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

***Study Code*:** MAA-1

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
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Significance: The term autism refers to a spectrum of congenital pervasive developmental disabilities. Autistic adults who are verbal and whose autism might not be immediately recognizable to others often initially present in a clinical setting with a co-morbid diagnosis of anxiety or depression. Comparative studies suggest that autistic adults are at greater risk for lifetime and current co-morbid psychological disorders, especially social anxiety. Social anxiety is characterized by fear of scrutiny and avoidance of social interactions and frequently compounds the considerable social challenges experienced by autistic adults. There are currently no FDA-approved pharmacologic treatments for autistic adults, although off-label prescription of selective serotonin reuptake inhibitors (SSRIs) are on the rise in this population. Risperidone (Risperdal) and aripiprazole (Abilify) are the only pharmacologic treatments approved for irritability associated with autism in children and adolescents. Conventional anti-anxiety medications lack clinical effectiveness in this population, potentially due to physiological differences between autistic and typically developing individuals. Given the paucity of confirmed efficacy in clinical trials and clinical practice, the search for supportive treatments for social anxiety in autistic adults is highly relevant.

Preliminary Data: [redacted] 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.

Introduction: MAPS is proposing a double-blind, randomized, placebo-controlled exploratory pilot study with dose escalation to assess safety and feasibility of MDMA-assisted therapy to treat 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 in this underserved population, who tend to experience greater anxiety, depression and victimization than typically developing 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.

The primary outcome measure for the study will be the clinician-administered Liebowitz Social Anxiety Scale (LSAS) administered by a blinded Independent Rater. This study is designed to assess treatment-related changes in social anxiety, social perception, and neuromodulators such as oxytocin (OT), arginine vasopression (AVP) and cortisol (CORT), that are critically involved in anxiety and social behavior. 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. Outcomes from this study, if promising, will inform the dose, endpoints and treatment regimen for subsequent studies.

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

Dose Selection: The MDMA doses to be used in this study have been used in previous and ongoing MAPS-sponsored studies. Previous researchers have also used doses within this range up to 225mg. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy. Each MDMA dose is expected to produce the commonly reported effects of MDMA and are not expected to differ in treatment outcomes, so they will be combined for estimates of effect size. 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. 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 Serious

Adverse Events (SAEs), 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.

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 are common in the adult autistic population as evaluated by standard clinical measures.

Primary Outcome Measure:

- Social Anxiety Severity: Liebowitz Social Anxiety Scale (LSAS)

Secondary Outcome Measures:

- Biomarker Analysis: levels of OT, AVP, and CORT in peripheral blood
- Social Perception: The Awareness of Social Inference Test (TASIT)
- Emotion labeling: Toronto Alexithymia Scale-20 (TAS-20)
- Emotion regulation: Emotion Regulation Questionnaire (ERQ)
- Depression symptoms: Beck Depression Inventory-II (BDI-II)
- Perceived stress: Perceived Stress Scale (PSS)
- Empathy: Interpersonal Reactivity Index (IRI)
- Self-esteem: Rosenberg Self-Esteem Scale (RSES)
- State and trait anxiety: State-Trait Anxiety Index (STAI Form Y)
- Quality of Life Questionnaire (QoL-Q)

Diagnostic Measures:

- Autism: Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2, Module 4)
- Psychological Disorders: Structured Clinical Interview according to DSM-IV (SCID)

Process Measures:

- Effectiveness of double-blind: Belief of Condition assignment
- Perceptions about study procedures: Qualitative interview and Feedback Questionnaire.
- Feasibility: enrollment rates, dropout rates, and completion of assessments and study procedures

Safety Measures:

- Vital signs: Blood pressure, pulse, body temperature
- Subject distress: Subjective Units of Distress (SUD)
- Risk of suicide: Columbia Suicide Severity Rating Scale (CSSRS)
- SAEs, AEs, and spontaneously reported reactions
- Symptoms specific to the study population

Recruitment and Subject Population*:* Subjects may be male or female, aged 21 or older, with a confirmed diagnosis of autism and without intellectual disabilities, as evidenced by 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 a diagnosis of Autistic Disorder or Asperger's 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.

***Study Procedures**:* After giving written informed consent, prospective subjects will be screened for eligibility, and 12 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 5 times the medication half-life 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 outside therapists or psychotherapy type.

The PI will clinically evaluate all subjects to determine autistic status, including those with a prior autism diagnosis. In addition, autistic status will be confirmed with the gold-standard diagnostic measure of autism in adults with the ADOS-2, Module 4 and diagnosis of co-morbid psychological disorders will be conducted according to DSM-IV criteria with the SCID 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.

Upon enrollment, subjects will meet with the study therapists for three 1-hour preparatory sessions scheduled within the month prior to the first experimental session. During preparatory sessions, subjects will learn what to expect during experimental sessions. 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.

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. 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.

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 researchers. All in-person sessions will 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 after the study.

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 on the night following the experimental session. 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 every two weeks during the month following each experimental session. During integrative 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.

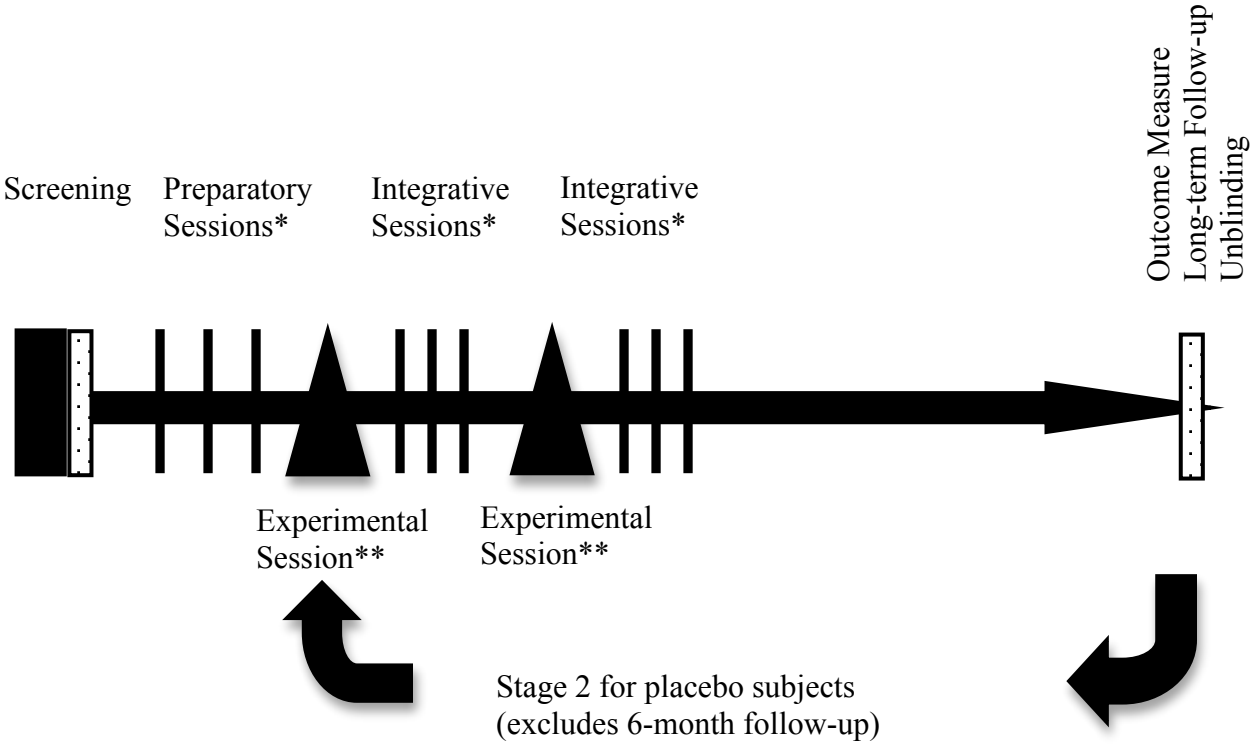
This study will employ biomarker analyses in combination with clinical outcome measures to provide useful insights into the underlying mechanism of the psychosocial and anxiolytic effects of MDMA. It will also allow correlations of any biological differences to treatment responses. The time course of biomarker concentrations will be used to determine if MDMA-assisted therapy causes lasting changes in biomarker levels in comparison to baseline. Blood samples will be obtained from all subjects for biomarker analysis including plasma OT, AVP and CORT, which will be used to explore as potential 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.

Statistical Analysis: 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. 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. All three MDMA doses will be combined since the specific doses are not expected to differ in treatment outcomes. Descriptive statistics will be computed overall for MDMA in comparison to 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.

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, the Feedback Questionnaire, safety and feasibility data will inform the sponsor of the appropriate active dose, expectancies, and perceptions about study procedures for future studies powered for efficacy assessment. 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.

Figure 1. Study Structure Overview



* Pre-treatment and post-treatment outcome measures are spread across these sessions to reduce participant fatigue
** The TASIT will be conducted during these sessions