

PROTOCOL MAA-1
IND #63,384

Original Protocol Version 1: February 22, 2013

Original Protocol Version 2: May 21, 2013

A Placebo-controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA-assisted Therapy for Social Anxiety in Autistic Adults

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1.0 List of Abbreviations

ADOS-2	Autism Diagnostic Observation Schedule, Second Edition (Module 4)
AE(s)	Adverse Event(s)
A:G	Albumin : Globulin ratio
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AS	Asperger's Syndrome or Disorder
ASD	Autism Spectrum Disorder
AST/SGOT	Aspartate Aminotransferase
AVP	Arginine Vasopressin
BDI-II	Beck Depression Inventory II
BUN	Blood Urea Nitrogen
C	Celsius
CI	Clinical Investigator
CORT	Cortisol
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
ECG/EKG	Electrocardiogram
ED	Emergency Department
ERQ	Emotion Regulation Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
IRI	Interpersonal Reactivity Index
ISF	Investigator Site File
LSAS	Liebowitz Social Anxiety Scale
MAOI	Monoamine Oxidase Inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-Methylenedioxymethamphetamine
MP-1	MAPS' first clinical trial of MDMA-assisted psychotherapy for PTSD
OT	Oxytocin

PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
PI	Principal Investigator
PRN	As Needed
PSS	Perceived Stress Scale
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RSES	Rosenberg Self Esteem Scale
SAE(s)	Serious Adverse Event(s)
SCID	Structured Clinical Interview for Diagnoses Axis I Research Version
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Index
SUD	Subjective Units of Distress
TAS-20	Toronto Alexithymia Scale – 20
TASIT	(The) Awareness of Social Inference Test
TD	Typically Developing
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

2.0 Introduction, Background, and Rationale

2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit research and educational organization, is proposing a double-blind, randomized, placebo-controlled exploratory pilot study with dose escalation to assess safety and feasibility of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for social anxiety in 12 MDMA-naïve adults on the autism spectrum. This study will also obtain estimates of effect size based on response to two experimental sessions of MDMA-assisted therapy in comparison to an inactive placebo control group in order to properly power subsequent investigations. The study will be conducted in association with researchers at Los Angeles Biomedical Research Institute (Harbor-UCLA Medical Center, main site) and Stanford University Medical Center (collaborating site). The sponsor has ongoing studies using MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD) that will be used to inform the safety and dosing aspects of this new investigation as a potential therapy for social anxiety that could benefit the quality of life of adults on the autism spectrum.

Based on the known effects of MDMA, as well as individual reports, the sponsor intends to conduct this exploratory study which will focus on enhancing functional skills and quality of life in this underserved population, who tend to experience greater anxiety, depression and victimization than typically developing (TD) adults. The exploratory elements of this study are: group sequential dosing, refinement of the treatment method, study endpoints, assessment of clinical response, appropriateness of the chosen measures, and biomarker analysis of response to treatment. This study is designed to explore treatment-related changes in social anxiety, social perception, and neuromodulators such as oxytocin (OT), arginine vasopressin (AVP) and cortisol (CORT), that are critically involved in anxiety and social behavior. Outcomes from this study, if promising, will inform the dose, endpoints and treatment regimen for subsequent studies.

2.2 Background

2.2.1 Autism

The term autism refers to a spectrum of congenital pervasive developmental disabilities. A complex developmental and biopsychosocial condition, autism is characterized by a combination of six or more types of behaviors under the following symptom domains in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [1]:

- (A) Qualitative impairment in social interaction;
- (B) Qualitative impairments in communication;
- (C) Restricted repetitive and stereotyped patterns of behavior, interests and activities.

At present, the DSM-IV criteria for Autistic Disorder also apply to varying degrees to Asperger's Disorder (AS) and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS). However, individuals with AS do not present with marked language or cognitive development delays, motor skills problems (i.e., clumsiness,

awkward gait) are more prevalent than with other autistic conditions, and, in the majority of cases, intelligence quotient (IQ) scores range from average to superior. However, they tend to lack requisite skills for social adaptability among the TD population, such as interpreting facial expressions, body language, and subtle nuances of social communication such as figures of speech and sarcasm. A major revision of autism diagnostic criteria is anticipated in the upcoming 5th edition of the DSM (DSM-V), which would eliminate the distinctions between autism categories and combine them under Autism Spectrum Disorders (ASD). Therefore, the AS and PDD-NOS diagnostic categories may become obsolete prior to completion of this study; thus, in this protocol we have chosen to utilize autism or ASD as the diagnostic term in anticipation of the new version of the DSM.

AS was first defined in English-language medical literature in 1981[2]. The condition is often misdiagnosed or not identified until adolescence or early adulthood, after the period when developmentally appropriate social skills would need to be developed. PDD was the more common diagnosis utilized for milder forms of autism throughout the 1980s and early 1990s, whereas AS was not employed until later. As recently as the 1980s, ASDs were considered rare [3]. However, in 2008, the prevalence of ASDs in 8-year-old children at 14 Autism and Developmental Disabilities Monitoring Network sites across the United States was estimated at one in 88, an increase of 78 percent since 2002 [4]. The increase in diagnoses may be due to increased awareness of the diagnostic criteria among clinicians, increased public awareness and education, as well as improved accuracy in recognizing spectrum disorders in females and minority populations. These factors were found to contribute to increases in prevalence estimates, but a true rise in cases could not be ruled out. As a result, the Centers for Disease Control and Prevention consider escalating prevalence rates of autism in the general population as an urgent public health concern. This dramatic rise in prevalence has led some to propose that autism is more accurately conceptualized as variations of cognitive differences that have always presented in humans as opposed to an epidemic or spectrum of disorders [5].

Autistic adults often present for treatment of common co-occurring conditions such as anxiety, trauma, depression, and social adaptability challenges. However, responses to conventional prescription medications developed in TD individuals are often ineffective in autistics [6], and difficulties with establishing therapeutic rapport with therapists can interfere with conventional psychotherapy [7]. The search for new supportive treatments for autistic adults is relevant in the absence of established or effective treatment options.

2.2.2 Social Anxiety and Autism

Social anxiety, also known as social phobia, is characterized by fear of scrutiny and avoidance of social interactions. Social anxiety is prevalent [8], begins early [9, 10], and follows a chronic course [11]. Impairment is substantial in TD individuals [12] and it interferes with ability to work and attend school, as well as developing relationships, leading to low quality of life [13, 14]. Social anxiety is differentiated from anxiety proneness[15], and is described in the DSM-IV as:

- (A) Marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.
- (B) Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.
- (C) The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.
- (D) The feared social or performance situations are avoided or else are endured with intense anxiety or distress.
- (E) The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
- (F) In individuals under the age of 18, the duration is at least 6 months.
- (G) The fear or avoidance is not due to the direct physiological effects of a substance (e.g., drug abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).
- (H) If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa.
- Specify if:* Generalized: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder)

Autistic adults who are verbal and whose autism might not be immediately recognizable to others often initially present in a clinical setting with symptoms of anxiety or depression [16]. Autistic adults are at an increased risk for developing co-morbid anxiety and depression as they are faced with increasing amounts of exposure to social situations compared to children [2, 17]. Long-term multi-cohort studies following autistic children into early adulthood have found that co-morbid behavior and emotional problems remain high in adulthood [18]. Comparative studies suggest that autistic adults, especially those who are verbal and whose autism might not be immediately recognizable to others and who are faced with strong pressure to conform to non-autistic social norms, are at greater risk for lifetime and current co-morbid psychological disorders, especially social anxiety [19-21]. Social anxiety frequently compounds the considerable social challenges experienced by autistic adults [22].

There are currently no pharmacologic treatments approved for autistic adults, although off-label prescription of selective serotonin reuptake inhibitors (SSRIs) are on the rise in this population [23]. The antipsychotics risperidone and aripiprazole are the only pharmacologic treatments approved by the FDA for irritability associated with autism in children and adolescents. Conventional anti-anxiety medications, including SSRIs, monoamine oxidase inhibitors (MAOIs), and benzodiazepines, lack clinical effectiveness in autistic adults, potentially due to physiological differences between autistic and TD individuals. There is some evidence for a lower number of benzodiazepine binding sites in the brains of autistic adults [24]. Although serotonergic dysfunction has been proposed as a potential neurobiological basis for autism, efficacy data on SSRIs in the treatment of symptoms associated with autism are of varied nature, with some trials finding efficacy for global severity and repetitive behaviors [23] and a large multi-site trial finding no efficacy for repetitive behaviors [25]. Given the paucity of confirmed efficacy in clinical trials and clinical practice, the search for supportive treatments for social anxiety in autistic adults is relevant in the absence of established or effective treatment options.

2.2.3 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative. Chemists at the Merck pharmaceutical company first synthesized it in 1912 [26, 27], though its clinical effects were not subject to formal investigation until the 1980s. MDMA is a potent monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [28-33].

In TD healthy volunteers, MDMA administration acutely decreases activity in the left amygdala [34], a brain region involved in interpretation of negative cues, and attenuates amygdalar response to angry faces [35]. This action of MDMA is compatible with its reported reduction in fear of emotional injury or defensiveness [36]. Thus, brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [35]. Based on functional brain imaging studies with anxiogenic stimuli in autistic individuals, the amygdala may be differentially activated [37] or it may signal in an altered manner to the fusiform gyrus, a key brain region for facial recognition, resulting in differences in social perception [38]. A recent study in TD healthy volunteers found correlations between plasma OT levels, amygdalar volume, and extraverted personality [39].

OT is a neuropeptide associated with pair bonding and social affiliation in mammals that also attenuates amygdalar response to anxiogenic stimuli [40, 41]. OT administration is associated with increased interpersonal trust and changes in social perception, including attenuated reactivity to threatening faces [42-44]. OT administration also improves empathic accuracy in some individuals who are shy or lack adequate social skills [45]. Alterations in OT signaling have also been proposed as a potential mechanism for the underlying neurological basis for the core social differences in autism and has been implicated as a possible novel therapy [41]. These claims are now supported by several clinical trials of intranasal OT treatment for the core social impairments in autism [46-49].

MDMA elevates OT in peripheral blood [50-52], which is an imperfect but somewhat

reliable indicator of elevated OT in the brain [41]. Findings of an association between elevated OT and detectable MDMA in peripheral blood were first reported in a naturalistic study of London nightclub attendees with and without detectable plasma MDMA levels [50]. Dumont and colleagues reproduced these results in humans and found that MDMA significantly elevated peripheral plasma OT levels in a placebo-controlled study in healthy volunteers [51], in addition to a positive association between elevated levels of OT and prosocial feelings. Hysek and colleagues replicated these results and further reported that administering a serotonin reuptake inhibitor, but not a norepinephrine uptake inhibitor nor several adrenergic antagonists, attenuated the effects of MDMA on OT levels, suggesting a serotonergic mechanism in producing elevated OT [52]. The effects of MDMA on OT could be partially responsible for changes in personality [53] and empathy [54]. However, the multi-level effects of MDMA on monoaminergic signaling and OT, combined with a therapeutic setting focused on enhancing functional skills, are more likely to provide the opportunity for a corrective emotional experience greater than OT alone, and could be useful in the treatment of social anxiety in autistic adults.

In addition to increased OT release, MDMA also results in increased secretion of the highly related neuropeptide AVP [50]. AVP neurobiology has been linked to social behavior in animal models and has been shown to increase social cognition when administered to healthy adult volunteers [46, 55, 56].

Also of interest is the stress-related hormone CORT, the major output of the hypothalamic-pituitary-adrenal (HPA) axis. MDMA has also been shown to increase CORT levels and it has been proposed that these changes are related to the stimulating effects of the drug [57]. In addition to the extensive prosocial behavioral effects of OT and AVP, their release has been shown to modulate other neuroendocrine systems, particularly the stress responsive activity of the HPA axis, that is dysregulated in individuals with social anxiety [58, 59].

2.2.4 MDMA-Assisted Therapy

MDMA-assisted therapy is an innovative mode of treatment that combines therapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of therapy. The therapeutic method that is most appropriate for this population will be adapted from therapy techniques that have been empirically developed in adults with an AS diagnosis [7]. The main features of the therapy will focus on developing a therapeutic relationship with the subjects that will provide a permissive setting to learn and practice social skills.

MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to therapy. MDMA is capable of inducing unique psychological effects, including:

- Decreased feelings of fear
- Increased feelings of wellbeing
- Increased sociability
- Increased interpersonal trust

- Alert state of consciousness
- Increased awareness of some domains of empathy[36, 60, 61]

Early observers in clinical settings noted increased acceptance of self and others in the TD population, increased tolerance of emotionally upsetting materials, and the ability to address these issues without extreme disorientation or ego loss [36, 60-64]. In the U.S., MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists in the treatment of neuroses, relationship problems, and PTSD [61, 62, 65, 66] before it was placed in Schedule 1 in 1985, as a result of extensive non-medical use [36, 64, 67]. Placement in Schedule 1 prohibited it for use, except within federally-approved research settings.

As part of her dissertation at the Institute of Transpersonal Psychology, co-investigator Alicia Danforth, Ph.D. Candidate, gathered 100 surveys, 90 anecdotal reports, and conducted interviews with 24 individuals on the autism spectrum who have taken Ecstasy, a street drug purported to contain MDMA, in non-medical settings. A majority of these individuals reported the experience to be helpful in their learning to cope more effectively in social situations [68]. From a list of commonly reported MDMA effects, 72% of survey respondents (N=100) reported experiencing “more comfort in social settings,” with 12% indicating that the change lasted over two years. 78% of respondents reported “feeling at ease in my own body,” with 15% experiencing this effect for over two years. 77% reported “easier than usual to talk to others,” with 18% reporting that the effect lasted up to a year or longer. These anecdotal reports suggest that MDMA may be a suitable pharmacologic agent for the treatment of social anxiety in autistic adults and warrants further investigation in a randomized controlled clinical trial.

In contrast to daily administrations of SSRIs, MDMA-assisted therapy consists of only a few drug-assisted sessions interspersed within a brief course of non-drug therapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as SSRIs and benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found that a small percentage of non-medical, recreational users exhibit problematic use of Ecstasy (material represented as containing MDMA, though often the object of drug substitution of compounds other than MDMA, including methamphetamine and other addictive psychostimulants) [69, 70]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [71]. Hence, MDMA may have moderate abuse potential in a subset of individuals. A comprehensive review of MDMA research is included in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.2.5 Previous Clinical Experience with MDMA

Classification as a Schedule 1 drug has hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and effectiveness of MDMA-assisted therapy has become more feasible due to an open IND with the FDA [72-74]. The first double-blind, placebo controlled U.S. Phase 1 study sanctioned by the FDA was conducted by the Principal Investigator (PI) of this study at Harbor-UCLA Medical

Center in 1994, with findings that suggested MDMA may cause a statistically significant increase in body temperature, heart rate, and blood pressure in some healthy volunteers [75]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [51, 75-80]. The elevation in body temperature noted in healthy volunteers was not clinically significant in sponsor-supported studies at normal ambient temperatures [81, 82]. As of May 2013, MDMA has been administered to more than 845 research subjects, in both Phase 1 and Phase 2 studies, and the sponsor has not been informed of or seen published reports of any unexpected MDMA-related Serious Adverse Events (SAEs) in research studies [28, 31, 35, 36, 52, 54, 75, 76, 79-122].

The potentially therapeutic effects of MDMA were initially investigated in a placebo-controlled, blinded dose response pilot study funded by MAPS in Spain, in six female survivors of sexual assault with treatment-resistant PTSD [101]. In this study, doses ranging from 50 mg to 75 mg demonstrated mild signs of improvement without any adverse events (AEs) or signs of deteriorating mental health [101]. MAPS went on to sponsor the first randomized, placebo-controlled Phase 2 pilot study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, which demonstrated promising results in a sample of 20 subjects [82]. Findings from the long-term follow-up of this study indicate that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [123]. The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland, which found a trend toward significant improvement in subjects receiving full dose MDMA, when compared to a 25 mg active placebo MDMA, at two-month follow-up. The improvement continued to increase during the twelve-month follow-up [81]. These studies have shown promise for MDMA-assisted psychotherapy to help people overcome PTSD, an anxiety-related disorder, that suggest this treatment could also be useful in treating social anxiety in autistic adults.

2.3 Protocol Purpose

This is a double-blind, randomized, placebo-controlled, dose-finding Phase 2 pilot study designed to explore the safety and the therapeutic potential of MDMA-assisted therapy for treating social anxiety in 12 MDMA-naïve adults on the autism spectrum. This study will provide an estimate of effect size based on response to two experimental sessions of MDMA-assisted therapy in autistic adults on measures of safety, social anxiety, social perception, and psychiatric symptoms in comparison to a placebo control group. The primary outcome measure for the study will be the clinician-administered Liebowitz Social Anxiety Scale (LSAS) administered by a blinded Independent Rater (IR). Self-report measures will correspond to indications that often co-present with autism, including anxiety, stress, depression, emotion regulation, alexithymia, differences in some empathy domains, and other psychosocial challenges. Subjects will receive ongoing social support during the study in the form of non-drug therapy and active involvement of a support partner.

This study will employ biomarker analyses in combination with clinical outcome measures to provide useful insights into the underlying mechanism of MDMA's psychosocial and anxiolytic effects, and to examine any biological differences to treatment responses. The time course of biomarker concentrations will be used to determine if MDMA-assisted therapy causes lasting changes in biomarker levels in comparison to baseline.

Each of the 12 subjects will participate in two blinded experimental sessions, assisted by either MDMA or placebo, of seven hours in duration within a brief course of non-drug therapy, including three hour-long preparatory sessions at the start of the study and three hour-long integrative sessions during the month after each experimental session at two week intervals. This study is designed as a dose escalation study to assist with the exploration of safety and finding the most effective dose in this population. Based on anecdotal reports, subjects in this population may be more sensitive to the standard dose of 125mg MDMA that has indications of efficacy for PTSD [68]. Subjects assigned to the MDMA group will receive two of three different doses, either 75mg, 100mg, or 125mg MDMA. Overall, eight subjects (66.7%) will be randomized to the MDMA group and four subjects (33.3%) will be randomized to the placebo group. During the study, there will be a maximum of 24 experimental sessions with MDMA, with eight sessions in each dose group, and eight experimental sessions with placebo. Observations before, during, and after experimental sessions will be compared between these groups of equal size to explore the effects of MDMA-assisted therapy in the first double-blind, randomized, placebo-controlled trial of this treatment for social anxiety in a sample of autistic adults.

2.4 Rationale of Dose Selection

The MDMA doses of 75mg and 125mg to be used in this study have been used in previous and ongoing MAPS-sponsored studies in the U.S., Switzerland, and Israel [81, 82]. Previous researchers have also used doses within this range up to 225mg [75, 76, 78, 79, 91, 99, 116, 124-126]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [36, 62, 64]. Each MDMA dose is expected to produce the commonly reported effects of MDMA.

Anecdotal reports suggest a potential for increased sensitivity to the effects of MDMA in autistic individuals who experience sensory hyperarousal [68]. Therefore, subjects will only receive a single administration of MDMA during experimental sessions, and the lower 75 mg and 100 mg doses will be administered to assess for enhanced sensitivity during the first experimental session to subjects randomized to MDMA. MDMA subjects will only escalate to a 25mg higher dose in the second experimental session that they receive one month later. If any subjects within each dose group experience a drug-related SAE, the dose escalation procedure will not continue for remaining subjects in the same dose group in the interest of subject safety. If this occurs, the institutional Data Safety Monitor and Sponsor Medical Monitor will be consulted to determine the course of action. Any subject who experiences a drug-related SAE will be excluded from any additional experimental sessions, but will continue with non-drug therapy and follow-up assessments whenever possible.

Table 1. Dose Regimen

Group # /Randomization /Sample	Stage 1		Stage 2 Open-Label Extension	
	Session 1 Month 1	Session 2 Month 2	Session 1 Month 6	Session 2 Month 7
Group 1 active N=4	75 mg	100 mg	N/A	N/A
Group 1 placebo N=2	Placebo	Placebo	75 mg	125 mg
Group2 active N=4	100 mg	125 mg	N/A	N/A
Group 2 placebo N=2	Placebo	Placebo	75 mg	125 mg

3.0 Protocol Objectives

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

3.1 Primary Objective:

To estimate effect sizes of social anxiety symptom reduction between MDMA and placebo, as measured by the clinician-administered LSAS administered by a blinded IR, at baseline, one day, two weeks, and one month after each experimental session, and at 6-month follow-up.

3.2 Secondary Objectives:

The following objectives will compare MDMA subjects to placebo subjects in Stage 1:

- To assess effects on levels of OT, AVP, and CORT in peripheral blood at baseline, once during each experimental session between hours 2 – 3, one month after the second experimental session, and at 6-month follow-up.
- To assess effects on social perception using The Awareness of Social Inference Test (TASIT) at baseline, once during each experimental session between hours 2 – 3, one month after the second experimental session, and at 6-month follow-up.
- To assess effects on emotion labeling using the Toronto Alexithymia Scale-20 (TAS-20) at baseline, one month after each experimental session, and 6-month follow-up.
- To assess effects on emotion regulation using the Emotion Regulation Questionnaire (ERQ) at baseline, one month after each experimental session, and 6-month follow-up.
- To assess effects on depression symptoms as measured by the Beck Depression Inventory-II (BDI-II) at baseline, one day, two weeks, one month after each

- experimental session, monthly by mail during the 5 months leading up to the 6-month follow-up assessment.
- To assess effects on perceptions of stress as measured by the Perceived Stress Scale (PSS) at baseline, within 24 hours after each experimental session, one month after each experimental session and monthly by mail leading up to the 6-month follow-up assessment.
 - To assess effects on four aspects of empathy, as measured by the Interpersonal Reactivity Index (IRI) at baseline, within 24 hours after each experimental session, one month after each experimental session, and at the 6-month follow-up assessment.
 - To assess effects on self-esteem as measured by the Rosenberg Self-Esteem Scale (RSES) at baseline, within 24 hours after each experimental session, one month after each experimental session, and at the 6-month follow-up assessment.
 - To assess effects on state and trait anxiety as measured by the State-Trait Anxiety Index (STAI Form Y) at baseline, one day, two weeks, and one month after each experimental session, and monthly by mail leading up to the the 6-month follow-up assessment.

The following objectives will compare effects in specified subjects:

- To conduct a within-subject comparison of Stage 1 LSAS outcomes to Stage 2 open-label LSAS outcomes.
- To conduct a hierarchical regression analysis using condition assignment in Stage 1 and TAS-20 scores and OT, AVP, and CORT at baseline as predictors and LSAS outcomes as dependent variables.

The following objectives will include exploratory analyses intended to inform protocol design:

- To assess the ability of the investigators and subjects to accurately guess condition assignment in Stage 1.
- To assess perceptions about dose and study procedures at baseline and 6-month follow-up using a qualitative interview and feedback questionnaire.
- To determine feasibility of recruiting, testing and treating subjects on the autism spectrum with MDMA-assisted therapy as measured by enrollment rates, dropout rates, and completion of assessments and other study-related procedures.

3.3 Safety Objectives:

The safety of subjects will be assured during and after the experimental sessions by assessing physiological effects, psychological distress, AEs, spontaneously reported reactions and suicidality.

- Vital signs (BP, HR, temp.) will be measured at baseline and every hour during experimental sessions until they return to baseline.
- Participant distress will be measured by the Subjective Units of Distress (SUD) scale at baseline and every hour during experimental sessions until return to baseline.

- Risk of suicide will be measured by the Columbia Suicide Severity Rating Scale (CSSRS) during all in person visits, as well as twice during each experimental session at two hours after drug administration and the end of the experimental session, and on Day 2 and Day 7 after each experimental session.
- SAEs and AEs will be assessed throughout the study and spontaneously reported reactions, defined as expected AEs, will be assessed during each experimental session and for seven days after each experimental session, or until resolution.
- In addition to spontaneously reported reactions, symptoms specific to the study population will be collected at baseline and tracked throughout the study.

4.0 Protocol Design

Twelve subjects meeting eligibility criteria will be enrolled. Throughout the study, the study therapists will maintain communication with the referring physician or therapist and any other health care providers requested by the subject. In consultation with their prescribing physician, any individuals taking psychiatric medications will taper off these medications, allowing for a washout period of at least 5 times the medication and active metabolite half-lives plus one week for stabilization before the experimental session. During the study, benzodiazepines or atypical antipsychotics may be used to alleviate severe distress or panic responses if other interventions are ineffective. Subjects who are in psychotherapy with an outside therapist at the time of enrollment may continue that therapy during the treatment period without increasing the number or type of sessions or changing type of psychotherapy until after the outcome assessment, one month after the second experimental session in Stage 1. After the treatment period, subjects may resume psychotropic medications and may change therapists or psychotherapy type.

Each of the 12 subjects will participate in two experimental MDMA-assisted therapy sessions of seven hours in duration within a brief course of non-drug therapy, including three preparatory sessions at the start of the study and three integrative sessions during the month after each experimental session. During preparatory sessions, subjects will learn what to expect during experimental sessions and complete pre-treatment assessments. The second preparatory session will include a comprehensive tour of the treatment location and introductions to all available research and support personnel who subjects are likely to see during experimental sessions. In-person visits will occur in a private room in an outpatient research facility. All in-person sessions after enrollment may be video recorded for the purposes of evaluating structural elements of therapy for effectiveness and feasibility. Video recordings will be used for research and training purposes during and after the study.

Upon enrollment, the first six subjects (Group 1) will be randomized to receive one dose of either placebo (N=2) or 75 mg MDMA (N=4). In the second experimental session one month later, Group 1 subjects randomized to MDMA will escalate to 100 mg MDMA, unless contraindicated by safety and tolerability concerns. The second six subjects (Group 2) will be randomized to receive one dose of either placebo (N=2) or 100 mg MDMA (N=4). In the second experimental session one month later, Group 2 subjects randomized to MDMA will escalate to 125 mg MDMA, unless contraindicated by safety and tolerability concerns. Subjects randomized to placebo in Group 1 and Group 2 will

receive placebo in both experimental sessions also scheduled one month apart. The blind will be maintained through the six-month follow-up for each individual subject, after which the blind will be broken. Placebo subjects will be offered an open-label extension (Stage 2) with two experimental sessions scheduled one month apart, in addition to three hour-long integrative sessions during the month after each experimental session. Stage 2 subjects will receive 75 mg MDMA in the first experimental session and will escalate to 125mg MDMA in the second experimental session, unless contraindicated by safety and tolerability concerns from other subjects in Stage 1.

During experimental sessions, there will be periods of structured and unstructured interactions. The structured interactions will be selected based on elements of therapeutic interventions that are currently in use in this population for the treatment of social anxiety and to enhance functional skills [7]. The unstructured interactions will include an array of therapeutic activities and approaches that would be appropriate for subjects to engage in during experimental sessions. All subjects will follow the same schedule of structured alternating with unstructured periods but will be able to choose from a selection of activities during each unstructured period. Examples include, but are not limited to, working with art supplies, listening to preselected music, writing in journals, silent introspection, and engaging in rapport-building interactions with researchers.

An overnight stay at a hotel located close to the site will be offered to subjects, accompanied by their support partners, if they live further than 30 miles from the site. Subjects will attend a 1-hour follow-up integrative therapy session on the day after the experimental session. Two additional integrative sessions will be conducted within the month following each experimental session, prior to outcome assessments being conducted one month after each experimental session. During integrative therapy sessions subjects will receive support in integrating their experiences and insights from the experimental session. The second experimental session will be scheduled approximately one month after the first experimental session, after outcome assessments have been completed.

All subjects, even those who have a prior diagnosis, will be clinically evaluated by the PI to determine autistic status. In addition, autistic status will be confirmed with the gold-standard diagnostic measure of autism and diagnosis of co-morbid psychological disorders will be conducted according to DSM-IV criteria at screening. Outcome measures will be assessed prior to treatment, during the treatment period, one month after each experimental session, and during the 6-month follow-up according to the Time and Events table. The sponsor will conduct an ongoing review of videos of therapy sessions, entry criteria, vital signs, and reaction data for completed sessions and any AEs. The sponsor will provide ongoing feedback to the co-therapist teams to ensure subject safety.

For all subjects blood samples will be obtained for biomarker analysis at baseline and during the study according to the Time and Events Table. Biomarker analyses including plasma OT, AVP, and CORT will be explored as surrogate endpoints at baseline, two hours after drug administration during the second experimental session, one month after the second experimental session, and at 6-month follow-up. Blood will be collected during the open-label extension Stage 2 two hours after drug administration during both

experimental sessions and one month after both experimental sessions. Biomarkers will be evaluated for predictive and prognostic power.

4.1 Planned Duration of Study

- Subjects in Stage 1 and follow-up: 8 months
- Subjects in Stage 1, follow-up, and Stage 2: 10 months

These lengths of time do not include screening, which may take up to two months. The total duration of the study will depend on enrollment rates, but is expected to last at least 22 months. Any delay between visits would result in a corresponding extension of study duration.

Table 2. Time & Events Stage 1

Study Phase	Baseline	Baseline	Preparatory Sessions			Experimental Session	Integrative Sessions			Experimental Session	Integrative Sessions			Follow-up	6-Month Follow-up
Visit #	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	(remote)	V14
Visit Timing			Week 1	Week 2	Week 3		1 day later	2 Wks later	2 Wks later	Appr.1 Month after V6	1 day later	2 Wks later	2 Wks later	Monthly By Mail	6 Months after V10
Informed Consent	✓														
Medical/Psychiatric History & Evaluation	✓														
SCID	✓														
General Physical Exam (includes neurological)		✓													
Screening Clinical Lab Tests, EKG		✓													
ADOS-2		✓ ^H													
LSAS		✓ ^{G, H}					✓ ^G	✓ ^G	✓ ^G		✓ ^G	✓ ^G	✓ ^G		✓ ^G
C-SSRS		✓			✓	✓ ^{A, C, D}	✓ ^E	✓	✓	✓ ^{A, C, D}	✓ ^E	✓	✓		✓
Feedback Questionnaire, Qualitative Interview		✓													✓
Study Enrollment if Eligible			✓												
Collect Concomitant Medication	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Start Medication Taper (if applicable)			✓												✓ ^I
Collect Serology Samples (OT, AVP, CORT)		✓								✓			✓		✓
Record to Video			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
General Wellbeing			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Pregnancy Screen (if applicable), Drug Screen		✓				✓				✓					
BDI-II, STAI			✓				✓	✓	✓		✓	✓	✓	✓	✓
PSS			✓				✓				✓		✓	✓	✓
IRI, RSES			✓				✓				✓		✓		✓
TASIT				✓		✓				✓			✓		✓
ERQ, TAS-20					✓								✓		✓
QoL-Q					✓										✓
Administer Drug + Therapy						✓				✓					
Monitoring of BP, Pulse, and Temperature, SUD						✓ ^{A, B, C}				✓ ^{A, B, C}					
Belief of Condition Assignment							✓				✓				
Integrative Therapy Session							✓	✓	✓		✓	✓	✓		
Start 7 Days Phone Contact							✓				✓				
Spont. Reported Reactions & All Adverse Events						✓	✓ ^F	✓		✓	✓ ^F	✓			
Symptoms at Baseline	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Adverse Events Requiring Doctor's Visit			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Adverse Events Causing Withdrawal, SAEs			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Unblinding & Termination															✓ ^J
Approximate Hours for Study Visit	3	1.8	1.5	1.5	1.8	8.0	1.9	1.7	2.1	8.0	1.9	1.7	2.6	0	2.2

A = At the beginning of the session; B = Approximately every sixty minutes; C = As needed; D = Approximately six hours post drug; E = Day 2 and Day 7 phone calls only; F = Reactions collected for seven days post experimental session; G = Independent Rater administered; H = May be recorded to video; I = Stage 2 subjects only; J = Only MDMA subjects will terminate.

Table 3. Time & Events Stage 2

Study Phase	Experimental Session	Integrative Sessions			Experimental Session	Integrative Sessions		
Visit #	V15	V16	V17	V18	V19	V20	V21	V22
Visit Timing		1 day later	2 Wks later	2 Wks later	Appr. 1 Month after V15	1 day later	2 Wks later	2 Wks later
LSAS		✓ G	✓ G	✓ G		✓ G	✓ G	✓ G
C-SSRS	✓ A, C, D	✓ E	✓	✓	✓ A, C, D	✓ E	✓	✓
Feedback Questionnaire, Qualitative Interview								✓
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓
End Medication Taper (if applicable)	✓ ^I							
Collect Serology Samples (OT, AVP, CORT)	✓			✓	✓			✓
Record to Video	✓	✓	✓	✓	✓	✓	✓	✓
General Wellbeing	✓	✓	✓	✓	✓	✓	✓	✓
Drug Screen	✓				✓			
Pregnancy Screen (if applicable)	✓				✓			
BDI-II, STAI		✓	✓	✓		✓	✓	✓
PSS		✓				✓		✓
IRI, RSES		✓				✓		✓
TASIT	✓				✓			✓
ERQ, TAS-20								✓
Administer Drug + Therapy	✓				✓			
Monitoring of BP, Pulse, and Temperature, SUD	✓ A, B, C				✓ A, B, C			
Integrative Therapy Session		✓	✓	✓		✓	✓	✓
Start 7 Days Integrative Phone Contact		✓				✓		
Spont. Reported Reactions & All Adverse Events	✓	✓ ^F	✓		✓	✓ ^F	✓	
Symptoms at Baseline	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events Requiring Doctor's Visit	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events Causing Withdrawal	✓	✓	✓	✓	✓	✓	✓	✓
SAEs	✓	✓	✓	✓	✓	✓	✓	✓
Termination								✓
Approximate Hours for Study Visit	8.0	1.9	1.7	2.1	8.0	1.9	1.7	2.7

A = At the beginning of the session; B = Approximately every sixty minutes; C = As needed; D = Approximately six hours post MDMA; E = Day 2 and Day 7 phone calls only; F = Reactions collected for seven days post experimental session; G = Independent Rater administered; H = May be recorded to video; I = At least 5 half-lives and 1 week before the experimental session.

4.2 Recruitment and Subject Population

Subjects may be male or female, aged 21 or older, with a confirmed diagnosis of autism and two years of college-level education or comparable vocational training. Verbal and written proficiency in English will be required. Subjects communicating with text-to-speech technology will also be permitted. Therefore, the researchers anticipate that all subjects will have an AS diagnosis or a diagnosis of Autistic Disorder, as defined in the DSM-IV, coupled with strong verbal proficiency. Subjects must meet all protocol inclusion criteria and no exclusion criteria at baseline. Subjects must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Subjects must be MDMA-naïve. Subjects will be asked to confirm that they will not take MDMA outside of the context of study participation during the study. Subjects will be recruited through printed advertisements, internet advertisements and discussion forums, referrals from other psychiatrists, psychotherapists or physicians, and through word-of-mouth.

4.2.1 Inclusion Criteria

Individuals eligible to be enrolled into this protocol are subjects who:

1. Meet diagnostic criteria for Autism Spectrum Disorders;
2. Have an LSAS score of 60 or higher, indicating moderate social anxiety symptoms;
3. Are MDMA-naïve;
4. Have completed two years of college-level education or comparable vocational training;
5. Are at least 21 years old;
6. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the investigators to communicate directly with their therapist;
7. May not change therapists, increase the frequency of therapy or commence any new type of therapy until one month after the second experimental session unless absolutely necessary;
8. Are willing to refrain from taking any psychiatric medications for at least 5 half-lives of the drug and active metabolites plus one week for stabilization prior to the experimental session. 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 at least 5 half-lives and one week before the experimental session and do not restart for 10 days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician;
9. Agree to refrain from taking, for one week preceding each experimental session:
 - a. Any herbal supplement (except with prior approval of the research team).
 - b. Any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).

- c. Any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team); Note: Must have approval of prescribing physician.
10. Agree to refrain from eating or drinking except alcohol-free liquids after midnight the evening before each experimental sessions;
11. Agree to refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session;
12. Agree to refrain from using caffeine or nicotine for 2 hours before and 6 hours after ingesting the drug, or until the PI deems it safe to do so;
13. Are willing to commit to preparatory sessions, medication management, experimental sessions, follow-up sessions and to complete evaluation instruments;
14. Agree not to use MDMA outside of the study for duration of study participation, including the follow-up period and during Stage 2;
15. Are willing to be driven home after the experimental sessions, either by a driver or support person arranged by the subject or by the site personnel or taxi;
16. Are willing to be contacted on a daily basis for a week after each experimental session;
17. Are willing to provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by investigators, accompany the subject during some or all of the study visits, and complete study measures;
18. Agree to inform the investigators within 48 hours of any planned medical interventions;
19. Are willing to refrain from participating in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period;
20. If female subjects of childbearing potential, must have negative pregnancy test results, be willing to have pregnancy tests and must agree to use an effective form of birth control during the treatment period;
21. Are proficient in speaking and reading English. Subjects communicating with text-to-speech technology will also be permitted to enroll.
22. Willing to give blood samples.

4.2.2 Exclusion Criteria

Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control;
2. Have a history of, a family history in first-degree relatives, or current primary psychotic disorder or bipolar affective disorder type 1.
3. Have current confirmed diagnosis of borderline personality disorder;
4. Are diagnosed with dissociative identity disorder or an eating disorder with active purging;
5. Have evidence or history of significant (controlled or uncontrolled) hematological, endocrine, cerebrovascular, cardiac, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including epilepsy or other seizure disorder, valvular heart disease or any

- other medical disorder judged by the investigator to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);
6. Diagnosed with hypertension, using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions);
 7. Have evidence or history of liver disease;
 8. Have Diabetes Type I or II or other significant kidney disease;
 9. Have history of hyponatremia or hyperthermia;
 10. Are HIV positive;
 11. Weigh less than 48 kg;
 12. Would present a serious suicide risk, as determined through psychiatric interview, responses to CSSRS and through clinical judgment of the investigator, or who are likely to require hospitalization during the course of the study;
 13. Have used “Ecstasy” (material represented as containing MDMA) prior to enrollment;
 14. Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
 15. Meet DSM-IV criteria for substance abuse or dependence for any substance in the past 60 days save caffeine or nicotine;
 16. Have glaucoma;
 17. Have any current problem, which in the opinion of the investigator or medical monitor, might interfere with participation in the study;
 18. Are not able to give adequate informed consent.

5.0 Methods

5.1 Measures

The following diagnostic, outcome, safety, and process measures will be used in the study. All therapy sessions, including experimental sessions, may be recorded to audio and video, with all recordings preserved for research and training purposes.

5.1.1 Diagnostic Measures

The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2, Module 4) is a semi-structured social interaction to assess autism and autism-spectrum disorders in adults [127]. It takes 40 to 60 minutes to administer ADOS-2 Module 4. The assessment includes a construction task, semi-structured conversation with the assessor, emotional and creative responses to cartoons and pictures, describing an unusual event and telling a story. The assessment is scored by an algorithm and assessment is made on observation of participant nonverbal and verbal behavior, restricted or stereotyped behavior and degree of empathy. Most factors of the original Module 4 were reliable, with kappa greater than 0.60 and inter-rater reliability was high, from 0.83 for “repetitive /restrictive” to 0.93 for “social” [127]. Subsequent specific examination of the measure found that Module 4 could reliably detect ASD in adults, and that it could differentiate between autism spectrum disorders, psychopathy and typical development [128]. The activities

used in the ADOS-2 are identical to those used in the original version of the ADOS, but instructions have been revised. A certified assessor will administer the ADOS-2 at screening to confirm autistic status.

The Structured Clinical Interview for Diagnoses Axis 1 Research Version (SCID-I-RV) is a structured interview used to assess and diagnose psychiatric conditions listed in the DSM-IV [129]. The interview is designed for use in adults and is suitable for use with psychiatric and non-psychiatric populations. The SCID consists of ten modules. Modules are based upon the symptoms listed for diagnoses as set out in the DSM-IV. The SCID can take from 30 to 90 minutes to perform. The SCID will be used to assess for psychological disorders. The PI will administer the SCID once at screening.

5.1.2 Outcome Measures

The primary outcome measure for the study will be the clinician-administered LSAS [130]. The LSAS is a 24-item, semi-structured interview on the severity of Social Anxiety Disorder, which has been widely used in clinical studies, including research on social anxiety in autistic adults [16]. The LSAS separately assesses fear (0 to 3 = none, mild, moderate, severe) and avoidance (0 to 3 = never, occasionally, often, usually) of 24 social situations, providing an overall social anxiety severity rating and subscale scores for performance fear, performance avoidance, social fear, and social avoidance. The overall scores are interpreted as: 55-65 moderate, 65-80 marked, 80-95 severe, and greater than 95 very severe social anxiety. The LSAS has been shown to have good internal consistency (score inter-correlations ranging from 0.81 to 0.96), reliability, convergent validity with other measures of anxiety, and sensitivity to treatment response. The LSAS was also demonstrated to be sensitive to the effects of pharmacological treatments of social phobia in comparison to placebo and to have convergent validity [15]. A qualified blinded IR, who will not be present during experimental sessions, will complete the LSAS assessment. Subjects will be instructed not to inform the IR of any beliefs they or others have concerning their condition assignment during the assessment.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [131, 132], that will serve as a measure of depression according to DSM-IV criteria [133]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability, and is not overly sensitive to daily variations in mood. It takes five to ten minutes to complete [133]. 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. The BDI-II will be completed according to the Time and Events table.

The PSS is a 10-item self-report measure that is widely used in research to assess stress in persisting conditions and takes about 1 – 2 minutes to complete. The PSS includes six negative items that are intended to assess lack of control and negative affective reactions and four positive items that measure the degree of ability to cope with existing stressors. Individuals indicate how often they felt or thought a certain way during the last month (0 = *never*, 4 = *very often*). The PSS was correlated with depressive symptomatology and

social anxiety in TD populations [134]. The PSS will be completed according to the Time and Events table.

The IRI assesses four aspects of empathy: social functioning, self-esteem, emotionality, and sensitivity to others [135-137]. Empathy is not a discrete emotion. More accurately, empathy is a set of constructs. Therefore, the IRI accounts for the fact that each construct concerns an individual's responses to the observed experiences of other people, yet each construct is distinctive from the others. The self-report questionnaire includes 28 items that are rated on a 5-point, Likert-type scale. The four 7-item subscales include two measures of cognitive empathy and two measures of affective empathy. The internal reliabilities for the four scales range from .71 to .77, and test-retest reliabilities range from .62 to .71 [135]. One study [138] administered the IRI to 21 adults with Asperger's Syndrome and to 21 matched controls. As anticipated, the Asperger's group scored lower on the measures of cognitive empathy, but they scored similarly to controls on the Empathic Concern scale, and scored higher than controls on the Personal Distress scale. In the absence of an abundance of robust validity testing of empathy assessments with adult autistic populations, the IRI provides a good option for a multidimensional assessment of empathy factors. The IRI will be completed according to the Time and Events table.

The RSES is widely used in clinical research to assess two facets of self-esteem: self-competence (instrumental value) and self liking (intrinsic value) [139]. The RSES is a simple, 10-item scale with five questions for each facet, and it can be completed in 1 – 2 minutes. In anecdotal accounts, autistic adults have reported increased self-esteem and self-competence following MDMA use, attributes that influence anxiety, affective states, and interpersonal style. The RSES satisfies tests of item convergent and discriminant validity, internal consistency and reliability, and floor and ceiling effects [140]. Cronbach's α has been shown to be substantial ($M = 0.81$) across cultural contexts [140]. The RSES will be completed according to the Time and Events table.

The STAI Form Y is a widely used self-report instrument for assessing anxiety in adults that includes separate measures of state and trait anxiety [141, 142]. The STAI evaluates the essential qualities of feelings of apprehension, tension, nervousness, and worry. The STAI differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The STAI state scale asks for feelings at the moment of filling out the questionnaire, and the STAI trait scale asks subjects to indicate how they generally view themselves. The proposed study will use the 20-item trait scale with questions about how respondents generally feel. Response options are based on a 4-point Likert-type scale (1=almost never, 2=sometimes, 3=often, 4=almost always). The STAI will be completed according to the Time and Events table.

The TASIT is an audio-visual test of social perception and emotional expression comprehension presented in video vignettes of interpersonal interactions [143]. Standardized response probes assess understanding of emotional expression. The 3-part test includes The Emotion Evaluation Test, the Social Inference-Minimal, and the Social Inference-Enriched test. Each part takes approximately 10 – 15 minutes to complete. The

TASIT has demonstrated adequate test-retest reliability (range = 0.74 for “Emotional Evaluation” to 0.88 for “Social Inference - Minimal”) and high internal consistency $\alpha = 0.71$ [144, 145]. The TASIT will be completed according to the Time and Events table.

The ERQ is a brief measure of self-reported emotion-regulation. It consists of ten items that is intended to assess means of coping with emotions via changing them, as through reappraisal, or suppressing them [146]. Respondents rate indicate the extent of their agreement or disagreement with each item by selecting a point on a 7-point Likert scale, where 1= strongly disagree and 7 = strongly agree. The ERQ should take four to six minutes to complete. Specific items are summed to produce two separate scales, Reappraisal and Suppression. The measure is reliable, with Reappraisal obtaining a Cronbach’s alpha of 0.79 and Suppression an alpha of 0.73, and test-retest reliability of 0.69 [146], and scores on the ERQ are correlated with other measures of degree of emotional expressivity. Studies in people with Asperger’s or ASD suggest difficulties with emotion regulation that include less use of reappraisal and greater numbers of negative versus positive emotions [147]. The ERQ will be completed according to the Time and Events table.

The TAS-20 is a 20-item measure of self-reported difficulties with recognizing and verbalizing emotions[148, 149]. Responses are made on a 5-point Likert scale where 1 = strongly disagree and 5 = strongly agree. Estimated time of measurement is 5 to 10 minutes. The scale is comprised of three subscales; Difficulty Describing Feelings, Difficulty Identifying Feelings and Externally-Oriented Thinking, with all scales summed to create a total score reflecting presence and degree of alexithymia. The TAS-20 can be used diagnostically with a score of 61 or higher indicative of alexithymia. The TAS-20 is reliable and has good test-retest reliability (Cronbach’s alpha = 0.81, test-retest of 0.77). It is an established measure of alexithymia. There is some suggestion of an overlap between this condition and Asperger’s syndrome, with samples of people with Asperger’s syndrome showing greater rates of alexithymia than age and gender-matched controls [147, 150]. The TAS-20 will be completed according to the Time and Events table.

The QoL-Q is a 40-item measure of quality of life. It is administered as an interview and assesses eight domains [151]. The QoL-Q assesses the following domains; self-determination, (autonomy and decision-making), social inclusion (acceptance by others within the community, supports), material well-being (financial security and socioeconomic status), personal development (education, skills and competence), emotional well-being (spirituality, happiness, sense of safety) interpersonal relations (intimacy, affection, friendship), rights (voting, privacy, legal rights and protections) and physical well-being (health, nutrition, mobility). It is estimated to take between a half hour to an hour to complete the QoL-Q. It can be used in diverse populations, including autistics and other developmentally disabled people [152, 153]. The measure has excellent internal reliability (alpha = 0.90) and strong test-retest reliability (alpha = 0.87). The QoL-Q will be completed according to the Time and Events table.

5.1.3 Safety Measures

Safety measures will be applied, as described below, to minimize risks associated with drug-assisted therapy sessions. The co-therapist or PI 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 integrative telephone calls for seven days. Results of this scale are intended to assist therapists in maintaining subject safety throughout the treatment period of the study.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [154]. It consists of a Baseline form that 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 a face-to-face interview or over the telephone. Suicidality will be assessed at Baseline, once during any face-to-face visit, during the second and seventh days of integrative telephone contact, and twice during each experimental session. Subjects who are discontinuing medication to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS data will be collected on Case Report Forms (CRFs) for all administrations except for the second integrative session, unless the therapists observe an increase in suicidality. C-SSRS data from the second integrative session after each experimental session will be kept with the subject's Source Record.

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 and pulse monitor. Blood pressure and pulse will be measured at the outset of the experimental session, once approximately every hour, or as needed. More frequent measures will be taken if there are symptoms, such as chest pain, shortness of breath, or neurological symptoms that may be indicative of hypertension. The therapists will measure subject body temperature approximately every 60 to 90 minutes. The timing of these measurements will be adjusted so that they do not interfere with the therapeutic process.

All AEs and spontaneously reported reactions will be collected, as described in Section 8.5. 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.

As an additional safety and support measure, all subjects will be required to designate a family member, close friend, or significant other who knows them well to provide ongoing support for the duration of their active participation in the study. Precedence for the importance of post-session support has been established in earlier similar studies [155]. Responsibilities of the designated support person include:

- Providing reliable transportation, as required, to and from pre- and post-session appointments and participating in study visits, as appropriate.
- Driving the subject home or to another secure location following sessions. No participant will be allowed to drive themselves home after experimental sessions.
- Remaining available to attend to basic comfort needs and to talk with subject in person, by phone, or online for 24 hours post-session.

5.1.4 Process Measures

All therapy sessions, including experimental sessions, may be recorded to audio and video, with all recordings preserved for research and training purposes.

Belief of condition assignment and certainty will be collected from each therapist responsible for treating the subject and the subject at the integrative session on the day after each blinded experimental session in Stage 1. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the blinding of MDMA-assisted therapy.

The Feedback Questionnaire has been developed internally by the sponsor to assess perceived benefits and harms of MDMA-assisted therapy, feedback on therapeutic methods, and prior treatments received. The questionnaire will be completed as a self-report measure and then reviewed with the subject in order to ask follow-on questions during a semi-structured qualitative interview, which may be video recorded. This questionnaire will be completed at baseline and at the 6-month follow-up visit.

5.2 Study Procedures and Visit Descriptions

5.2.1 Prescreening and Screening

The therapist team for this study will consist of the PI, Charles Grob, M.D., and co-investigator Alicia Danforth, Ph.D. Candidate, and all study visits will be completed at Harbor-UCLA Medical Center. Prospective subjects will be prescreened by telephone or email 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. 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 and Support Partner. Written informed consent must be obtained from the subject 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. Collect perceptions about the study using the Feedback Questionnaire.
- e. Administer C-SSRS to assess suicide risk.
- f. Administer the SCID-I-RV to assess co-morbid psychological disorders.
- g. Administer ADOS-2, Module 4 to confirm autistic status.
- h. A blinded IR will administer the LSAS.
- i. Obtain medical and psychological history by interview.
- j. Collect symptoms at baseline specific to the study population.
- k. Collect information on pre-study and current medications.
- l. 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)
 - Urine-dip pregnancy test on females with childbearing potential
 - Urinary drug test
- k. Conduct Electrocardiogram (ECG/EKG)
- l. Collect information on phase of menstrual cycle for female subjects.
- m. Collect samples for clinical lab assessments, including:
 - Blood for screening clinical lab assessments (see Section 10.1)
 - Blood for baseline OT,AVP, and CORT analysis (see Section 10.2)

Results of HIV serology will be kept confidential and appropriate referral for counseling may be necessary in accordance with state law. The clinical laboratory values will be used to establish eligibility and will be kept with the subject's Source Record. 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. 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.

5.2.2 Preparatory Sessions and Baseline Measures

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 3 is scheduled but the final confirmation will occur at Visit 3. If all inclusion criteria and no exclusion criteria are met, eligibility will be confirmed with the subject.

- Complete a final review of inclusion/exclusion criteria.
- Assess general wellbeing.
- Confirm eligibility and willingness to participate in study.
- Enroll subject and issue subject number.
- Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications, as described in Section 8.5 and Section 9.0.
- Assess status of symptoms at baseline specific to the study population.
- 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 given its half-life, with the first experimental session scheduled to occur after complete washout.

The subjects will undergo three preparatory sessions lasting approximately sixty minutes each with their therapist team, prior to their first experimental session. The first preparatory session will take place at Visit 1 after enrollment confirmation. Baseline measures will be spread out among preparatory sessions in order to reduce participant fatigue from completion of measures.

The therapists will work with the subject to prepare for MDMA-assisted therapy. The therapists and subject will seek to form a strong working relationship with each other as the therapists help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe set and setting for confronting emotions and are intended to develop therapeutic alliance.

During preparatory sessions:

- a. Therapists may record all sessions to audio and video. Subjects may access video recordings from these sessions upon request via a secure and password protected website.
- b. Collect AEs and medications, as described in Section 8.5 and Section 9.0.
- c. Assess status of symptoms at baseline specific to the study population.
- d. 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.
- e. The subject and therapists will discuss goals for the experimental session and will review what will happen during the experimental session.
- f. During one of the preparatory sessions, the therapists will introduce the subject to the staff at the outpatient research center who they will be most likely to encounter before, during, or after treatment sessions.
- g. The Support Partner will meet with the therapists prior to the first experimental session to review and confirm their role and responsibilities and sign an ICF addendum. There must be mutual agreement between the subject and therapists concerning the presence of the Support Partner.
- 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. At the end of the first preparatory session, subjects will complete:
 - a. BDI-II
 - b. STAI
 - c. PSS
 - d. IRI
 - e. RSES
- k. At the end of the second preparatory session, subjects will complete the TASIT.
- l. The second preparatory session will include a comprehensive tour of the treatment location and introductions to all available research and support personnel who subjects are likely to see during experimental sessions.
- m. At the end of the third preparatory session, subjects will complete:
 - a. ERQ
 - b. TAS-20
 - c. QoL-Q
- n. 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:
 - Refrain from eating after 24:00 (midnight) the evening before the experimental session.
 - 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 24 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.

5.2.3 Experimental sessions

Subjects will receive two blinded experimental sessions of therapy assisted by MDMA or placebo, scheduled one month apart after integrative sessions are complete. Procedures for drug-assisted therapy will remain the same across all sessions. During experimental sessions, there will be periods of structured and unstructured interactions. The structured interactions will be selected based on elements of therapeutic interventions that are currently in use in this population for the treatment of social anxiety. Structured interactions during experimental sessions are intended to develop the therapeutic relationship between subjects and therapists and to enhance skills of social perception through administration of the TASIT. The unstructured interactions will include an array of therapeutic activities and approaches that would be appropriate for subjects to engage in during experimental sessions. All subjects will follow the same schedule of structured alternating with unstructured periods but will be able to choose from a selection of activities during each unstructured period. Examples include, but are not limited to, working with art supplies, listening to preselected music, writing in journals, silent introspection, and engaging in rapport-building interactions with therapists. 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. 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 interpersonal contact. Therapists will use music to support the experience without being intrusive.

Table 4. Schedule of Procedures for Experimental Sessions

Approximate Time	Procedure or Action
9:00	Urine drug screen and pregnancy test. Subject acclimated to environment, C-SSRS
9:45	Baseline Blood Pressure (BP), Pulse, SUD
10:00	MDMA Administration , begin recording to audio and video
11:00	BP, Pulse, SUD, BT
12:00	BP, Pulse, BT, SUD, During 2 nd exp. session only: Blood draw
12:15	Start TASIT (EET, SM-I, SM-E)
13:00	BP, Pulse, BT, SUD
14:00	BP, Pulse, BT, SUD
15:00	BP, Pulse, BT, SUD

16:00	BP, Pulse, BT, SUD, C-SSRS, General Wellbeing
17:00	BP, Pulse, BT, SUD, End of session

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 one to one and a half hours prior to drug administration.
- c. Confirm continuing eligibility by reviewing inclusion/exclusion criteria.
- d. Collect information on phase of menstrual cycle for female subjects.
- e. 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.
- f. If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.
- g. If the subject continues to meet criteria and the subject reports that they followed appropriate rules and restrictions, the session will proceed.
- h. Review procedures for the experimental session with the subject.
- i. Record the entire session to video and audio. Subjects may review video recordings of their experimental sessions upon request.
- j. The session will last for approximately seven hours or longer.
- k. The therapists will administer the C-SSRS prior to drug administration.
- l. Before drug administration, discuss and review the subject's goals, intentions, and concerns and some of the commonly experienced effects of MDMA.
- m. Instruct the subject not to use caffeine or nicotine two hours before or six hours after the dose of drug.
- n. Subject body temperature will be measured at baseline prior to administration of the initial dose and approximately every hour after that. The therapists may make more frequent measurements if body temperature exceeds more than 1°C above baseline.
- o. Subjects will complete the SUD at baseline prior to administration of the initial dose. 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 therapy process where a natural break occurs. If necessary, the therapists can make a greater number of measurements, as their clinical judgment dictates.
- p. Measure BP, pulse, and BT at baseline prior to drug administration.

During:

- q. At approximately 10:00 in the morning, subjects will receive the initial dose of drug along with a glass of water.
- r. 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.
- s. Measure BP, pulse, and BT once every hour throughout the experimental session. More frequent measures will be taken if clinical signs and symptoms of hypertension are observed. If BP values are sustained at 180 systolic and/or 110 diastolic, the PI

will make a decision about whether to conduct additional measurements or to provide treatment. Measurements may be repeated until they have been decreasing for 15 minutes or have stabilized at a level judged by the PI to be safe.

- t. 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.
- u. Approximately two hours after drug administration during the second experimental session, prepare the subject for the blood draw for biomarker analysis. Bring in the phlebotomy technician when the subject is emotionally ready for the blood draw.
- v. Initiate the TASIT. The TASIT administration may be spread out between hours two and three to fit around the therapeutic process.
- w. Record any spontaneously reported reactions during the session.
- x. Provide water and electrolyte containing fluids throughout the session but not to exceed 3 L overall.
- y. Provide food during the latter part of the session.
- z. 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. The C-SSRS is required at least once during the session. It is preferable to administer it towards the end of the session, about six hours after the initial dose.
- aa. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory, and emotionally stable.

Post-drug:

- bb. The therapists will depart from the site when they have concluded that the subject is emotionally and medically stable. Therapists shall remain available to subjects during the experimental session and for one week after via 24 hour cellular phone for integration, as needed.
- cc. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
- dd. Assess status of symptoms at baseline specific to the study population.
- ee. After the experimental sessions, an overnight stay at a hotel located close to the site will be offered to subjects, accompanied by their support partners, if they live further than 30 miles from the site.
- ff. During the night of the experimental session, subjects will be given the following measures to complete prior to the integrative session on the next day:
 - a. RSES
 - b. IRI
 - c. PSS

5.2.4 Integrative Sessions 24 Hours after Experimental Session

The subject and support partner (if applicable) will receive pagers (or similar device) that will allow them to contact the therapists during the period after the first in-person office visit following treatment sessions in the case of an emergency or request for additional

support. Subjects will be encouraged to use much of the time during the 24-hours post-session for rest and for a period of reflection and integration in a quiet atmosphere. On the morning after each experimental session, the therapists will meet with the subject for a 60-minute integrative therapy session.

Activities during 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 sessions:

- a. The integrative session may be recorded to audio and video. Subjects may receive access to copies of the recordings on a secure, password-protected website upon request.
- b. The therapists will administer the C-SSRS during each integrative session.
- c. 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 accessible any time the subject needs support outside the scheduled integration sessions.
- f. Assess the subject's mental health and the presence of any remaining reactions during the integrative session.
- g. Integrative 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. At the end of the session, subjects will complete:
 - a. BDI-II
 - b. STAI
- i. The IR will administer the LSAS.
- j. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
- k. Assess status of symptoms at baseline specific to the study population.
- l. After the integrative 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.

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

5.2.5 Daily Contact for Seven Days after an Experimental Session

During daily contact:

- a. Starting on the day of the integrative session following each experimental session, one of the therapists will contact the subject via telephone or email on a daily basis for seven days. The goal of daily contact is assessment of changes in general wellbeing, safety of the subjects, and offering support for subjects.
- b. The integrative phone contact will be for a brief check-in lasting five to fifteen minutes or as long as necessary to address any concerns a subject has and to assess subject's wellbeing. Additional telephone contact can be initiated at the request of the therapists or subject.
- c. On the second and seventh day of contact after the experimental session, one of the therapists will administer the C-SSRS.
- d. General wellbeing will be assessed at each phone call.
- e. Assess status of symptoms at baseline specific to the study population.
- f. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.

5.2.6 Biweekly Integrative Sessions

In addition to the integrative session the morning after each experimental session, the subject will have two additional integrative sessions with the therapists lasting 60 minutes with the therapists between each experimental session scheduled at two-week intervals following the last integrative session. The therapists may conduct more or longer integrative sessions if they and the subject deem it necessary.

Activities 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.

During integrative sessions:

- a. Record each integrative session to audio and video. Subjects may receive access to copies of the recordings on a secure, password-protected website 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. The subject and therapists will continue to work on supporting the subject as she or he considers his or her experiences during experimental sessions.
- e. 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 session, through continuing contact, or at the next regularly scheduled integrative session. The subject may also initiate contact with the therapists at any time throughout the study.
- f. At the second integrative session after the second experimental session, blood will be drawn for biomarker analysis.
 - g. At the second integrative session after the second experimental session, collect information on phase of menstrual cycle for female subjects.
 - h. At the beginning or end of each integrative session, subjects will complete:
 - a. BDI-II
 - b. STAI
 - i. At the beginning or end of each integrative session, the IR will administer the LSAS.
 - j. At the beginning or end of the third integrative session, subjects will also complete:
 - a. ERQ
 - b. TAS-20
 - c. TASIT
 - k. Spontaneously reported reactions, AEs, and concomitant medications will be collected, as described in Section 8.5 and Section 9.0.
 - l. Assess status of symptoms at baseline specific to the study population.
 - m. Remind the subject that the last integrative session in Stage 1 that this will be the last in-person visit prior to the 6-month Follow-up visit, and that some measures will be collected monthly by mail.
 - n. Review how to use the Memory Aid Card with the subject. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the 6-month follow-up visit. Memory Aids will not be collected.

5.2.7 6-Month Follow-up

Subjects who have withdrawn from treatment but have continued for follow-up will also complete these assessments whenever possible. During the follow-up period:

- a. Subjects may return to taking psychiatric medications or change frequency or method of psychotherapy received from outside therapists if necessary.
- b. The following self-report measures will be completed by subjects and collected monthly at two, three, four, and five months after the second experimental session by mail:
 - a. BDI-II
 - b. STAI
 - c. PSS
- c. At the 6-month follow-up, an in-person visit will be conducted.
- d. The IR will administer the LSAS.
- e. Collect information on phase of menstrual cycle for female subjects.
- f. Blood will be drawn for biomarker analysis.
- g. Subjects will complete self-report outcome assessments, including:

- a. ERQ
- b. TAS-20
- c. TASIT
- d. QoL-Q
- e. RSES
- f. IRI
- g. BDI-II
- h. STAI
- i. PSS
- j. Feedback Questionnaire
- h. Review specified AEs and medications as described in Section 8.5 and Section 9.0. Subjects should bring the Memory Aid Cards to this visit, to be used as aids in recollection. These cards will not be collected.
- i. Assess status of symptoms at baseline specific to the study population.
- j. One of the therapists will assess suicidality with the C-SSRS.
- k. General wellbeing will be assessed.
- l. The therapists will review the responses to the Feedback Questionnaire assessing effects of the study with the subject. During the qualitative interview, additional follow-on questions may be asked to elucidate self-reported responses on the questionnaire.
- m. After all assessments are complete, the therapists will break the blind for the individual subject.
- n. Subjects who were randomized to the MDMA group will complete the termination visit at this time.
- o. Subjects who were randomized to the placebo group will be offered participation in Stage 2 with open-label MDMA.

5.2.8 Open-Label Stage 2

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, but with 75 mg MDMA during the first experimental session and will escalate to 125mg MDMA during the second experimental session, unless contraindicated.
- c. Subjects will have the same sequence of experimental sessions and integrative sessions as subjects receiving MDMA in Stage 1 in an open-label context. Visits will be scheduled consecutively according to the Time and Events Table.
- d. The same outcome measures completed by subjects receiving full dose MDMA in Stage 1 will be administered during Stage 2.
- e. The same safety measures as those in Stage 1 will be administered during Stage 2.
- f. Biomarker samples will be collected 2 hours after drug administration during both experimental sessions and one month after both experimental sessions during Stage 2.
- g. Stage 2 subjects will not complete an additional 6-month follow-up.

- h. Stage 2 subjects will complete the termination visit at the end of the final integrative session.

5.3 Randomization and Subject Numbering

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "S001". Subjects who meet all inclusion criteria and no exclusion criteria will be enrolled into the study and will be assigned a four-digit subject number. The first two digits will be "A1" and will identify the protocol number. The next two digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be A101, the second will be A102, etc.

In total, 12 subjects will be enrolled in the study. Stage 1 will be blinded and randomized and there will be an 8:4 ratio between subjects in the MDMA and placebo conditions. An unblinded Randomization Monitor will generate the randomization list. Subjects will be assigned subject numbers and this number will be used to ensure that confidentiality and HIPAA compliance is maintained throughout the study. Upon enrolling a subject, the PI will be provided with an enrollment code for that subject. Container numbers will be pre-printed on the container labels corresponding to doses for individual experimental sessions. Randomization will be performed at least 24 hours before the experimental session for each subject. The therapists will utilize a web-based randomization program to obtain the container assignment for each experimental session. Blinded personnel will conduct all study evaluations in the randomized portion of the study until the blind is broken for each subject per protocol via the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The PI will be provided with sealed emergency unblinding envelopes corresponding to each enrollment code. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study.

5.4 Removal of Subjects from the Study

Subjects can withdraw consent at any time without prejudice. The therapists can withdraw a subject if, in their 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 or for the scientific integrity of the study. If the therapists withdraw a subject from the study, the therapists will explain the reason for withdrawing the subject. The reason for early termination will be recorded in the subject's Source Records and CRF.

If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy, or requiring use of 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

follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI, Data Safety Monitor, Medical Monitor, and/or sponsor.

Subjects discontinuing treatment before the first experimental session will be replaced until blinded data has been collected from 12 subjects. Subjects who discontinue participation after the first experimental session will not be replaced, and an intent-to-treat analysis will be conducted with all available data. Subjects discontinuing treatment prior to the second experimental session will be asked to complete integrative therapy sessions, outcome assessments prior to discontinuation and complete the six-month follow-up assessment if possible. The blind will not be broken for these subjects until after the six-month follow-up assessments have been completed.

5.5 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 retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and state regulations.

6.0 Investigational Product

6.1 Description of Active Compounds

The investigational product to be used in this protocol is MDMA. This ring-substituted phenethylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [156-158]. MDMA primarily releases serotonin but also releases adrenaline and dopamine. It is also an indirect serotonin receptor agonist. See Section 2.2.3 and the IB for more information and references on the investigational product.

6.2 Preparation and Administration

6.2.1 Doses

Doses of MDMA to be used in this study will be 75 mg, 100 mg or 125 mg MDMA. Upon enrollment, the first six subjects (Group 1) will be randomized to receive one dose of either placebo (N=2) or 75 mg MDMA (N=4). In the second experimental session one month later, Group 1 subjects randomized to MDMA will escalate to 100 mg MDMA, unless contraindicated by safety and tolerability concerns. The second six subjects (Group 2) will be randomized to receive one dose of either placebo (N=2) or 100 mg MDMA (N=4). In the second experimental session one month later, Group 2 subjects randomized to MDMA will escalate to 125 mg MDMA, unless contraindicated by safety

and tolerability concerns. Subjects randomized to placebo in Group 1 and Group 2 will receive placebo in both experimental sessions also scheduled one month apart. The blind will be maintained through the six-month follow-up for each individual subject, after which the blind will be broken. Placebo subjects will be offered an open-label extension (Stage 2) with two experimental sessions scheduled one month apart, in addition to three hour-long integrative sessions during the month after each experimental session. Stage 2 subjects will receive 75 mg MDMA in the first experimental session and will escalate to 125mg MDMA in the second experimental session, unless contraindicated by safety and tolerability concerns from other subjects in Stage 1.

6.2.2 Compounding and Encapsulation

All drug shipments will be conducted in compliance with national and international controlled substance laws. Schedule 1 licenses will be obtained from the U.S. Drug Enforcement Agency (DEA) whenever applicable. MDMA in bulk will be sent from the Schedule 1 storage facility to the Schedule 1 license holder for the study. The Schedule 1 license holder and unblinded Randomization Monitor will oversee compounding by a pharmacist in a manner that will maintain the blind for the Schedule 1 license holder. The pharmacist will provide bulk lactose for compounding MDMA capsules. The pharmacist will compound the MDMA in bulk and then weigh the MDMA into doses of 75 mg, 100 mg, and 125mg (calculated as the weight of the hydrochloride salt) and place it in gelatin capsules with lactose. Placebo capsules will contain only lactose. All capsules will be compounded so that they weigh the same amount, but contain varying amounts of MDMA and lactose.

6.2.3 Labeling

During compounding, bulk MDMA will be stored in a holding box prior to encapsulation. Each holding box will be labeled with the protocol code, drug name, lot number, sponsor name, and a statement that the drug is for clinical trial use only (see box label).

The doses of MDMA for a single subject to complete one experimental session will be stored in a single container labeled with the protocol code, drug name, lot number, unique container number, sponsor name, and a statement that the drug is for clinical trial use only (see container label). Each dose of MDMA for each experimental session will be labeled and stored individually within the container (see container labels for each session and dose). Labels will be provided by the sponsor and applied by the pharmacist. During packaging and labeling, the randomization list will be hidden from the PI and therapists to assure blinding. All drug labels will comply with federal and state regulations.

Figure 1. Holding Box Label

Box Label
MAPS Study #: MAA-1
Investigational Product: MDMA
Dose: 75 mg, 100 mg OR 125 mg
Lot #: XXXXX
Administer as per Protocol
Caution: Limited by Law to Investigational Use Only

Figure 2. Container Labels

Container Label	Container Label
MAPS Study #: MAA-1	MAPS Study #: MAA-1
Container #: XXX	Container #: XXX
Subject #: _____	Subject #: _____
Stage 1: Blinded	Stage 2: 75mg OR 125mg
Administer as per Protocol	Administer as per Protocol
Caution: Limited by Law to Investigational Use Only	Caution: Limited by Law to Investigational Use Only

Each dose will consist of the specified amount of racemic MDMA mixed with lactose, to prevent the therapists from distinguishing doses through weight or appearance of the capsules. Each dose of investigational product will be administered along with a glass of water or electrolyte-containing fluid. Investigational product will be administered in the same manner during each experimental session.

6.3 Drug Accountability

Forms will be provided to track drug accountability and administration throughout the study. Drug accountability will be reviewed during routine monitoring visits.

6.4 Drug Storage and Handling

MDMA is a Schedule 1 compound and will be stored and handled in compliance with all relevant federal and state regulations. In accordance with these requirements, the Schedule 1 license holder will be responsible for storing, dispensing, and administering the investigational product. It will be stored in a secure safe, in accordance with international, federal and state regulations.

Investigational product will only be removed from the safe for one experimental session at a time prior to the session and the investigational product will not leave the control of the Schedule 1 license holder until consumed by the designated subject. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with all relevant regulations.

6.5 Stability

Complete details on the chemistry, manufacturing, and control of the MDMA to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption in 1985 by David Nichols, Ph.D., at the Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997, as described in DMF # 6293, and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor prior to starting MAPS' first U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA is currently in use in an ongoing investigation of MDMA-assisted psychotherapy in the U.S. The MDMA is currently stored at Organix, Inc. and will be shipped from that facility for the study.

7.0 Risks of Participation

7.1 Risks and Discomforts Associated with Non-drug and Experimental Sessions and Assessment of Measures

In preparation for drug-assisted therapy sessions, blood draws and a full medical examination are required to establish eligibility for the study and for biomarker analyses. 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 therapy sessions and assessment of study measures, subjects will be asked to think about and discuss their thoughts and emotions relating to social anxiety symptoms. They may experience intense emotional responses to recalling and speaking about this material. In a therapeutic context, thinking about and discussing the effects of social anxiety on life function can produce distress during and immediately after non-drug therapy, experimental, and open-label sessions. Therapy is conducted as part of this study, and people undergoing therapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because therapy is an integral part of the research study design, the potential distress arising from therapy is unavoidable.

All in-person sessions after enrollment may be recorded to 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. Subjects will receive information on who will have access to any of their recordings outside of a research and training setting and will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

7.2 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 and PTSD subjects 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, parasthesias (odd somatic feelings, such as tingling or 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 are reported less often than acute effects. More information on spontaneously reported reactions is described in the IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [78, 109, 159]. 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 [114]. For this reason, subjects will stay close to 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 IB.

7.2.1 Cardiovascular and Sympathomimetic Effects

The MDMA dose of 125 mg 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 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 PI will be present throughout and 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, 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, the Data Safety Monitor and the Medical Monitor. Subjects who are excluded from receiving another experimental session would continue in integrative therapy sessions and follow-up assessments whenever possible.

If a subject has a sustained blood pressure of 180 systolic and/or 110 diastolic without evidence of end organ damage (such as chest pain, shortness of breath, signs of encephalopathy), then the responsible physician should make a judgment about possible treatment. In most cases, the most appropriate course would be to monitor the subject clinically and wait for the hypertensive effect of the MDMA to wear off. If the blood pressure remains elevated above 180 systolic and/or 110 diastolic and is not decreasing three to four hours after MDMA administration, or if for some other reason the PI deems gradual treatment appropriate, then oral carvedilol would be a good choice because of its mixed alpha and beta blocking effects [160]. If the blood pressure is in the range of 180 systolic and/or 110 diastolic or higher with accompanying evidence of end organ damage, then a hypertensive emergency would be indicated and the subject should be transported to the medical Emergency Department at the site for definitive evaluation and treatment with intravenous drugs for more rapid management of the blood pressure and any complications. Reasons for moving a patient to the medical Emergency Department 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 medical Emergency Department for closer monitoring and additional treatment.

The PI will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). If any subject has neurological deficits, as assessed by the PI, whether or not they are associated with hypertensive crisis, they will receive oxygen and will be monitored, as described below. If evaluation at the medical Emergency Department reveals a nonhemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the three-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [161, 162].

The PI 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, he or she will receive heart rhythm monitoring, oxygen, and will be monitored as described above. If necessary, he or she will be transported to the Harbor-UCLA Medical

Center medical Emergency Department or a location in the hospital where appropriate care can be given. The subject will be given nitroglycerin 0.4 mg SL q 5 minutes as needed (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 acute myocardial infarction (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 [163].

7.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [76, 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 little as five minutes or for as long as five hours or more. In addition, psychological distress could arise following an experimental 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 PRN use of benzodiazepines for anxiety. In this study, subjects spontaneously might confront and work through unpleasant experiences. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the therapeutic 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, psychotic disorders)
- Preparatory non-drug therapy 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 therapy sessions

During the preparatory sessions, subjects will be made aware of the fact that difficult emotions, including grief, rage, anxiety, 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 seven 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, 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 the subject implement the self-soothing and stress inoculation techniques presented during the preparatory sessions. If this situation should occur during an integrative session, at least one of the therapists will be available to stay with the subject for at least two additional hours.
- If a subject remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the PI will decide between the following options:
 1. The Harbor-UCLA psychiatric Emergency Department will admit the subject for direct monitoring until the time of his or her appointment with the therapists the next day. The therapists will then meet with the subject daily if necessary until the period of destabilization has passed.
 2. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the PI may prescribe a benzodiazepine, atypical antipsychotic, or zolpidem as a “rescue medication.” Any atypical antipsychotic medications used during the experimental session or the week after should not be primarily metabolized by CYP2D6, such as quetiapine instead of risperidone. This medication will be captured on the concomitant medications CRF page. The physician should not prescribe an SSRI, SNRI, or MAOI in this context, unless it has been determined that the subject will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up therapy visits with the therapists.
 3. Hospitalization for stabilization. If a subject should become psychotic, arrangements will be made to stabilize them and transfer them to the psychiatric Emergency Department at Harbor-UCLA Medical Center if necessary.

Subjects hospitalized after a severe panic or anxiety reaction will be suspended from the protocol until after recovery or stabilization, at which time the PI will carefully evaluate the subject’s emotional status. Subjects will continue with non-drug integrative therapy visits and follow-up assessments whenever possible.

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 PI, the management of any psychiatric complications will be undertaken by them in their capacity as the subject's therapist.

7.2.3 Body Temperature

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

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 present at all times and will determine the need for further evaluation and treatment.

7.2.4 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 [164, 165], and a third reported some developmental delays in mothers reporting use of ecstasy and other drugs during pregnancy [166]. These studies are discussed in the IB.

Pregnant and lactating women will be excluded from participation in the study. 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.

7.2.5 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [167]. 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 [168]. 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.

7.2.6 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, subjects will be excluded from receiving future experimental sessions, unless approved by the PI, Data Safety Monitor, and the Medical Monitor.

7.3 Abuse Liability

Findings in humans and animals suggests 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.

To ensure MDMA-assisted therapy does not cause autistic adults to develop symptoms of drug abuse after the treatment period of the study, drug use is monitored during the follow-up period. 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 a 12-month follow-up period.

Diversion is not an issue in this protocol because MDMA will only be administered in a controlled environment 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.

8.0 Adverse Events

8.1 Adverse Events

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

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 by the therapists until resolution or, if the AE becomes chronic, a cause can be identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the CI and/or 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:

1. “Not Related”: The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, 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.
2. “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.
3. “Probably Related”: Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

8.2 Spontaneously Reported Reactions

Commonly expected spontaneously reported reactions to MDMA 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. Reactions that persist beyond the seven days after each experimental session will be recorded as AEs on the AE CRF page.

8.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

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

AEs 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 SAE 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 a study-related 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.

8.4 Medical Emergencies

The sessions will be conducted in an outpatient research building on the campus of the Harbor-UCLA Medical Center, which is a 10 minute walk from the Emergency Department. The PI will conduct all experimental sessions accompanied by co-investigator Alicia Danforth. The co-therapist or PI will be available via mobile phone or pager throughout the study if any problem occurs when a subject is not at the site. Subjects will continue to see their outside therapist throughout the study. For a recently completed Phase 2 trial, the sponsor has established contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of literature

described in the current IB. The same contingency plans and equipment will be used in this protocol.

8.5 Adverse Event Collection

The PI will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The co-therapist or 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 CI's awareness of their occurrence. All SAE reports should be faxed to the sponsor. A fax number will be provided to the site in separate site-specific instruction for SAE reporting. In addition to the fax, the PI, or designee should call the Clinical Research Associate (CRA) during normal working hours and verbally inform the CRA of the SAE. During off business hours or if medical advice is needed immediately, the sponsor Medical Monitor will be called. SAE reporting instructions with all contact numbers will be provided to the site prior to study start.

The following symptoms will be assessed at baseline and exacerbations during the study will be tracked and categorized as mild, moderate, or severe on a separate Symptoms CRF log page: Persistent feelings of alienation, Rigidity, Tremor, Dystonic Symptoms, Akathisia, Increased Motor Activity, Decreased Motor Activity, Sensory Hyperarousal, Excitement/Agitation.

AEs to be collected during the study are:

- Serious Adverse Events (SAEs) will be collected from enrollment through termination.
- All AEs and spontaneously reported reactions will be collected on the day of and seven days after each experimental session or until they resolve.
- AEs requiring medical attention, including a doctor visit or treatment with prescription medication, will be collected from the first experimental session through the final integrative session after the second experimental session.
- AEs 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 AE leading to withdrawal will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.
- Any exacerbations of Symptoms recorded at Medical History will be collected throughout the study.

A Memory Aid Card will be provided to the subject on the last visit prior to the 6-month follow-up to record information on medications taken to treat SAEs, AEs leading to

withdrawal and psychiatric AEs during the follow-up period during the follow-up period. 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 CI.

8.6 Medical Monitor

Michael C Mithoefer
Email: mmithoefer@mac.com
Telephone: (843)-849-6899
Fax: (843)-278-9188

9.0 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 experimental session to avoid the possibility of any drug interactions (the interval will be at least five times the particular drug's half-life).

Table 5: Medication Washout Table for MDMA studies

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

trazodone	Desyrel	9	2
venlafaxine	Effexor	12	3
ziprazidone	Geodon	7	2
zolpidem	Ambien	2.5	<1

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 experimental session. From the end of the seven days after the last experimental session through the 6-month follow-up visit, 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 specified in Section 8.5 and all changes to psychiatric medications will be collected, including discontinuations or additions. Medications will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications during treatments received in Stage 1 and Stage 2. 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 utilize a washout period of at least five half-lives of the drug and active metabolites plus one week for stabilization before each experimental session and do not restart for ten days after each experimental session.

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). Rescue medications may be benzodiazepines such as lorazepam, or sedative hypnotics such as zolpidem, or atypical antipsychotics. Any atypical antipsychotic medications used during the experimental session or the week after should not be primarily metabolized by CYP2D6, such as quetiapine instead of risperidone. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

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

- They will refrain from taking any herbal supplement (except with prior approval of the research team).
- 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 may return to taking psychiatric medications and discontinue birth control during the follow-up period if necessary. Subjects will receive a Memory Aid Card to record these medications between the final integrative visit in Stage 1 and the 6-month follow-up, as described in Section 8.5. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the 6-month follow-up visit. Memory Aids will not be collected.

10.0 Clinical Laboratory Assessments

10.1 Screening Assessments

A central laboratory will perform clinical laboratory tests conducted at screening to establish medical eligibility. Effective clinical lab normal ranges will be provided by the clinical laboratory and kept on file in the ISF. Abnormal clinically significant clinical laboratory results will be reported as a part of Medical History and must be recorded on the Medical History CRF page. The PI will examine laboratory assessments gathered during screening to assess subject eligibility using the appropriate 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, which includes:

- 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
- Globulin, total
- Glucose, serum
- Potassium, serum
- Protein, total, serum
- Sodium, serum

CBC, which includes:

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

Urinalysis, which includes:

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Occult blood
- Leukocyte esterase
- Nitrite
- Bilirubin
- Urobilinogen

Thyroid function, which includes:

- TSH high sensitivity
- Free T4
- Free T3

HIV serology will be performed.

A **urine-dip pregnancy test** for females of childbearing potential will be performed. The urinary pregnancy tests and drug tests will be performed at the study site.

The central laboratory that will perform screening assessments, other than the urine drug screen and pregnancy tests, is:

LabCorp
21501 Avalon Blvd Suite 150
Carson, CA
Phone: (310) 513-0701
Fax: (310) 513-0702

10.2 Biomarker Analysis

Biomarker laboratory analyses will be performed using plasma for OT, AVP, and CORT collected from all subjects at the Harbor-UCLA Medical Center according to the Time and Events Table. For blood samples, a butterfly needle will be used to draw 30mL of blood into chilled EDTA vacutainer tubes. Samples will be immediately placed on wet ice. Plasma will be extracted by centrifugation in a refrigerated (4°C) centrifuge at 1,300g for 10 minutes, aliquotted into individual tubes, and stored at -80°C at Harbor-UCLA Medical Center prior to shipment to the collaborating site at Stanford University Medical Center. Biomarker analyses will be performed by Dr. Dean Carson and Dr. Karen Parker in Dr. Parker's laboratory at the Stanford University Medical Center in Stanford, California (collaborating site). Concentrations of OT and AVP will be quantified using

commercially available enzyme immunoassay kits (Enzo Life Sciences, Farmingdale, New York) and concentrations of CORT will be quantified using radio immunoassay kits (Siemens, Deerfield, Illinois) that have been validated for use in humans. These kits are highly specific and exclusively recognize OT, AVP and CORT respectively, and not related peptides. Plasma samples are extracted using Strata-X columns and then assayed in duplicate and measured using a tunable microplate reader for 96-well format according to manufacturer's instructions.

11.0 Study Monitoring, Auditing, and Documentation

Prior to trial initiation, the CI must provide to MAPS a fully executed and signed FDA Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms also must be completed for all sub-investigators listed on the Form 1572 who will be directly involved in the treatment or evaluation of research subjects in this trial.

The CI, therapists, and study staff will be trained prior to the start of the study. The trial will be administered and monitored by employees or representatives of the sponsor. The site and collaborating sites will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each subject enrolled. Study monitor contact information, monitoring and auditing procedures will be supplied in a separate document.

During or after the 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.

12.0 Data Analysis

This study is primarily a safety study that will also obtain estimates of effect size comparing MDMA vs. placebo using observer-blind data from the LSAS as the primary outcome measure. MDMA doses are not expected to differ greatly in treatment outcomes and will be combined for effect size estimates. Descriptive statistics will be computed overall for MDMA and placebo, and within the MDMA dose groups 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. Effect size for all outcome measures will be estimated using Cohen's techniques.

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

and placebo subjects differ upon a demographic variable, then the effects of this variable will be taken into account when looking at safety analyses. No systematic differences are expected.

Primary and secondary outcome measure scores will be plotted across each time of administrations for trend analyses. The number of intervals will vary in accordance with times listed for each measure, but will include in most cases baseline, one or more times after the first experimental session, one or more times after the second experimental session and at six month follow up. Plots will be made for MDMA and placebo subjects, and if trends occur for MDMA subjects, separate exploratory plots will be made for outcome measures after 0, 75, 100 and 125 mg MDMA.

The main estimates of effect size from blinded data will be conducted after the outcome measure assessments at the six-month follow-up are complete for all subjects. Data from all doses of MDMA during Stage 1 (n=16), to be compared with all data from placebo sessions (n=8), with each experimental session treated as an independent observation. The MDMA condition will encompass both Group 1 and Group 2 MDMA doses. Estimates of effect size will be obtained from BDI-II, STAI, PSS, IRI, RSES, ERQ, TAS-20, and QoL-Q scores collected pre-treatment, during and after each experimental session, and the follow-up period, with p value set at 0.05. Effect size will be used to determine the appropriate sample size for future studies.

Scores for BDI-II, STAI, PSS, IRI and RSES completed after each of the experimental session will be averaged to produce mean scores for these periods, including a post-experimental session 1 and post-experimental session 2 average score. BDI-II, STAI and PSS scores gathered via postal mail at monthly intervals from two to five months after the second experimental session will be averaged to produce mean scores for the follow-up period. Missing responses will be replaced with the sample average. These averages will be used for estimates of effect size.

TASIT scores will be compared assessing baseline, after experimental session 1, after experimental session 2, at integrative session six and at 6-month follow up. Correlations between TASIT scores and LSAS scores at the time point following each TASIT score will be made to see whether increased awareness of social cues is associated with reduced social anxiety. MDMA dose will be used as a covariate in order to examine the potential relationship between dose and changes in one or more variable, with dose (75, 100 or 125 mg) serving as the covariate.

Biomarkers will be evaluated for predictive and prognostic power. Separate estimates of effect size will be performed for OT, AVP and CORT. Changes in biomarker concentrations from pre-treatment levels will be used to analyze effects of acute dosing and to determine the time-course of elevated OT and AVP levels post-drug. Pre-treatment biomarker concentrations will be evaluated for predictive power using an exploratory hierarchical regression analysis with condition assignment in Stage 1 and biomarker concentrations at baseline as predictors and treatment outcomes as dependent variables. One regression will be performed with biomarker values taken at the second experimental

session. A second regression will be performed on biomarker values taken two weeks after the second experimental session.

TAS-20 scores will be evaluated for predictive power using an exploratory hierarchical regression analysis with condition assignment in Stage 1 and TAS-20 scores at baseline as predictors and with LSAS scores as dependent measures. One regression will examine the predictive power of condition and baseline TAS-20 scores upon LSAS scores one month after the first experimental session and the other will investigate whether condition and baseline TAS-20 and will predict LSAS score at one month after the second experimental session.

Subjects who discontinue treatment prior to the second experimental session will be asked to complete the final outcome assessment prior to continuing to the 6-month follow-up whenever possible. 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 combined for an exploratory intent-to-treat effect size estimate to examine results without bias towards subjects more likely to complete the study per protocol.

Stage 1 and Stage 2 outcomes in extension subjects will be compared after the outcome measure assessments are complete for all extension subjects.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will compare pre-drug and post-drug peak blood pressure, heart rate, and body temperature during and after all experimental sessions by condition and MDMA dose. Analyses will compare peak vital signs between MDMA and placebo subjects, and a separate analysis will consider the effects of dose (0, 75, 100 or 125 mg MDMA) upon vital signs.

Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs. Number and severity of spontaneously reported reactions will be compared in MDMA and placebo subjects using a one-way analysis of variance (ANOVA). The effects of MDMA dose upon number and severity of spontaneously reported reactions will also be assessed. Presence and degree of exacerbated symptoms across MDMA and placebo participant will also be examined.

Perceptions of study participation will be examined at baseline, 6-month follow-up, and end of Stage 2 using the Feedback Questionnaire and a qualitative interview. The results of this qualitative analysis will inform the sponsor of expectancies and perceptions about study procedures for future protocol development. Similarly, belief of condition assignments collected during Stage 1 will be used to assess the effectiveness of the double-blind in preparation for future studies. Results from the Feedback Questionnaire and safety data will be utilized to find the appropriate active MDMA dose for future studies.

To facilitate the planning of future studies, a preliminary estimate of effect size may be performed after all the subjects have completed the outcome assessments, one month after the second experimental session, but not all subjects have completed the six-month follow-up evaluation. This preliminary estimate will consist of safety and outcome measures. Results of the preliminary estimate will have no effect on study conduct.

12.1 Statistical Power

This is a pilot study intended to collect estimates of effect size of MDMA compared to placebo. The study is likely to be underpowered for detection of differences of a small or moderate effect size and it may detect differences if the effect size is large. Statistical power estimates were not available for this study, as this is the first prospective clinical trial of MDMA-assisted therapy for social anxiety in this population.

13.0 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki.

The protocol, ICF and accompanying documents given to subjects must be reviewed and approved by a properly constituted IRB and FDA before study start. Signed and dated documentation of IRB and FDA approvals must be provided to the sponsor. Prior to study start, the PI is required to sign an Investigator Agreement page confirming her/his agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

14.0 Informed Consent

A properly executed, written ICF, in compliance with the Declaration of Helsinki, ICH-GCP Guidelines, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a, b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), and applicable state regulations, will be obtained by a study therapist from each subject and support partner prior to entering the trial. In addition to the explanation of study visits, the ICF should include a HIPAA release giving the PI permission to access original medical records and processing of coded personal information. A copy of the ICF will be submitted by the PI to the IRB for review and approval prior to the start of the study.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol, including screening activities). Information about the study must be given orally and in an understandable form. Written information about the trial will also be provided. The subject and support partner should have the opportunity to inquire about details of the study and adequate time to consider participation. Subjects will be informed in the ICF that they may receive either MDMA or placebo during the study. The ICF and the HIPAA authorization must be signed and

dated by the subject and support partner and must be countersigned by the qualified therapist who conducted the informed consent discussion (according to local, national, and international agreements and laws). The therapist will provide a copy of the signed ICF to each of the subjects and support partners, and will maintain the original in the subject's source records.

The subject and Support Partner are to be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical study. The communication of this information is to be documented. The written ICF and any other written information to be provided to subjects and support partners should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised ICF and written information should receive approval from an IRB before use.

Subjects can withdraw consent at any time without prejudice. If a subject withdraws consent but does not revoke the HIPAA authorization, the PI will have full access to the subject's medical records, including termination visit information. If a subject revokes only the HIPAA authorization, the PI will have full access to all of the subject's medical records prior to the date and time of revocation.

15.0 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 only to approved researchers should prevent the dissemination of confidential data, with or without identifying information. Except for the screening log, the informed consent and a subject contact information sheet that will be stored separately from other documents, all data will be identified only by the subject's initials on the source document and four-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening. 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 PI who are directly involved in conducting the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means.

All in-person visits after enrollment may be recorded to video. Diagnostic assessments may also be video recorded to establish inter-rater reliability. These recordings will be used for treatment manual development and potentially for training therapists to perform MDMA-assisted therapy to reproduce results in subsequent studies. Recordings are intended to document the events occurring during in-person visits, and will not serve as outcome measures. Full names and addresses will not appear in these recordings. Copies of video recordings intended for sharing with subjects will only be marked with the subject's subject number.

16.0 Costs to Subjects

There will be no costs to the study subjects. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of the subject's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the subject or to the subject him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of subjects who previously received therapy from the PI and who will continue to receive ongoing treatment that is not related to participating in the study.

17.0 Treatment and Compensation for Study Related Injury

Costs for treatment of a study-related emergency would first be billed to a subject's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a subject's health insurance. Some study-related emergencies can be treated by the PI, as described under Section 8.4. If the PI cannot treat a study-related emergency, then there are contingency plans for the transport of subjects to the appropriate Harbor-UCLA Medical Center Emergency Department.

18.0 Record Retention

The PI is responsible for retaining all study records required by the sponsor and applicable ICH-GCP and FDA regulations in a secure and safe facility. The PI must consult a representative of the sponsor 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. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the PI or institution as to when these documents no longer need to be retained.

19.0 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.

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