnitus or chronic pain during each phase of administration, including baseline, experimental and integrative sessions, the primary endpoint, and two-month follow-up. The sponsor will plot out and examine all Changes in Tinnitus and/or Pain visual analog scale scores across both groups and in the full dose and comparator dose groups for trends. Formal analysis of Changes in Tinnitus and/or Pain visual analog scale scores will only occur if more than six subjects complete Changes in Tinnitus and Pain visual analog scale at baseline and primary endpoint. Likewise, formal between-groups analyses will not be performed if all primary endpoint scores are from subjects assigned to the same condition. The sponsor will perform an independent t-test on the difference between baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores in the full dose and comparator dose conditions, with p. set at 0.05. If the only scores available are for subjects in a single condition, then a paired t-test will be performed comparing baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores, with p. set at 0.05.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will compute peak blood pressure, heart rate, and body temperature for subjects after sessions with full dose MDMA or comparator dose MDMA whenever possible. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

The sponsor will collect ratings of adherence to the treatment manual from specifically selected types of sessions. Descriptive statistics will be computed for each adherence scale within a specific type session. The sponsor will explore the factors and structure of the measures of adherence to assist in further development of adherence and competence measures. If sufficient data is available, the sponsor will correlate the mean adherence...
ratings for adherence scale and session type with Global CAPS scores to investigate the
effects of adherence to the treatment manual on reduction in PTSD symptoms. If it is
found that there are specific factors within the adherence scales, then the factor will be
correlated with global CAPS score.

The sponsor will compute descriptive statistics for SOCQ scores from after each MDMA-
assisted psychotherapy session, and average SOCQ scores for blinded experimental
sessions will be compared between conditions. The data will be explored for effects of
condition on domain scores in the SOCQ.

Perception of experimental sessions will be examined during Stage 1 and Stage 2, before
and after subjects have undergone a third experimental session. The results of this
analysis will inform the sponsor of expectancies and the value of the third session for
future protocol development. These data may be correlated with difference scores
calculated from the primary/secondary endpoint CAPS data compared to end of Stage
1/Stage 2 CAPS data to assess the potential contribution of expectation and self-reported
response to changes in PTSD symptoms.

Subjects who discontinue treatment prior to the primary endpoint will be asked to
complete an outcome assessment prior to continuing to the long-term follow-up. The data
from these subjects will be tested for equivalence to data from subjects completing the
study per protocol. If found to be equivalent, data from these subjects will be presented as
an exploratory intent-to-treat analysis to examine results without bias towards subjects
more likely to complete the study per protocol.

An interim analysis may be completed when all subjects have completed Stage 1 and
Stage 2, but not all subjects have completed the 12-month follow-up evaluation.
Additionally, an interim analysis may be performed after all subjects have completed
Stage 1 but not necessarily before all eligible subjects complete Stage 2. This analysis
will address safety, efficacy and process measures. Results of the interim analysis will
have no effect on study conduct.

12.1 Statistical Power

This study is a pilot investigation intended to estimate effect sizes of the safety and
efficacy of MDMA-assisted psychotherapy in people with PTSD. Because of their
exploratory nature, pilot studies are often underpowered for detecting the desired effect.
Because it is a pilot study in a small sample, statistical power is difficult to assess but it is
likely to be low. Analyses of MAPS’ completed US study of MDMA-assisted
psychotherapy in 20 people with PTSD found an effect size of 1.24 for treatment
efficacy, as represented by changes in CAPS score [77]. The estimated effect size for this
study may be lower as a result of comparing the full dose of MDMA with a comparator
dose of MDMA instead of with inactive placebo. The sponsor intends to combine effect
size estimates to develop a dose response curve as a meta-analyses of CAPS scores across
MAPS-sponsored pilot studies.
The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 0.75 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms [169], reducing the effect size to account for the hypothesized effects of using a comparator dose. The software calculated an estimated power of 0.21, indicating an underpowered study. Had we used the higher effect size of 1.1, power analysis still indicates that this study is underpowered, with an estimated effect size of 0.37. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

13.0 Risk Mitigation

Careful review of medical screening data will be utilized to exclude potential subjects with pre-existing exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the IB. Ambient temperature will be kept at a comfortable level during experimental sessions. Subjects will not be allowed to drink more than 3L of fluids over the course of the experimental session, and fluid intake will be spread out appropriately during the session. Fluids administered will include electrolytes. If a subject exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an experimental session, the subject will not receive an other experimental session unless it is approved by the PI and the Medical Monitor.

13.1 Medical Emergencies

Psychotherapy sessions will take place in the offices of the PI. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. They can be heated or cooled with fans. One therapist can reach the offices within five to 10 minutes of contact if necessary. The study site will contain equipment for assessing blood pressure, pulse, and body temperature and there will be an automatic external defibrillator (AED) on site. The Clinical Investigators will maintain basic life support (BLS) certification or its equivalent in Canada in cardipulmonary resuscitation (CPR) including training in using an AED. The site is five minutes from the University of British Columbia emergency department and eight to 15 minutes away from St. Paul’s Hospital emergency department. In the event of a medical emergency paramedics will be summoned and study subjects will be transported to either hospital as appropriate. This is an adequate level of emergency backup based on experience with previous Phase 2 studies in the U.S. and Switzerland during which there have been no adverse events during experimental sessions requiring emergency treatment.

The first U.S. Phase 2 trial with MDMA was conducted in an outpatient setting with a "crash cart" of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately 10 minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study, MDMA was administered on 51 different occasions at a dose of either 125 mg by mouth or 125 mg followed in 2 to 2.5 hours by an additional 62.5 mg. Blood pressure, pulse, and
14.0 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the PI and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the PI as:

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

The relationship of the study treatment to an AE will be determined by the PI based on the following definitions:

- “Not Related”: The AE is not related if exposure to the investigational product has not occurred, or 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, i.e., there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.

- “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.
14.1 Serious Adverse Events

A serious adverse event (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 PI, 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 a 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.

Adverse events which do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the PI, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or abortion does not result in an SAE report unless, in the view of the PI, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

14.2 Adverse Event Collection

The PI will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The PI will collect AEs during study visits after enrollment.

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours of the PI's awareness of their occurrence. All SAEs...
A Memory aid card will be provided to the subject on the last visit prior to the 12-month follow-up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the follow-up period between the end of Stage 1/Stage 2 and the 12-month follow-up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the Clinical Investigator. This information may be collected by phone.

SAE Reporting:
MAPS Office
Telephone: 831-429-6362, ext. 104
Fax: 831-429-6370

Medical Monitor:

Study Monitor contact information will be provided in a separate contact list.

Adverse events that will be collected for the duration of the protocol are:

- All SAEs will be collected through subject termination.
- All AEs and spontaneously reported reactions will be collected on the day of drug administration and for seven days after each experimental session.
- Events requiring medical attention will be collected from enrollment through the subject’s last two-month follow-up.
- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any adverse Event leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

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- Events requiring medical attention will be collected from enrollment through the subject’s last two-month follow-up.
- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any adverse Event leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

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14.3 Spontaneously Reported Reactions

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate, or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Gait/Balance, Impaired Judgment, Increased Irritability, Insomnia, Jaw Clenching or Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Rumination (increased private worries), Sensitivity to Cold, Thirst, and Weakness. Spontaneously reported reactions will be collected during the experimental session and the seven days of telephone contact following the integrative session that occurs on the day after each experimental session. Each reported reaction will be followed during follow-up phone calls or visits until resolution.

14.4 Collection of Concomitant Medications and Tapering Instructions

The PI will record concomitant medications during screening. If the subject is being treated with psychiatric drugs at the time he or she is recruited into the study, the prospective subject will be encouraged to discuss medication tapering with his or her outside treating physician, if any, and will be required to give the PI permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug’s and active metabolites half-life).

The therapists will request information about any changes in medication just prior to each experimental session. The PI will be responsible for reviewing and confirming all medications collected during the study.

All medications, over the counter (OTC) and prescription will be collected from screening through seven days after the last MDMA session. From seven days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected. Throughout the protocol all medications used to treat AEs will be collected, as described in Section 14.0, and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications during Stage 1 and Stage 2, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for 10 days after each experimental session.
Table 6. Medication Tapering Table

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Half-life (hours) including active metabolites</th>
<th>Days for Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam</td>
<td>Xanax</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>Abilify</td>
<td>75</td>
<td>16</td>
</tr>
<tr>
<td>atomoxetine</td>
<td>Strattera</td>
<td>5-24</td>
<td>5</td>
</tr>
<tr>
<td>bupropion</td>
<td>Wellbutrin</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>citalopram</td>
<td>Celexa</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>clonazepam</td>
<td>Klonopin</td>
<td>30-40</td>
<td>8</td>
</tr>
<tr>
<td>diazepam</td>
<td>Valium</td>
<td>20-70</td>
<td>15</td>
</tr>
<tr>
<td>duloxetine</td>
<td>Cymbalta</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>escitalopram</td>
<td>Lexapro</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>Prozac</td>
<td>7-9 (days)</td>
<td>45</td>
</tr>
<tr>
<td>imipramine</td>
<td>Tofranil</td>
<td>6-18</td>
<td>4</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>Lamictal</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>lorazepam</td>
<td>Ativan</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>Remeron</td>
<td>20-40</td>
<td>8</td>
</tr>
<tr>
<td>olanzapine</td>
<td>Zyprexa</td>
<td>21-54</td>
<td>11</td>
</tr>
<tr>
<td>paroxetine</td>
<td>Paxil</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>prazosin</td>
<td>Minipress</td>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>quetiapine</td>
<td>Seroquel</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>risperidone</td>
<td>Risperdal</td>
<td>3-20</td>
<td>4</td>
</tr>
<tr>
<td>sertraline</td>
<td>Zoloft</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restoril</td>
<td>8-12</td>
<td>3</td>
</tr>
<tr>
<td>trazodone</td>
<td>Desyrel</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>Effexor</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>zimirizidone</td>
<td>Gedon</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>zolpidem</td>
<td>Ambien</td>
<td>2.5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Rescue medications may be a benzodiazepine, zolpidem or other anxiolytic or sedative according to the physician’s clinical judgment. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

Subjects must agree that, for one week preceding the MDMA session:

a. They will refrain from taking any herbal supplement (except with prior approval of the research team),

b. They will refrain from taking any prescription or nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs, acetaminophen, birth control pills, thyroid hormones, or other medications approved by the research team).
Subjects will receive a memory aid card for use between the end of Stage 1/Stage 2 visit and the 12-month follow-up. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications and discontinue birth control after the final two-month assessment if necessary.

14.5 Clinical Laboratory Assessments

The PI will examine laboratory assessments gathered in screening for assessing subject eligibility. The PI will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects with abnormal values, after consultation with the medical monitor.

The following laboratory assessments will be performed as a part of screening:

- Serum electrolytes and metabolic profile
  - ALT/SGPT
  - Albumin:globulin (A-G) ratio
  - Albumin, serum
  - Alkaline phosphatase, serum
  - AST/SGOT
  - Bilirubin, total
  - BUN:creatinine ratio
  - Calcium, serum
  - Carbon dioxide
  - Chloride, serum
  - Creatinine, serum
  - Glucose, serum
  - Potassium, serum
  - Protein, total, serum
  - Sodium, serum

- CBC
  - Hematocrit
  - Hemoglobin
  - MCV
  - MCH
  - MCHC
  - RDW
  - Percentage and absolute differential counts
  - RBC
  - Red blood cell count
  - White blood cell count

- Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
15.0 Study Monitoring, Auditing, and Documentation

The clinical lab assessments and ECG will be performed by:

LifeLabs Medical Laboratory Services
3680 Gilmore Way
Burnaby, BC, V5G 4V8

16.0 Risks of Participation

16.1 Risks and Discomforts Associated with Psychotherapy Sessions and Assessment of Measures

- Protein
- Glucose
- Ketones
- Blood in urine
- Leukocyte esterase
- Nitrite

- Thyroid function,
  - TSH high sensitivity
  - Free T4
  - Free T3

- HIV serology,
- Urine-dip pregnancy test for females of childbearing potential.
- Urinary drug test will be performed.

The clinical lab assessments and ECG will be performed by:

LifeLabs Medical Laboratory Services
3680 Gilmore Way
Burnaby, BC, V5G 4V8

15.0 Study Monitoring, Auditing, and Documentation

The PI, therapists, and/or their study staff will be trained prior to the start of the study.

The clinical study site will be monitored by site visits and regular contact with the PI by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate to ensure compliance, including accurate and complete recording of data in CRFs, source documents, and drug accountability records, while maintaining the blind during Stage 1. CRFs will be supplied by the sponsor will be completed for each subject enrolled. Monitoring and auditing procedures of the sponsor will be followed in order to comply with GCP guidelines and to ensure validity of the study data. Monitoring and auditing procedures will be supplied in a separate document.

The sponsor will review the study documentation used for planning, conduct, and monitoring of the study in order to ensure compliance with GCP and local regulations.

This documentation includes as a minimum: the IB, the Protocol, the CRFs, and the Subject Information and Consent Form.

During or after the clinical study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs, and other protocol documentation for on-site audit or inspection.
In preparation for drug-assisted psychotherapy sessions, blood draws and a full medical examination are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

During screening, non-drug and drug-assisted psychotherapy sessions and assessment of study measures, subjects will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy, experimental, and open-label sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings, and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions may be recorded to audio and video for research and training purposes. Subjects may feel uncomfortable with having their sessions recorded. Subjects may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment and assessing adherence to the treatment manual. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

16.2 Risks of Receiving MDMA

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common reactions include lack of appetite, insomnia, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, ruminations, and thirst. Other slightly less common reactions include restlessness, paraesthesias (odd somatic feelings, such as tingling, feeling hot or cold), impaired judgment, perspiration, drowsiness, and nystagmus (eye-wiggling). While anxiety, headache, fatigue, insomnia and lack of appetite were spontaneously reported by 40% to 80% of subjects in both conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, subjects in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea.

These effects are transient and diminish as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, needing more sleep, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects
MDMA may produce mild alterations in sensory perception and altered experience of time [74, 170, 171]. Women may be more sensitive to these effects [124]. MDMA acutely affects attention, information processing, and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of complex scene changes [172]. For this reason, subjects will stay at the site overnight and will not be permitted to drive after experimental sessions.

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness.

Further information on the risks associated with MDMA, including information drawn from case reports and studies of ecstasy users, can be found in the sponsor’s IB.

### 16.2.1 Cardiovascular and Sympathomimetic Effects

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 1.5 to 2.5 hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. These changes should last no more than six hours. In less than 5% of volunteers in Phase 1 studies, peak blood pressure values were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of subjects and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the sponsor’s IB.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing hypertension and monitoring blood pressure and pulse, as described in Section 5.1.2. During experimental sessions, the co-therapists will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. Subjects reporting chest pain, shortness of breath or neurological symptoms or other potential indicators of hypertension will have more frequent measurements and assessment by the PI. Any subject who experiences medical complications during an experimental session will not be given another experimental session unless it is approved by the PI and the Medical Monitor.

In case of need, subjects will be transferred to the emergency room at the closest hospital, as described in Section 13.1. Reasons for moving a patient to an Emergency Department (ED) would include, but not be limited to, severe headache in the setting of hypertension, angina, or neurological deficits regardless of blood pressure. The PI may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The P will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The therapists will attend to any signs or symptoms of acute heart disease. The P will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The therapists will attend to any signs or symptoms of acute heart disease.

In studies similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants.
symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress, and will notify the PI if this occurs for on-site evaluation or a decision to initiate transfer to the ED. If any subject has neurological deficits, as assessed by the PI, whether or not they are associated with hypertensive crisis, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and, if necessary, they will be transported to the emergency department at the closest hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the three-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [173, 174].

The therapists will observe the subject and note any complaints of chest pain. If a subject experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and, if necessary, he or she will be transported to the ED or a location in the hospital where appropriate care can be given. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the subject has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [175].

16.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [72, 124, and see the IB]. Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately three to five hours after drug administration), or even later. Anxiety or distress during the session may last for as long as five hours or for as long as five hours, or more. In addition, psychological distress could arise following an MDMA session as a result of subjects having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting, and have responded well to reassurance from the therapists, with occasional use of benzodiazepines for anxiety. In this study, subjects will have the intention of confronting and working through traumatic experiences. 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.
Proper preparation and follow-up support will reduce the difficulties subjects might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder-1 or with psychotic disorders).
- Preparatory non-drug psychotherapy sessions before the experimental session.
- Creating an atmosphere of trust during the experimental session.
- Close monitoring.
- Daily contact with subjects for the period of a week after the experimental session.
- Providing non-drug integrative psychotherapy sessions.
- Subjects will remain at the study site for the night of each experimental session to further reduce psychological distress. Qualified personnel will be available during the overnight stay to respond to the needs of the subject. Attendants will be instructed to contact the therapists upon request or at the appearance of signs of a potential serious adverse event.

During the preparatory sessions, subjects will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during experimental sessions. Every effort will be made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the experimental session, including empathic listening on the part of the therapists and performance of diaphragmatic breathing by subjects.

At the end of the six to eight hour experimental session, if the subject is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the subject is anxious, agitated, in danger of any self-harm or is suicidal at the end of the experimental session, one or both of the therapists will remain with the subject for at least two more hours. During this time, the therapists will employ affect management techniques, will talk with the subject to help him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the preparatory session. If this situation should occur during an integrative therapy session, at least one of the therapists will be available to stay with the subject for at least two additional hours.
They reported a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-γ and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings (Connor 2000; Connor II). Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine (Pacifici et al. 2000; Pacifici et al. 2001). Because of their limited duration, these changes are not likely to have clinical significance beyond an increased risk of the common cold or similar illness for several days. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose.

Subjects hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the Clinical Investigators will carefully evaluate the subject’s emotional status.

For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject’s outside therapists will be involved in the management of any psychiatric complications. For those subjects engaged in an ongoing psychotherapeutic relationship with the Clinical Investigator(s), the management of any psychiatric complications will be undertaken by them in their capacity as therapists.

### 16.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [124] and ambient temperature does not enhance or attenuate this slight elevation in humans [75].

If temperature rises more than 1°C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. If at any time the temperature rises more than 1.5°C above baseline despite these efforts, the PI will be consulted for further evaluation and treatment.
16.2.4 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [176, 177], and a third reported some developmental delays in mothers reporting use of Ecstasy and other drugs during pregnancy [178].

Pregnant and lactating women will be excluded from participation in the study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control for the treatment portion of the study.

16.2.5 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [179]. However, they are basing their case on studies that employed inappropriately high doses of MDMA utilized in animal studies, and on human studies comparing the effects of repeated use of ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [180]. We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the IB.

16.3 Abuse Liability

Findings in humans and animals suggest that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine. More information on abuse liability is provided in the IB.

Whether MDMA-assisted psychotherapy will cause PTSD patients to develop symptoms of abuse is an open question that the sponsor is addressing on an ongoing basis. Based on long-term follow-up data from two sponsor-supported studies (N=32), only one subject took Ecstasy after completing the study and failed to reproduce the experience from the study, and a number of subjects volunteered that they would never seek out Ecstasy outside a legal, controlled, therapeutic setting. In addition, negative results from MDMA-specific drug testing data obtained from the Swiss study MP-2 (N=12) supports that none of these subjects took Ecstasy outside of the study during the long-term follow-up period.

Diversion is not an issue in this protocol because MDMA will only be administered a few times under the supervision of the PI and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.
16.4 Risks and Discomforts of Receiving the Comparator Dose of Study Drug

Receiving the comparator dose of 50 mg MDMA followed 1.5 to 2.5 hours later by 25 mg MDMA may be associated with some of the risks above. People receiving low doses of MDMA report only a few subjective effects and do not exhibit significant cardiovascular changes. It is possible that the addition of the supplemental dose will produce slight increases in positive and negative mood and slightly elevate blood pressure, as reported after administering approximately 35 mg to 40 mg. The comparator dose of MDMA is not expected to produce most or all of the potentially therapeutic effects of the drug, such as increased positive mood, facilitated recall, changed perception of meaning, and increased feelings of closeness to others. Hence people receiving comparator doses may experience a lesser reduction in PTSD symptoms from MDMA-assisted sessions.

17.0 Alternative Treatments and Procedures

The decision not to participate in this research study will not in any way alter or compromise the care offered to individuals receiving therapy from the PI or any physician involved in this research study.

The PI will discuss alternatives to study participation, including other available treatments, with all potential participants. There are a number of recognized treatments for PTSD. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments for PTSD include anxiety management (stress inoculation training), cognitive therapy, exposure therapy, and psychoduction. Psychodynamic psychotherapy and Eye Movement Desensitization and Reprocessing are also used to treat PTSD.

Drugs available in Canada for treating PTSD include paroxetine, and in the US, sertraline and paroxetine are approved for use in treatment of PTSD. Sertraline has been shown to decrease the hyperarousal and avoidance symptoms, but not the re-experiencing symptoms, of PTSD. Paroxetine has been shown to have an effect on all three categories of symptoms in approximately 62% of patients. Other medications commonly used are other SSRIs, nefazodone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem, and mood stabilizers.
18.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of subjects in their role as research subjects. Removing identifying information from data and restricting access to researchers directly involved in assessing the subjects should prevent the dissemination of confidential data, with or without identifying information. Except for the screening log, the ICF, and a subject contact information sheet that will be stored separately from other documents, all data will be identified only by the subject’s secondary identifier number on the source document and five-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening for protocol enrollment.

All psychotherapy sessions and the 12-month follow-up may be recorded to video and audio. In addition the CAPS assessment may also be recorded to audio and video to establish inter-rater reliability. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses will not appear in these recordings. Audio and video recordings will only be marked with the subject’s subject number. Video data will be stored on a HIPA-compliant remote server with encryption and authentication in place to ensure confidentiality. Study subjects will only be able to view their own video data by logging into a secure HIPA-compliant server. Only HIPA-certified researchers who have signed a Data Confidentiality Agreement, completed Good Clinical Practice training, and received approval from the PI will be permitted to access video data for research and training purposes.

Any materials mailed to subjects will be sent along with stamped return envelopes using the office address of the PI both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the Clinical Investigators directly involved in the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means, such as social security number.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.
Administering the study drug exposes study participants to a number of potential risks and discomforts that would not otherwise occur. The experimental dose of MDMA is liable to produce common physiological and psychological side effects during each experimental dose MDMA-assisted session, such as increased blood pressure or elevated anxiety. People with PTSD receiving MDMA within a therapeutic setting may very well experience strong negative emotions during the session, as fear, rage or grief. There are reports of a number of serious adverse events in people in uncontrolled, non-medical settings after taking ecstasy. However, there is good evidence that conducting three separate experimental sessions administering initial doses of 125 mg followed by 62.5 mg MDMA in a clinical setting poses a low risk to participants.

20.0 Record Retention

The PI must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility for 25 years in accordance with Health Canada regulations. The PI must consult a MAPS representative before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the PI as to when these documents no longer need to be retained.

21.0 Publication Policy

The sponsor recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the PI that the information generated in this study will be used by the sponsor in connection with the development of the investigational product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the PI is obliged to provide the sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analysis is done on the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician.

Any results of medical investigations with the sponsor products and/or publications/lectures/manuscripts based thereon, shall be exchanged and discussed by the PI and the sponsor clinical research representative(s) prior to submission for publication or presentation. Due regard shall be given to the sponsor’s legitimate interests, e.g. manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other studies in the...
same field.

The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.
A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

(To be submitted to Ethics Board Health Canada and, if approved, to FDA under IND#63,384)

[November 17, 2008]

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Study Period
2008-2009
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**Introductory Statement**

This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). This study has been designed as part of an international, multi-site program of research sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org), a USA-based non-profit research and educational organization. MAPS’ long-term goal is to develop MDMA into a prescription medication approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA) and Health Canada. MAPS is currently the only organization in the world of which we are aware sponsoring research into the therapeutic potential of MDMA.

MAPS is currently sponsoring under FDA IND #63,384 a nearly completed pilot study of MDMA-assisted psychotherapy in 21 patients with treatment-resistant posttraumatic stress disorder (PTSD), taking place in Charleston, South Carolina under the direction of . Twenty out of 21 subjects have already completed the protocol. The final experimental session for the 21st subject occurred on July 18, 2008 and the final two-month follow-up evaluation will take place around September 18, concluding the study. Preliminary results are remarkably promising with no drug-related Serious Adverse Events (SAEs) and statistically significant results supporting the efficacy of MDMA-assisted psychotherapy (Wagner 2008, personal communication). A separate longer-term follow-up of participants a year or more after study participation has been approved by our IRB and will be initiated soon.

MAPS is sponsoring two additional ongoing pilot studies of MDMA-assisted psychotherapy in patients with PTSD, one in Switzerland under the direction of and one in Israel, under the direction of . Both of these studies are designed for twelve subjects and are scheduled to be completed before the end of 2009. All studies are using the same primary outcome variable, the Clinician Administered PTSD Scale (CAPS), enabling examination of results across all studies, and meta-analyses of data pooled across each pilot study. All of MAPS’ studies conducted outside of the US have been approved by regulatory authorities in those countries and have been submitted to FDA and are also being conducted under FDA IND 63,384.

MAPS has also helped initiate and fund an FDA-approved study investigating MDMA-assisted psychotherapy in people with anxiety related to advanced-stage cancer. This study is taking place at Harvard Medical School’s McLean Hospital, under the direction of the Sponsor/Investigator. The second of twelve subjects has been enrolled. The first subject has completed the study safely with reports of reduced anxiety and pain (Halpern 2008).

This proposed Canadian pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, eight of 12 people will receive a dose of MDMA expected to be fully therapeutic (experimental dose) and four of 12 will...
MDMA became illegal in the US and then internationally shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia, prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD (Adamson 1985; d'Otalora 2004; Greer and Tolbert 1998; Metzner and Adamson 2001). Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can “reduce or somehow eliminate fear of a perceived threat to one’s emotional integrity” (Greer and Tolbert 1998). Elimination of these “conditioned fear responses” can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender 1990). The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD (Adamson 1985; d'Otalora 2004; Greer and Tolbert 1998; Metzner and Adamson 2001). Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can “reduce or somehow eliminate fear of a perceived threat to one’s emotional integrity” (Greer and Tolbert 1998). Elimination of these “conditioned fear responses” can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender 1990). The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

MDMA became illegal in the US and then internationally shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia,
PTSD affects an estimated 8% of the general population at some point during their lifetime (Kessler et al. 1995), as reported in a national survey of mental disorders in the general population of the US. There are still questions concerning what are the best treatments for this debilitating psychiatric disorder (Montgomery and Bech 2000). People

A. Exposure to a significant traumatic event accompanied by an intense acute emotional response.
B. Persistent re-experiencing of the event or aspects of the experience.
C. Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life.
D. Persistent symptoms of increased arousal.
E. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD.

PTSD affects an estimated 8% of the general population at some point during their lifetime (Kessler et al. 1995), as reported in a national survey of mental disorders in the general population of the US. There are still questions concerning what are the best treatments for this debilitating psychiatric disorder (Montgomery and Bech 2000). People
with PTSD face challenges in relationships and with work productivity (Brady et al. 2000). An array of psychotherapeutic options exists for treating PTSD, and two SSRIs (Zoloft and Paxil) are approved as PTSD treatments in the US. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies (Foa et al. 1999; Resick and Schnicke 1992), and at least one study of Paxil indicated that men with PTSD did not respond to this drug (Brady et al. 2000). These findings suggest that there is still substantial need for innovative treatments for PTSD.

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including subthreshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased to 10.3%. (Perkonigg et al. 2000). A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate (Frise et al. 2002). A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers who were deployed more than once (Richardson et al. 2007). These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. Acting Inspector General Jon A. Wooditch testified to the US Congressional Committee On Veterans’ Affairs Subcommittee On Disability Assistance And Memorial Affairs that in 2004, the US Veterans Administration spent over $4.3 billion on disability payments to over 215,000 veterans with PTSD (2005). The search for novel and more effective treatments is therefore of major public health and economic significance. In the US National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of the patients still had symptoms several times per week after 10 years (Kessler et al. 1995). Generally, the number of people who do not improve after treatment can be high, between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group still were diagnosed with PTSD with high enough CAPS scores (Resick et al. 2002) and another study reported similar figures (Foa et al. 1999).

**PTSD and MDMA-assisted psychotherapy**

To date the treatment of PTSD has primarily been a psychotherapeutic treatment, the effect size for psychotherapy being higher than for psychopharmacologic treatment. Cognitive behavioral therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and EMDR also proved to be effective in treating some aspects of PTSD symptoms (Ursano et al. 2004). Some people may have to
undergo more than one treatment to reduce or resolve PTSD symptoms (Hamner et al. 2004). However, a recent meta-analysis concluded that all “bona fide” psychotherapies, including all those listed above, are similarly effective with PTSD (Benish et al. 2008).

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998). Treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a brief to moderate course of non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD.

Anecdotal accounts, an uncontrolled clinical trial, and data from an ongoing controlled trial described above all suggest that MDMA may provide unique benefits to people with PTSD when administered in combination with psychotherapy. It may assist people in confronting memories, thoughts and feelings related to the trauma without increasing fear in response to this confrontation. An increase in self-acceptance and increased feelings of closeness to others may also assist people with PTSD as they work with psychotherapists.

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Paxil and Zoloft are the only two drugs approved by the FDA in the US for treating PTSD, and are known to affect the serotonergic components of PTSD. They may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD (Nibuya et al. 1996). Another approach to treatment of PTSD is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and re-enforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala (Gamma et al. 2000). This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD (Davis and Shi 1999; Rasmusson and Charney 1997).

To date, Phase I trials have been conducted by eight research teams in the United States, England, Spain, Switzerland, and the Netherlands, with MDMA administered to approximately 390 subjects overall without the occurrence of any serious adverse events (see for example Cami et al. 2000b; Chang et al. 2000; Dumont and Verkes 2006, review;
Prior to its scheduling and international regulation, MDMA was used in psychotherapy to treat neuroses, relationship difficulties, and PTSD (Adamson 1985; d’Otalora 2004; Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998). Anecdotal and narrative accounts of MDMA-assisted psychotherapy reported successful treatment of PTSD. People reported reduced PTSD symptoms and improved quality of life.

It should be noted that during this period in time, MDMA may have been given to thousands of individuals without any fatalities or serious adverse events (Holland 2001; Rosenbaum and Doblin 1991). Greer and Tolbert's (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29

Previous Clinical Experience with MDMA

Acute effects reported in controlled studies are in agreement with those reported in earlier uncontrolled studies (Downing 1986; Greer and Tolbert 1986) and anecdotal reports (Adamson 1985; Widmer 1998). These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication (Vollenweider et al. 1998).

There has been no evidence of significant or lasting toxicity in subjects participating in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g. Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Reneman et al. 2001; Thomasius et al. 2003). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. As described in more detail below, more recent retrospective and prospective studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.