Treating PTSD with MDMA-Assisted Psychotherapy:

Product Development Status and Proposed Design for Phase 3 Clinical Trials

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INTRODUCTION

The following is an edited excerpt from the recent Multidisciplinary Association for Psychedelic Studies (MAPS) and MAPS Public Benefit Corporation (MPBC) regulatory submissions in support of a Type B Formal End of Phase 2 Meeting with the Division of Psychiatry Products at the U.S. Food and Drug Administration (FDA) for MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD). The submission presents evidence that PTSD is a serious and debilitating disorder leading to increased mortality and morbidity, and that PTSD patients who are insufficiently treated continue to suffer from an unmet medical need. A summary of initial indications of safety and efficacy based on Phase 2 clinical trial results, as well as what is known about the toxicology, pharmacology, and abuse liability of MDMA, is presented as well as plans for the Phase 3 clinical program.

BACKGROUND

PTSD is a stress-related psychiatric condition that can occur following traumatic events such as war, natural disasters, sexual abuse, violence, terrorism, and accidents. According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5),* there are four main symptom categories for PTSD: arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares. These symptoms can be severe and long-lasting. PTSD negatively impacts a person's daily life, often resulting in fractured relationships, depression, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization ($34.9 billion in inflation-adjusted charges for hospitalizations in the U.S. from 2002-2011, Haviland et al., 2016), and increased risk of suicide. Currently available medications for PTSD effectively treat only a fraction of patients. Approximately 7% of the U.S. population (Kessler et al., 2005), and up to 17% of military veterans (Hoge et al., 2004), will have PTSD sometime in their life. In 2012, there were 572,612 veterans on disability for PTSD (VA Annual Benefits Report, 2013). As of June 2016, more than 868,000 veterans with PTSD were receiving disability compensation, with an estimated cost of $17 billion per year (Solon, 2016). In the general population, 27% of suicides are associated with PTSD (Tarrier, 2004). In a nationally representative sample, PTSD was the only anxiety disorder found to be associated with suicidal ideation or attempts (Sareen et al., 2005).

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy is a novel treatment package that combines psychotherapeutic techniques with MDMA as a pharmacological adjunct to enhance certain aspects of psychotherapy. MDMA is a psychedelic compound in the Entactogen class. MDMA inhibits reuptake of monoamines, with greatest effects on serotonin and norepinephrine, and to a lesser extent in humans, dopamine. MDMA binds to the serotonin reuptake transporter, similar to the approved PTSD medications, which are both selective serotonin reuptake inhibitors (SSRIs). Unlike SSRIs, MDMA is a potent releaser of monoamines (Rothman & Baumann, 2002), and at higher doses evokes sustained glutamate release in the hippocampus (Anneken & Gudelsky, 2012). These combined effects may facilitate fear extinction learning, by triggering neuroplasticity via Brain Derived Neurotrophic Factor (BDNF) expression, and assist with the recoding of traumatic memories (Young et al., 2015), thus treating the core psychopathology of PTSD (see Table 1).

MDMA produces anxiolytic and prosocial effects (Bedi et al., 2010), which counteract avoidance and hyperarousal in therapy. PTSD increases activity in the amygdala, causing heightened encoding of fearful memories and decreasing blood flow to the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala and hippocampus, and increases blood flow to the prefrontal cortex (Carhart-Harris et al., 2015). MDMA also increases serum levels of the affiliative neurohormones oxytocin and arginine vasopressin, which likely helps to increase trust and reduce reactivity to threatening cues such as traumatic memories (Kirkpatrick et al., 2014). The combined neurobiological effects

of MDMA can increase compassion for self and others, and diminish psychological defenses and fear of emotional injury, while enhancing communication and capacity for introspection. The subjective effects of MDMA may therefore create a desirable psychological state that enhances the therapeutic process.

The two currently available PTSD medications—the SSRIs sertraline (Zoloft) and paroxetine (Paxil)—have small to medium effect sizes (0.31-0.37 and 0.45-0.56, respectively) and require daily dosing for 12 weeks, as compared to MDMA-assisted psychotherapy (effect size 0.9) which requires single-dose administrations. Sertraline and paroxetine demonstrated superiority on the Clinician-Administered PTSD Scale (CAPS-4) over placebo in two 12-week pivotal trials, with dropout rates trending higher in SSRI groups. The differential effects for these medications over placebo were small when compared with MDMA, as shown by CAPS-4 reductions in Table 2.

Despite treatment with SSRIs, many patients still meet diagnostic criteria for PTSD, as seen in the large numbers of veterans remaining on disability. Maintenance treatment is common, but symptoms often return upon discontinuation, which is more likely when adverse effects of maintenance SSRI treatment—such as sexual dysfunction, weight gain, and sleep disturbance—are more severe. Given the chronic nature of PTSD, high dropouts from treatment, and limited recovery using current medications, PTSD patients suffer from serious unmet medical need.

STATUS OF PRODUCT DEVELOPMENT

In 2000, based on past reports of MDMA use, nonclinical studies, and results from investigator-initiated trials, MAPS launched an international Phase 2 Clinical Development Program to obtain U.S. Food and Drug Administration (FDA) approval for the use of MDMA-assisted psychotherapy for patients with chronic and moderate or severe PTSD (scores of 50 or greater on the CAPS-4). Outcomes from six completed Phase 2 studies have been promising, and have generated a range of methodological information for the design of Phase 3 studies. MAPS-sponsored studies are now implemented through its wholly owned subsidiary, the MAPS Public Benefit Corporation (MPBC).

In Phase 2 studies, MDMA was administered in two or three single-dose sessions spaced three to five weeks apart. The onset of effects occurs about ½ to one hour after MDMA administration, with peak effects occurring 1¼ to two hours after the initial dose. The effects of the initial dose last three to six hours, which is extended to five to eight hours with a supplemental half-dose. In humans, orally administered MDMA has a half-life of seven to nine hours. Unlike currently approved medications for PTSD, MDMA has a rapid onset, and does not require daily dosing or steady blood plasma levels to be effective.

Our Phase 2 studies followed a randomized, double-blind, comparator or placebo-controlled, single-site design with the CAPS-4 as the primary efficacy measure. The basic design includ-

Table 1: How MDMA May Facilitate Fear Extinction Learning in Psychotherapy

Activity	Effects	Application in PTSD Psychotherapy
SEROTONIN Release Downstream Post-synaptic 5-HT1A 5-HT1B	↓ depressed mood ↓ anxiety ↓ fear recognition (amygdala) ↓ aggression and defensiveness ↑ self-confidence	• Facilitates experience of positive mood and reduced anxiety • Increases engagement and ability to focus on trauma without overwhelm
5-HT2A	↑ alterations in the perceptions of meaning	• Provides opportunity to see old problems in a new light
NOREPINEPHRINE Release DOPAMINE Minor ↑ secondary to Serotonin	↑ arousal ↑ alertness ↑ conscious of external stimuli	• Increases motivation to engage in therapy • Improved recall of state-dependent memories • Works with other activity to create optimal arousal zone
ALPHA-2 ADRENO-CEPTORS ↑ activity	↑ relaxation ↑ calmness	• Reduces hypervigilance associated with PTSD • Works with other activity to create optimal arousal zone
HORMONAL EFFECTS Release of oxytocin, vasopressin, prolactin and cortisol	↑ attachment ↑ feelings of trust ↑ empathy ↓ perception of social rejection	• Improves capacity to reflect on traumatic memories • Improves therapeutic alliance • Improves discussion of social/emotional relationships
BDNF Upregulation	↑ neuroplasticity ↑ fear extinction learning	• Allows reflection on traumatic memories during psychotherapy without being overwhelmed • Facilitates memory reconsolidation
REGIONAL BRAIN CHANGES ↑ PFC activation ↓ amygdala activation ↓ cerebral blood- right amygdala and hippocampus	↑ detection of happy faces ↓ detection of fearful faces ↓ subjective fear response on recall of negative memories	• Enhances levels of shared empathy and pro-social functioning • Increases reflection on painful memories of trauma during psychotherapy

Source: (Sessa, 2016; Young et al., 2015)

Table 2. ITT LOCF Placebo/Comparator-Subtracted Mean CAPS Reduction

	Zoloft 12 weeks CAPS % dropout, N Rand	Paxil 12 weeks CAPS % dropout, N Rand	MDMA pooled 12-20 weeks CAPS % dropout, N Rand
Study 1	-6.8 29.3% from N=208	-10.8 41.7% from N=307	-26.2 7.6% from N=105
Study 2	-9.8 22.5% from N=169	-14.3 to -12.2 35.6% from N=551	N/A

ed three weekly preparatory psychotherapy sessions, followed by three treatment modules, each consisting of one eight-hour experimental session assisted with MDMA or comparator/placebo, plus three weekly 90-minute non-drug integrative psychotherapy sessions. Each treatment module was repeated two or three times, with experimental sessions scheduled approximately one month apart. Independent Raters (not present during treatment and blinded to condition assignment) administered the CAPS-4 at baseline and at the primary endpoint three to eight weeks after blinded treatment. Secondary endpoints included CAPS-4 assessments at three to eight weeks, and at least 12 months after the last active dose experimental session. Participants who completed at least one blinded experimental session and completed at least one follow-up CAPS-4 were included in the ITT analysis.

In 2016, we completed an ITT analysis of primary efficacy and safety data from our six Phase 2 clinical trials in the U.S., Switzerland, Israel, and Canada consisting of 105 blinded subjects with chronic PTSD. Two Phase 2 studies have been published, one in the U.S. with a long-term follow-up conducted an average of 3.8 years after the final MDMA-assisted psychotherapy session (Mithoefer et al., 2011; Mithoefer et al., 2013), and one in Switzerland (Oehen et al. 2013). Our first completed Phase 2 study was followed by a small open label extension study examining the treatment of relapse in three subjects with a single MDMA-assisted psychotherapy treatment and a 12-month follow-up. Three additional studies have completed treatments, and two international studies in Israel and Canada were terminated early for logistical reasons with partial datasets. These studies tested a range of designs, such as a placebo control (U.S. and Canada), low dose MDMA comparator control (U.S. and Israel), and three-arm dose response (U.S.).

The analysis of Phase 2 data shows that regardless of the original cause, PTSD is treatable with two to three sessions of MDMA-assisted psychotherapy. Mean baseline CAPS scores (84.7) indicated extreme chronic PTSD with an average duration of 17.8 years. At the primary endpoint across Phase 2 studies, an initial dose of 75-125 mg MDMA was statistically superior to an initial dose of 0-40 mg MDMA, demonstrating dose response. The dropout rate across Phase 2 studies was 7.6%, and MDMA was well tolerated. By long-term follow-up (at least 12 months following the final experimental session) the overall remission rate was 66.2%, with an average drop of 47.7 points on the CAPS.

MDMA transiently increases heart rate, blood pressure, and body temperature depending on dose, though none of these effects are problematic for physically healthy individuals. Most people do not experience elevations in cardiovascular measures exceeding those occurring after moderate exercise. These favorable efficacy and safety outcomes support expanding the research to include a larger sample of participants in Phase 3 clinical trials.

PROPOSED DESIGN OF THE PHASE 3 CLINICAL TRIALS

Our proposed Phase 3 trial is a confirmatory placebo-controlled, double-blind, randomized study, with primary outcomes assessed by a centralized Independent Rater pool, in 230 participants with severe PTSD. The Phase 3 trial will assess the efficacy, safety, and tolerability of a flexible dose of 80 or 120mg MDMA (plus supplemental half dose of 40 or 60mg unless contraindicated). One group will receive MDMA, and the other group will receive inactive placebo. The treatment package of MDMA-assisted psychotherapy includes three monthly experimental treatment sessions with manualized psychotherapy (maps.org/treatmentmanual), preceded by preparatory sessions and interspersed with 12 weeks of integrative psychotherapeutic sessions.

The study's primary objective will be to evaluate changes in participants' CAPS-5 scores between baseline and two-month follow-up, after the third experimental session. Phase 3 will also include a follow-up extension study to collect efficacy and safety data 12 months after treatment. This will be followed by an open-label extension study, to allow those participants who received placebo to receive the full experimental treatment. Data on drug response, safety, tolerability, and administration will also be collected. We will also request permission from the FDA for a single expanded access study to collect additional safety data in the PTSD population. Expanded access will make MDMA-assisted psychotherapy available to patients with PTSD who cannot participate in the Phase 3 trial due to closed enrollment or geographic accessibility.

THE FUTURE OF MDMA IN PSYCHOTHERAPY

Based on the data from MAPS' Phase 2 clinical trials, the risk/benefit profile for MDMA-assisted psychotherapy is favorable for participants with PTSD. Across the Phase 2 trials, 75-125 mg MDMA was statistically superior to 0-40 mg MDMA, and there was a large difference in the size of the effects between the two groups. The overall rates of adverse events and negative reactions across Phase 2 trials were also low. The Phase 3 study proposed by MAPS is intended to gather further information about abuse liability, safety, and efficacy, with the goal to obtain an approved New Drug Application (NDA) for MDMA-assisted psychotherapy in the treatment of PTSD in a controlled clinical setting.

It is anticipated that MDMA, with its unique pharmacological mechanisms and administration in conjunction with psychotherapy, can improve upon existing first-line PTSD treatments in terms of side effect profiles, efficacy, and durability of remission. MAPS will seek marketing approval for MDMA-assisted psychotherapy for PTSD in adults, based on evidence from Phase 2 trials and a confirmatory Phase 3 clinical trial, subject to feedback from the FDA on our proposed development plan.

If the FDA determines that the data supports a favorable NDA, MAPS proposes to collaborate with the FDA in the development of a Risk Evaluation and Mitigation Strategy (REMS) potentially consisting of:

- A sponsor-developed training or certification program for providers demonstrating proficiency in manualized MDMA-assisted psychotherapy
- Restricted distribution from a limited number of pharmacies
- Administration only in a clinical inpatient setting under continuous observation
- Continued restrictions on treatment of patients with renal and hepatic impairment until satisfactory completion of additional safety studies after approval
- Continued requirements of pregnancy testing and effective birth control during treatment
- Driving restrictions after receiving MDMA-assisted psychotherapy.

MAPS proposes a model of care in which treatment can be provided by certified practitioners at clinics with the following minimum capabilities:

- A physician holding a license of the appropriate schedule for MDMA;
- Physicians, nurses, counselors, or therapists from various specialties who are licensed according to state and local requirements to deliver psychotherapy, and who are certified by the sponsor to deliver MDMA-assisted psychotherapy upon satisfactory completion of training;
- Trained personnel under direct supervision of licensed psychotherapists to assist with delivery of the treatment package;
- Suitable facilities for treatments in a residential setting to limit risk of abuse, misuse, diversion, and accidental pediatric exposure.

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