MAPS Public Benefit Corporation

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Sarah Seung, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
5901-B Ammendale Road
Beltsville, MD 20705-1266

21 May 2019

RE: IND #063384, Serial No. 0117, MT2 Protocol Version 2

Dear Division of Psychiatry/CDER,

Enclosed in this submission is the MT2 Protocol Version 2, titled "*A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers*". As recommended by the FDA, the sponsor is requesting review of the MT2 Protocol Version 2 under IND #063384, as a healthy volunteer study assessing the development of self-compassion and potential reduction in burnout in treatment providers enrolled in MDMA therapy training (enrollment by invitation only).

The MT2 Protocol is intended to enroll trainees providing treatment under IND #063384, IND #142690, and future studies under IND #142908. The sponsor does not expect the database lock and completion of MT2 before the anticipated NDA approval date for IND #063384, so the sponsor will request to keep IND #063384 open after approval of the associated NDA. The sponsor will ensure that ongoing submissions of the IND annual reports are provided to the agency by the appropriate deadlines, as long as the IND is open.

The eligibility criteria for healthy volunteer studies of MDMA-assisted psychotherapy are updated in the MT2 protocol based on the sponsor's current experience with the ongoing MT-1 study. The current medical exclusions for this study are relative, not absolute contraindications for administration of MDMA. In the future, if MDMA is approved as a treatment for PTSD, it will be appropriate for physicians to carefully evaluate these conditions on a case by case basis, and to treat individuals with stable chronic diseases who are medically cleared to receive MDMA. The MT2 protocol will enable the sponsor to collect safety data in the defined healthy volunteer population to support expansion to similar eligibility criteria in future protocols.

To support the risk/benefit assessment of the MT2 protocol, the sponsor is providing safety data from the ongoing Phase 1 blinded study MT-1, which has data available from N = 76 healthy participants. In the ongoing MT-1 study, each participant receives MDMA and placebo in randomized order within the same week. Adverse event data presented below includes data from both conditions as the study is still blinded. Adverse events were defined as those that were not included in the list of Spontaneously Reported Reactions to MDMA per the study protocol. To date, 76% (55 of 76) of participants treated in MT-1 have not reported experiencing an adverse event in the study. Adverse events reported by blinded healthy participants in the ongoing placebo-controlled crossover study MT-1 are presented in Table 1 below.

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Table 1: Adverse Events At Any Severity Regardless of Relationship to IMP from Enrollment through Termination in Healthy Participants of MAPS-Sponsored MDMA-assisted Psychotherapy Phase 1 Study MT-1 (excludes adverse reactions in Table 2)

Adverse Events Body System/ Preferred Term	**Blinded Healthy Participants (N = 76)**
(Mild/Moderate/Non-Serious unless noted otherwise)	reports (%)
Gastrointestinal Disorders	
Glossodynia	1 (1.4%)
Swollen Tongue	1 (1.3%)
Vomiting	2 (2.6%)
Abdominal Pain Upper	1 (1.3%)
Psychiatric Disorders	
Depressed Mood	1 (1.3%)
Suicidal Ideation (severe)	1 (1.3%)
Intentional Self-Injury	1 (1.3%)
Stereotypy	1 (1.3%)
Nervous System Disorders	
Lethargy	1 (1.3%)
Dizziness	2 (2.6%)
Paraesthesia	1 (1.3%)
Syncope	1 (1.3%)
Musculoskeletal and Connective Tissue Disorders	
Muscle Spasms	1 (1.3%)
Muscular Weakness	1 (1.3%)
Trismus	1 (1.3%)
Arthritis (SAE)	1 (1.3%)
Infections and Infestations	
Upper Respiratory Tract Infection	2 (2.6%)
Eye Disorders	
Blindness (Loss of peripheral vision)	1 (1.3%)
Visual Impairment	2 (2.6%)
Vision Blurred	1 (1.3%)
Renal and Urinary Disorders	
Dysuria	1 (1.3%)
Reproductive System and Breast Disorders	
Dysmenorrhoea	1 (1.3%)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	1 (1.3%)
Nasal Congestion	1 (1.3%)
General Disorders	
Chest Discomfort	1 (1.3%)

The adverse events reported by MT-1 participants were mostly non-serious and mild or moderate, with the exception of arthritis (SAE) and suicidal ideation (severe AE). Participant [redacted] reported arthritis in their right hip which was diagnosed by a doctor on [redacted]. A right hip replacement surgery was facilitated by the external doctor, and the participant was admitted to the hospital on [redacted] for this surgery. After being discharged from the hospital on [redacted], the participant made a full recovery. IMP administration was found to be unrelated to the arthritis diagnosis and did not impact the hip replacement surgery.

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Participant [redacted] reported severe, active suicidal ideation with a specific plan following administration of IMP or placebo. Participant [redacted] also reported non-suicidal, self-harmful behavior the same day. Though there was a history of suicidal ideation in the lifetime assessment but no current ideation reported by this participant, these AEs were judged to be probably related to IMP, although the data remains blinded. Following these events, the investigators ensured the participant was given proper space to express, was kept physically safe, and was aware of boundaries and safety. The participant did not injure themselves. Clinical Investigators and co-therapists also ensured that the participant was supervised for 24 hours after the experimental session and was re-evaluated in the integrative session the morning after experimental session. Contact was established with the participant and follow-up was successful, and the participant experienced a full recovery and return to baseline.

Commonly reported adverse events from Phase 1 studies conducted without sponsor support and published between 1986 and 2012 were used to develop a list of adverse reactions, or Spontaneously Reported Reactions. This curated list of reactions was used to collect what are considered to be common reactions based on previous MDMA studies on the day of Experimental Sessions and for 7 days after the second Experimental Session in MT1 as a subset of adverse events. Table 2 presents adverse reactions reported on the day of and one day after blinded MDMA and placebo administration in the ongoing MAPS-sponsored study, MT-1 (N=76), in comparison to the blinded PTSD participants receiving 125mg MDMA (N=58). In summary, spontaneously reported reactions were typically observed during drug administration, but are transient and diminish as the drug is metabolized and excreted over the next 24 hours (see Day 1 data), with the majority of reactions resolving within several days and up to one week after dosing. Participants in MT-1 have reported similar adverse reactions to those observed in previous MDMA-assisted psychotherapy clinical trials in healthy volunteers conducted without sponsor support, such as jaw clenching/tightness, lack of appetite, muscle tension, headache.

The prevalence of reactions was greater in the PTSD population, which influences the risk/benefit profile in a population-specific manner. In contrast to healthy volunteers, more PTSD patients experienced anxiety (PTSD: 70.7% vs. MT-1: 25.0%), dizziness (PTSD: 44.8% vs. MT-1: 22.4%), insomnia (PTSD: 34.5% vs. MT-1: 3.9%), fatigue (PTSD: 48.3% vs. MT-1: 13.2%), increased irritability (PTSD: 25.9% vs. MT-1: 1.3%), nausea (PTSD: 43.1% vs. MT-1: 18.4%), and insomnia (PTSD: 34.5% vs. MT-1: 3.9%) on the day of Experimental Sessions. Adverse reactions are typically observed during IMP administration but are transient and diminish as the IMP is metabolized and excreted over the next 2-3 days after dosing and are self-limiting in both populations. Only jaw clenching/tightness and muscle tension were reported to be severe in a small number of healthy participants, and their symptoms were also transient and resolved within 2 or 3 days after dosing. In the PTSD population during the week following treatment, the most frequently reported reactions attributable to MDMA based on relative incidence were lack of appetite, muscle tightness in the jaw, restlessness, weakness, dry mouth, thirst, impaired gait/balance, sensitivity to cold. Severe anxiety, insomnia, fatigue, and depressed mood were commonly reported in PTSD studies in both placebo and MDMA groups and may be attributable to background events or the psychotherapy that both groups receive in conjunction with IMP.

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Table 2: Adverse Reactions At Any Severity Collected on the Day of and 1 Day After Experimental Sessions for Healthy Participants Receiving 125 mg MDMA in MAPS-Sponsored Study MT-1

Adverse Reactions Body System/ Preferred Term	Day 0 125mg MDMA PTSD Participants (N = 58)	Day 0 Blinded Healthy Participants (N = 76)	Day 1 Blinded Healthy Participants (N = 76)
(Mild/Moderate/Non-Serious unless noted otherwise)	reports (%)	reports (%)	reports (%)
Gastrointestinal Disorders			
Diarrhea	0 (0.0%)	2 (2.6%)	2 (2.6%)
Dry Mouth	14 (24.1%)	13 (17.1%)	4 (5.3%)
Psychiatric Disorders			
Anxiety	41 (70.7%)	19 (25.0%)	3 (3.9%)
Difficulty Concentrating	12 (20.7%)	6 (7.9%)	4 (5.3%)
Impaired Judgement	0 (0.0%)	1 (1.3%)	0 (0%)
Headache	29 (50.0%)	22 (28.9%)	17 (22.4%)
Increased Irritability	15 (25.9%)	1 (1.3%)	0 (0%)
Insomnia	20 (34.5%)	3 (3.9%)	15 (19.7%)
Low Mood	12 (20.7%)	4 (5.3%)	4 (5.3%)
Need more Sleep	5 (8.6%)	1 (1.3%)	6 (7.9%)
Restlessness	18 (31.0%)	8 (10.5%)	1 (1.3%)
Ruminations	9 (15.5%)	2 (2.6%)	0 (0%)
Nervous System Disorders			
Impaired Gait/Balance	15 (25.9%)	12 (15.8%)	1 (1.3%)
Drowsiness	7 (12.1%)	4 (5.3%)	3 (3.9%)
Dizziness	26 (44.8%)	17 (22.4%)	2 (2.6%)
Paresthesia	8 (13.8%)	6 (7.9%)	2 (2.6%)
Musculoskeletal and Connective Tissue Disorders			
Heavy legs	9 (15.5%)	5 (6.6%)	1 (1.3%)
Jaw Clenching/Tightness	37 (63.8%)	45 (59.2%)	13 (17.1%)
Severe	3 (5.2%)	3 (3.9%)	1 (1.3%)
Muscle Tension	20 (34.5%)	23 (30.3%)	8 (10.5%)
Severe	0 (0.0%)	0 (0.0%)	1 (1.3%)
Muscular Weakness	5 (8.6%)	4 (5.3%)	4 (5.3%)
Skin and Subcutaneous Disorders			
Perspiration	19 (32.8%)	17 (22.4%)	0 (0%)
Eye Disorders			
Nystagmus	9 (15.5%)	10 (13.2%)	0 (0%)
Metabolism and Nutrition Disorders			
Lack of Appetite	29 (50.0%)	27 (35.5%)	6 (7.9%)
Nausea	25 (43.1%)	14 (18.4%)	1 (1.3%)
General Disorders			
Sensitivity to Cold	23 (39.7%)	16 (21.1%)	3 (3.9%)
Fatigue	28 (48.3%)	10 (13.2%)	22 (28.9%)
Thirst	17 (29.3%)	8 (10.5%)	2 (2.6%)

Table 3 below presents vital signs data collected during blinded MDMA and placebo administration in the ongoing MAPS-sponsored study, MT-1 (N=76). As data remains blinded, and MDMA is known to have sympathomimetic and thermoregulatory effects that resolve back to pre-drug levels by the end of the Experimental Session, the range of data is presented based on

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data collected to date in the MT-1 study to give a sense of the effects of MDMA or placebo on these parameters.

Table 3: Range of Vital Signs Collected During Blinded Experimental Sessions for Healthy Participants in MAPS-Sponsored Study MT-1

Timepoint in Relation to Dosing	SBP Min/Max (mm Hg)	DBP Min/Max (mm Hg)	BT Min/Max (°C)	HR Min/Max (bpm)
Pre-drug	90/182	49/103	35.1/37.8	48/96
Before supplemental dose	89/194	50/109	35.4/ 38.6	44/134
End of Session	88/158	52/102	35.3/ 38	47/108

SBP = systolic blood pressure, DMP = diastolic blood pressure, BT = body temperature, HR = heart rate

In MAPS-sponsored Phase 2 PTSD studies that have been completed, doses of 75 and 125 mg MDMA produced greater elevation in SBP and DBP than lower doses that were not therapeutically active. SBP above 160 mm Hg was detected in 44.8% (26 of 58) of participants and DBP above 110 mmHg was detected in 10.3% (6 of 58) of participants who received 125 mg MDMA during blinded Experimental Sessions. At the end of Experimental Sessions, SBP and DBP returned to baseline levels across all doses of MDMA. In PTSD studies, MDMA increased peak heart rate compared with placebo, with a greater difference between pre-drug and peak values observed with therapeutically active doses. In PTSD studies, heart rate elevated above 110 bpm was detected in 50.0% (29 of 58) of participants receiving 125 mg MDMA in blinded Experimental Sessions. Elevation in body temperature was not dose dependent during Experimental Sessions. Body temperature above 1°C above pre-drug reading was detected in 44.8% (26 of 58) subjects who received 125 mg MDMA during blinded Experimental Sessions and in 20% (2 of 10) of subjects who received placebo. No subjects required medical intervention to decrease body temperature or cardiovascular parameters, and values returned to baseline as drug effects waned.

The benefits of MDMA-assisted psychotherapy for the PTSD population outweigh the risks, as adverse events and reactions were generally mild or moderate and not clinically alarming. The risk/benefit ratio of MDMA-assisted psychotherapy in healthy volunteers remains favorable as the risks are lower than the PTSD population. The objective of the MT2 study is to continue assessment of potential benefits in treatment providers (who are also participating in MDMA therapist training) in development of self compassion, improvements in professional quality of life and mood, and reduction in burnout and psychological inflexibility. In the absence of unreasonable or significant risk of illness or injury in the MT1 study and the data summarized in the Investigator's Brochure from previously published studies of MDMA in 1286 healthy volunteers, the sponsor concludes that the risk-benefit analysis of MDMA-assisted psychotherapy weighs in favor of testing a larger number of healthy volunteers in the open label safety study MT2 to continue evaluation of safety for this treatment.

Please find the following documents enclosed in submission serial No. 0117:

- FDA Form 1571 dated 20 May 2019
- FDA Form 3674 dated 20 May 2019
- MT2 Protocol Original Version 2 dated 20 May 2019
- MT2 Informed Consent Template Version 2 dated 20 May 2019
- MT2 Description of Case Report Forms Version 2 dated 20 May 2019

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- FDA Forms 1572 for MT2 Clinical Investigators
- Curriculum Vitae for MT2 Clinical Investigators
- MT2 Study Measures

Thank you for the Agency's time and consideration. If you have any questions or requests regarding the submission of the MT2 Protocol, please do not hesitate to contact Sponsor Designee, Amy Emerson, by email at [redacted] or by phone at [redacted]

Sincerely,

Amy Emerson
Electronically signed by:
Amy Emerson
Reason: I am the author
of this document
Date: 2019-05-21
15:05:52-07:00

Amy Emerson
MAPS Public Benefit
Executive Director and
Head of Clinical Development & Regulatory Affairs