December 1, 2020

FORMAL DISPUTE RESOLUTION REQUEST

Sponsor:	Multidisciplinary Association for Psychedelic Studies
Application:	IND 063384
Product:	3,4-methylenedioxymethamphtamine (MDMA)
Reviewing Division:	Division of Psychiatry
Review Level Requested:	Office of Neuroscience
Indication:	Posttraumatic Stress Disorder

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On behalf of our client, Multidisciplinary Association for Psychedelic Studies (MAPS, the Sponsor, or the Company), we hereby submit this Formal Dispute Resolution Request (FDRR) to resolve a scientific and regulatory disagreement between MAPS and the Division of Psychiatry (DP or the Division) regarding a clinical hold. MAPS submitted the protocol for Study MT-2 entitled "A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers" (Study MT-2) to its active Investigational New Drug Application (IND) 063384 on 21 May 2019 (SN 0117). Study MT-2 is intended to further assess the psychological effects of 3,4-methylenedioxymethamphtamine- (MDMA-) assisted psychotherapy when administered to healthy volunteers and to provide training to therapists in the conduct of MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD). On 05 August 2019, the Division issued a partial clinical hold (the Original Clinical Hold) for Study MT-2 alleging that Study MT-2 would involve an unreasonable and significant risk of illness or injury to its subjects and that Study MT-2 investigators were unqualified. MAPS provided responses to each of the Division's concerns in IND submissions dated 29 August 2019 (SN 0123), 11 October 2019 (SN 0126), and 31 December 2019 (SN 0136). The Division issued Continue Partial Clinical Hold Letters on 27 September 2019 and 30 January 2020 (together with the Original Clinical Hold, the Clinical Hold). The last of these restated the issues raised in prior letters without responding to the data, information, or arguments provided in the Sponsor's subsequent submissions. Finally, on 30 April 2020, the Division denied the Type A meeting request (Meeting Request) which MAPS had submitted (SN 0146) in an effort to resolve the impasse.

This FDRR requests that the Office of Neuroscience (ON or the Office) direct the Division to remove the Clinical Hold in light of the data and information presented by Sponsor.

I. Executive Summary

The Division takes the position that Study MT-2, which is intended to enroll healthy normal volunteers with education or training in psychotherapy, involves an unreasonable and significant risk of illness or injury. This assessment was based on a single event of suicidal ideation in a healthy volunteer that occurred and resolved during a blinded psychotherapy session with either MDMA or placebo in a prior Phase 1 study. Data from the Phase 2 and 3 programs, which enroll PTSD patients at higher baseline risk of suicidal ideation, reveal no signal for an MDMA-associated risk. The Division repeatedly notes that the single case in the healthy volunteer was de novo despite submitted evidence that the subject had a history of prior ideation and that the results of a lifetime Columbia-Suicide Severity Rating Scale (C-SSRS) administered during the study reflected a positive score of lifetime suicidal ideation and behavior. In an abundance of caution, MAPS has amended the Study MT-2 protocol to exclude subjects who present similar risks at baseline. Additional safeguards are embedded into the study design. The proposed population consists of healthy volunteers who by reason of education and training are particularly able to provide insight into the experience of undergoing MDMA-assisted therapy. This population is less vulnerable than the subjects in other studies that MAPS has conducted or is currently conducting in PTSD sufferers. The protocol requirement for a two-person therapy team ensures that subjects are attended by at least one, if not two, licensed therapists with specific training in conducting MDMA-assisted therapy during the entire day-

long session when they are under the influence of MDMA. The Division has not addressed the ability of these protocol modifications and other measures to address its concerns.

The purported risk of suicidal ideation and behavior provides the backdrop against which the Division finds that the potential for direct benefit to Phase 1 subjects would be necessary to offset the risk. While we disagree that such potential for benefit is required, MAPS has nonetheless presented evidence that it exists. The study involves multiple psychotherapy sessions, including several without drug, which by their very nature are generally beneficial to participants. Moreover, study subjects may derive enhanced understanding of the experience of patients undergoing MDMA-assisted therapy to better their practice if they choose to later administer MDMA to their PTSD patients. Perhaps more importantly, an individual potential benefit is not a requisite element of a Phase 1 study and the single case of suicidal ideation in a prior study does not alter that balance. Many standard Phase 1 studies, such as pharmacokinetic studies, provide no possibility of benefit to the subjects other than the opportunity to support research. Study MT-2 is designed to produce valuable data about the safety and pharmacodynamic effects of MDMA in a population that is uniquely qualified to provide insights into the psychological experience unconfounded by PTSD.

The Division also takes the position that novel investigator qualifications are necessary to ensure subject safety despite the safe conduct of numerous other MDMA studies under this IND without such requirements. The Division asserts, without explanation, that Study MT-2's investigator qualifications are less robust than those for the Phase 3 Study MAPP1 when, as a practical matter, they are essentially the same.[1]

The level of risk of illness or injury necessary to impose a clinical hold is "unreasonable and significant." The risk of suicidal ideation due to MDMA in heathy normal volunteers generally, and certainly in those healthy normal volunteers who meet the revised study entry criteria, does not meet either prong of this test. The benefits inherent in Phase 1 research, the opportunity to collect additional valuable information about the safety and effects of MDMA in a therapeutic setting, and the potential for direct benefit to study subjects significantly outweigh the theoretical risk, taking it even farther from the requisite "unreasonable and significant" standard.

II. Background

A. PTSD

PTSD is a stress-related psychiatric condition involving recurring, intrusive recollections, including nightmares and flashbacks, of an overwhelming traumatic event such as war, disaster, sexual abuse, violence, terrorism, or an accident. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5) are arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and

[1] The only practical difference is that MAPP1 requires both therapists to have completed the MDMA Therapy Training Program, while MT-2 permits a co-therapist to work on the protocol while still in the MDMA Therapy Training Program. Neither protocol requires doctoral-level therapists or a physician on site, both of which the Division asserts are necessary for Study MT-2 to proceed.

nightmares. These can manifest as a persistent and distorted sense of blame of self or others; estrangement from others; markedly diminished interest in activities; inability to remember key aspects of the event; aggressive, reckless, or self-destructive behavior; sleep disturbances; hypervigilance; or related problems.

Regardless of the original triggering event, PTSD is a serious debilitating psychiatric condition with clinically significant impacts on quality of life, resulting in fractured relationships, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization, and increased depression and suicide risk (Dorrington et al., 2014; Haviland et al., 2016; Tarrier et al., 2004). PTSD affects 7-8% of the total population of the US (Kilpatrick et al., 2013; Koenen et al., 2017) and more than 10% of US veterans with combat experience (Hoge et al., 2004). In 2012, the Department of Defense spent approximately $294 million and the Veterans Administration spent approximately $3 billion on PTSD care for service members and veterans, respectively (Institute of Medicine, 2014).

PTSD is generally treated with a combination of pharmacotherapy and psychotherapy. In terms of pharmacotherapy, the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are approved for the treatment of PTSD. Other SSRIs, as well as selective serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, may also be effective in some patients (Davidson et al., 2006). There is some evidence suggesting that prazosin can reduce nightmares. Mood stabilizers and atypical antipsychotics are occasionally prescribed to PTSD patients despite limited supporting evidence (Barnhill, 2020; Shiner et al., 2020). The need for additional therapies is evident in that an estimated 40-60% of PTSD patients do not respond adequately to available pharmacotherapies (Brady et al., 2000; Steenkamp et al., 2015) and many discontinue them due to common adverse events (AEs) including sexual dysfunction, weight gain, and sleep disturbance (Cipriani et al., 2018; Ferguson, 2001; Lee et al., 2016).

The primary form of psychotherapy in PTSD, exposure therapy, involves exposure to situations that the patient avoids because they may trigger recollections of the trauma. Such exposure seeks to achieve the induction and extinction of abnormal autonomic responses through revisiting the traumatic experience in therapy sessions (E.B. Foa et al., 2009). The degree of emotional engagement or “fear activation” that occurs when revisiting trauma during therapy cannot be so great that the patient experiences dissociation or overwhelming emotion (E B Foa, 2007). Difficulty in achieving this delicate balance can limit the effectiveness of such therapy. Therapists must be openly empathic and sympathetic, recognizing and acknowledging the patient’s mental pain and the reality of the traumatic events. Repeated imaginal exposure to the traumatic experience itself may lessen distress after some initial increase in discomfort. For treatment to be effective, patients must be able to relax and control anxiety before they can tolerate the exposure that tends to be a focus of PTSD treatment. Techniques such as mindfulness, breathing exercises, and yoga may be helpful. Not surprisingly, however, some patients remain incapable of successful participation in exposure therapy, and there remains a large unmet medical need in the treatment of PTSD.

B. MDMA-Assisted Psychotherapy For PTSD

MDMA acts primarily on the serotonin transporter, increasing release and reuptake inhibition of serotonin, with similar effects on norepinephrine and, to a lesser extent, dopamine, while also increasing levels of oxytocin and vasopressin (Farre et al., 2007; Forsling et al., 2001; Hysek et al., 2011; Hysek et al., 2014; Liechti et al., 2000a, 2000b, 2001; Tancer et al., 2007). The constellation of neurobiological effects of MDMA increases compassion, reduces defenses and fear of emotional injury, and enhances communication and introspection. MDMA is therefore a logical candidate therapy for treatment of PTSD because it can provide patients with the requisite state-of-mind to render psychotherapy more effective.

MDMA-assisted psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion (Bouso et al., 2008; Metzner et al., 2001; Mithoefer et al., 2011; Stolaroff, 2004). Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them with less likelihood of feeling overwhelmed by these emotions (Greer et al., 1998). In addition, MDMA-assisted psychotherapy has been demonstrated to bring about feelings of empathy, love, and deep appreciation, along with increased memory of traumatic events, a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present.

MDMA is currently classified as a Schedule I controlled substance in accordance with the federal Controlled Substances Act (CSA) (21 C.F.R. § 1308.11(d)(11)). Drugs placed in Schedule I include substances that, in addition to having a high potential for abuse, also have "no currently accepted medical use in treatment in the United States" and present a "lack of accepted safety for use of the drug or other substance under medical supervision" (21 U.S.C. § 812(b)(1)). Studies conducted under IND 063384 are intended to demonstrate safety and substantial evidence of efficacy of MDMA in PTSD sufficient to support approval of a New Drug Application and rescheduling under the CSA.

C. Relevant Regulatory And Clinical History

1. Clinical Development Plan (IND 063384)

IND 063384 was submitted to FDA on 11 October 2001. Since that time, one Phase 1,13 Phase 2 and 1 pivotal Phase 3 clinical studies of MDMA, enrolling a total of 366 subjects, have

been completed under the IND.[2] One Phase 1, one Phase 2 and one confirmatory Phase 3 studies are ongoing. Attachment 1 is a list of ongoing and completed studies under the IND.

a. Phase 2 Studies

Six of the Phase 2 studies in 107 subjects with PTSD (Studies MP-1, MP-2, MP-4, MP-8, MP-9, and MP-12, collectively, the Core Phase 2 Studies) were single-center, randomized, double-blind, low dose MDMA- or placebo-controlled trials. While study designs varied somewhat across these trials, following one or more preparatory psychotherapy sessions (Preparatory Sessions), experienced psychotherapists acting as investigators or sub-investigators administered MDMA (75 to 187.5 mg depending on the individual study design), placebo, or low dose MDMA active comparator (25 mg to 60 mg depending on the individual study design) to each randomized PTSD subject as a divided dose in each of two or three day-long psychotherapy sessions (Experimental Sessions). In each study, Experimental Sessions were spaced three to five weeks apart and each session was followed by at least three sessions of integrative psychotherapy (Integrative Sessions). For each individual subject, the psychotherapy team was the same for all Preparatory, Experimental and Integrative Sessions. The studies utilized change from baseline to a timepoint four to eight weeks following the second or third Experimental Session on the Clinician-Administered PTSD Scale (CAPS) as the primary efficacy measure. CAPS is a psychometrically validated measure of PTSD (Weathers et al., 2013) and was a key component in demonstrating efficacy of the two FDA-approved PTSD medications - ZOLOFT (sertraline hydrochloride) and PAXIL (paroxetine hydrochloride). (GlaxoSmithKline, 2017; Pfizer, 2016). Each of the Core Phase 2 Studies included an open-label extension phase in which subjects randomized to control groups had the option to cross-over to active dose MDMA after the primary outcome measure and individual unblinding.

Demographic and baseline criteria confirmed that the enrolled population suffered chronic (≥ six months), treatment-resistant moderate or severe PTSD (CAPS-4 score: ≥50). Pooled analyses of the Core Phase 2 Studies demonstrated a clinically and statistically significant effect of MDMA on CAPS-4[3] (Mithoefer et al., 2019). Efficacy was both dose-dependent and durable with the emergence of no unexpected safety signals. The Division agreed that these pooled Core Phase 2 Studies provide preliminary clinical evidence that MDMA-assisted psychotherapy may demonstrate substantial improvement over available therapy on a clinically significant endpoint and granted MDMA Breakthrough Therapy Designation for PTSD on 15 August 2017. In addition, on the basis of these studies, MAPS and the Division participated in an

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[2] Eleven of the Phase 2 studies, including three which terminated early, were conducted in subjects with PTSD: MP-1, MP-2, MP-3, MP-4, MP-8, MP-9, MP-12, MPVA-1,MPVA-6, MP16, and MP17. One was in subjects with autism (MAA-1) and one in subjects with anxiety related to life-threatening illness (MDA-1). One additional Phase 2 study, Study MP1-E2 was an extension of Study MP-1 enrolling subjects who relapsed.

[3] The CAPS outcome measure has been updated to CAPS-5 since publication of the DSM-5. CAPS-5 is being used in the MAPS Phase 3 studies.

End of Phase 2 meeting on 29 November 2016 and reached agreement on a Special Protocol Assessment for the design of the first Phase 3 study, Study MAPP1.

Education and licensing requirements for the investigative psychotherapy teams were not raised as an issue by the Division during these interactions despite that the Core Phase 2 study protocols did not specify requirements for their training, education, or licensure. For some of these single-site studies, the psychotherapy team included the clinical investigator who was a psychiatrist (e.g., Study MP-2). Minimum psychotherapy team qualifications were more specifically called out in the three subsequent Phase 2 studies. Beginning with Study MP-12, study protocols specified that each psychotherapy team must include at least one licensed psychotherapist. Protocols for Studies MP16 and MP17 required that the psychotherapy teams facilitating MDMA-assisted psychotherapy be comprised of at least one person licensed to provide psychotherapy under applicable law, and if the other person was unlicensed, they were to work under the direct supervision[4] of the licensed psychotherapist. A physician was required to assess subject safety at screening and throughout the study and to consult with the therapy team to make a decision about supplemental dosing. The physician was otherwise required to be available on-call but not physically present at the study site. These same requirements were utilized in the Phase 3 study, Study MAPP1, the design of which is the subject of the SPA agreement.

b. Phase 1 Studies

Two of the Phase 1 studies warrant specific discussion in this FDRR: Study MT-1, an ongoing study conducted in a similar population as that proposed for Study MT-2; and Study MT-2, which is the subject of the Clinical Hold.

(1) Study MT-1

Study MT-1, for which FDA initially issued a Study May Proceed letter in 2009, is a Phase 1, randomized placebo-controlled, multi-center, crossover study designed to assess the safety and psychological effects of MDMA when administered to healthy volunteers who are trainees in the conduct of MDMA-assisted psychotherapy or MDMA research.[5] A total of 89 of the planned 120 subjects have been enrolled in this ongoing study as of 01 December 2020.

In accordance with the crossover design, each subject participates in two Experimental Sessions during which they receive placebo or 125 mg MDMA followed by an optional supplemental half-dose of placebo or 62.5 mg MDMA administered one and a half to two hours later. Primary psychological effects are assessed via the Profile of Mood States Bipolar Scale (POMS-Bi), a self-report assessment of current mood state. Measures of interpersonal closeness and personality are also employed. Safety assessments focus on vital signs and a subjective

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4 The phrase “under the direct supervision of” has been updated to “under the direction of” in later protocols in keeping with psychotherapy licensure requirements.

5 Studies MT-1 and MT-2 require that subjects be enrolled in the MAPS training program (MDMA Therapy Training Program) for conducting MDMA-assisted psychotherapy or MDMA research. The MDMA Therapy Training Program is further discussed in Section IV.B.1. below.

measurement of psychological distress. The C-SSRS is used as a measure of suicidal behavior and ideation.

Study MT-1 was originally planned for a single study site at which the clinical investigator was a psychiatrist and the sub-investigator was a nurse. These two individuals were intended to comprise the psychotherapy team for all subjects. As such, the protocol did not specify any psychotherapist licensing or training requirements or include language regarding the need for a physician to carry out certain study-related activities. A second site, at which neither the clinical investigator nor either of the psychotherapy team members was a physician, was added by Amendment 3 on 16 April 2016. At the same time, the protocol was amended to require that a physician conduct medical screening of subjects to determine eligibility for participation in the study. The study physician was further required to be either on site or no more than three miles from the study site during Experimental Sessions (SN 0062). This physician requirement was updated in Amendment 4 (SN 0114) to eliminate the three mile limit, and indicate that the "study physician will be available (on site or on call) at each site during Experimental Sessions in case of medical emergencies."

(2) Study MT-2

Study MT-2, currently on clinical hold, is a Phase 1, open-label, single-arm, multi-center study intended to assess the safety and psychological effects of MDMA-assisted psychotherapy when administered to 150 healthy volunteers who are trainees in the conduct of MDMA-assisted psychotherapy or MDMA research.

As with Study MT-1, eligible subjects are not required to be diagnosed with a psychiatric disorder. Psychological effects are therefore measured via changes on validated measures of self-compassion. From a safety perspective, the educational and professional requirements for enrollment in this study and Study MT-1 are designed to ensure a subject population uniquely skilled to provide insight and important safety information about the use of MDMA to treat PTSD by isolating the psychological effect of the drug from those of PTSD itself. In addition, both studies serve to expand the training and knowledge of future treatment providers.

Each subject is intended to participate in a single one-day MDMA-assisted Experimental Session during which they will receive 120 mg MDMA followed by an optional supplemental dose of 40 mg or 60 mg MDMA administered one and a half to two hours later. The primary endpoint is the change in self-compassion between Visit 1 and Study Termination (60 days after the Experimental Session) measured using the Self-Compassion Scale (SCS). Study MT-2 endpoints also include measures of change in affect, psychological inflexibility, professional quality of life, and burnout.[6] A number of safety endpoints focused on the incidence and severity

[6] These exploratory, self-reported outcomes are measured using validated scales including the Positive and Negative Affect Schedule (PANAS), Acceptance and Action Questionnaire-II (AAQ-II), Professional Quality of Life Scale (PROQOL), and Maslach Burnout Inventory - Human Services Survey (MBI-HSS), respectively.

of AEs generally and in specific areas of special interest (AESIs) including suicidal ideation and behavior,[7] cardiac function, and abuse liability are included in the protocol.

In response to Division concerns regarding suicidal ideation and behavior, the protocol eligibility criteria were modified. Subjects with a current psychiatric diagnosis, a history of bipolar affective disorder type 1, or a history of a primary psychotic disorder assessed via the validated Mini-International Neuropsychiatric Interview (the MINI), and those presenting suicide risk (including subjects with a history of a suicide attempt within the last ten years or suicidal ideation (a score of one or greater on the C-SSRS) within the past year) are excluded. If a subject has a history or a mood disorder (other than bipolar affective disorder type I), anxiety disorder, insomnia, or ADHD, it must be resolved without requiring ongoing medication during the study. The Study MT-2 protocol also excludes any subject who requires ongoing concomitant therapy with a psychotropic drug or has any current moderate or severe alcohol or other substance use disorder based on clinical interview and on the results of the MINI.

Consistent with the Phase 3 studies, Study MT-2 requires that each site be staffed with a clinical investigator, physician, psychotherapists, and support personnel. The qualifications and responsibilities of the following personnel are of relevance to the Clinical Hold:

- Each study site has a site clinical investigator (Clinical Investigator) who is responsible for the conduct of the study. The Clinical Investigators for Study MT-2 are qualified by their scientific training and experience to conduct this MDMA study. A Clinical Investigator may or may not be a medical doctor (M.D.).

- Each study site at which the Clinical Investigator is not a physician has at least one M.D. or Doctor of Osteopath (D.O.) sub-investigator identified in the IND (the Site Physician). Site Physicians are required to be on-call and able to respond in case of a medical emergency during Experimental Sessions.[8]

- Each study site has at least one individual who holds a license from the Drug Enforcement Agency (DEA) to manage and administer Schedule I controlled substances (the Schedule I License Holder). A Schedule I License Holder may also be a Clinical Investigator, sub-investigator, and/or Site Physician.

- Each study site has at least one two-person psychotherapy team (each member, a Facilitator).

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[7] Suicide-related AESIs include the terms: suicides, suicide attempts, self-injurious behavior associated with suicidal ideation, and suicidal ideation judged to be serious or severe in the opinion of the investigator. Additionally, any elevation in C-SSRS score over baseline (any suicidal ideation or positive suicidal behavior which if present at screening would exclude study participation), is to be collected as an AESI.

[8] Notwithstanding a lack of clarity in the Study MT-2 protocol, the Site Physician is also responsible for making the determination as to whether a supplemental dose of MDMA will be administered during the Experimental Session. MAPS intends to amend the protocol to make this requirement more specific (as it has been in other of its protocols) before initiating the study.

- Each two-person team has at least one member who is licensed to provide psychotherapy according to state and local requirements and has completed the MDMA Therapy Training Program (Lead Facilitator). No specific educational pedigree is required beyond state and local requirements. Lead Facilitators are responsible for leading the Experimental Sessions. Lead Facilitators who are not Clinical Investigators are named as sub-investigators in the IND.

- The second Facilitator may be either another Lead Facilitator or be a Co-Facilitator Trainee who has at least a bachelor's degree and training in mental health (i.e., a student in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments, or 1000 hours of behavioral health experience), and either be enrolled in or have completed the MDMA Therapy Training Program.[9]

2. Clinical Hold

a. Original Clinical Hold And CR1

On 05 August 2019, the same day that FDA alerted MAPS to its concern with a suicidal ideation serious AE in Study MT-1, the Division issued the Original Clinical Hold for Study MT-2 citing its view that the study (1) presented an "[u]nreasonable and significant risk of illness or injury to human subjects," and (2) included "[u]nqualified clinical investigators." MAPS first addressed these concerns in a Clinical Hold Complete Response (CR1) on 29 August 2019 (SN 0123).

(1) Risk of Illness or Injury

The Original Clinical Hold asserted that the benefit:risk profile for subjects in Study MT-2 is unacceptable, noting cases of "blindness, severe suicidality, and intentional self-harm" in Study MT-1, questioning the scientific benefit of Study MT-2 in light of Study MT-1 and published literature reports of MDMA use in healthy volunteers, and implying that Study MT-2 would need to assess psychiatric illness (in its healthy volunteer population) in order to produce valuable data. Each of these assertions is discussed below.

(a) Extent and Management of Safety Risk

The Original Clinical Hold states,

> [t]he safety data submitted from MT-1 appears to reveal the potential for serious risk. You state that the benefit:risk ratio of

[9] An earlier version of the Study MT-2 protocol (Amendment 1 Version 1, dated 27 August 2019; SN 0123) suggested that, to the extent that the Lead Facilitator had not completed the MAPS MDMA Therapy Training Program, the second or Co-Facilitator was required to be another licensed mental health professional. Study MT-2 protocol Amendment 2 Version 1, dated 27 December 2019, removed this provision (SN 0136).

> MDMA-assisted psychotherapy in healthy volunteers remains favorable as the risks are lower than the PTSD population. However, there was a case of blindness, severe suicidality, and intentional self-harm in a population of 76 healthy subjects,

and requests that MAPS,

> justify why additional subjects (with, as you propose, a history of a mood or anxiety disorder) should be exposed to MDMA in an open-label design where all subjects would receive drug.

In response, CR1 first noted that the case of blindness referred to by FDA was, in fact, a case of blurred peripheral vision which had been incorrectly coded in the electronic case report form. The blurred vision resolved after three to four hours and before the end of the blinded Experimental Session without treatment. Including this subject, there are a total of two subjects who experienced an AE of Vision Blurred study-wide.

Regarding concerns of suicidal ideation and self-harm, CR1 noted that the eligibility criteria for Study MT-2 exclude subjects who suffer from PTSD and are thus at greater risk. CR1 also amended Study MT-1 to ensure the exclusion of potential subjects with psychiatric disorders and those with a history of mood or anxiety disorder that is not in remission ("Protocol and Synopsis MT-2 Amendment 1 Version 1," 27 August 2019 (SN 0123). Specifically, the revised protocol incorporated additional screening procedures that require subjects to be assessed for psychiatric disorders by a rater who is independent from the site and the Clinical Investigator (Independent Rater), and who is trained and experienced in use of the MINI. The Independent Rater can determine a subject is disqualified from participation in Study MT-2 on the basis of the results of the MINI. Independent Raters for Study MT-2 are taken from the same pool of professionals used for screening potential subjects in the Phase 3 study MAPP1 under the SPA. Additionally, CR1 noted that both the Site Physician and Sponsor medical monitor will review results from the MINI along with the subject's medical history, concomitant medications, physical exam, and lab test results as an extra measure before a potential subject may be enrolled in the study.

(b) Existing Data in Healthy Volunteers

The Original Clinical Hold requests that the sponsor justify a study in healthy volunteers in light of existing data, specifically noting:

> You describe Protocol MT-2 as an open-label safety study of up to 400 healthy volunteers. However, you state that a study of MDMA in 1286 healthy volunteers has already been conducted. You further state that this study will provide phase

> 1 healthy volunteer data to support new indications for MDMA-assisted psychotherapy,

and

> You must justify why MT-2 is necessary when you already are currently conducting a similar study (MT-1).

In response to FDA's stated concern, MAPS reduced the number of subjects planned for Study MT-2 from 400 to 150 in the revised protocol submitted to FDA concurrently with CR1 (SN 0123).

In addition, MAPS clarified that the Original Clinical Hold's implication that 1286 healthy volunteers had been exposed to MDMA under a MAPS-sponsored IND was incorrect. At the time of the Original Clinical Hold, MDMA had been administered to 286 subjects (including healthy volunteer subjects) under the MAPS-sponsored INDs. The additional 1000+ subjects emanated from studies reported in the published scientific literature and conducted without MAPS involvement. Consequently, MAPS did not and does not have access to systematically collected and monitored subject-level data from these studies. As noted in CR1, while these published data are supportive of the safety profile of MDMA in a controlled setting, they cannot substitute for systematically assessed data from a MAPS-sponsored study under its IND.

CR1 highlighted design differences between Study MT-1, a double-blind placebo-controlled crossover study, and Study MT-2, an open-label safety and training study. Study MT-2, by virtue of its larger size, is better positioned to provide important data regarding the safety profile of MDMA-assisted psychotherapy. The primary and exploratory outcome measures from Study MT-2 in healthy volunteers are intended to capture important data which are not being captured in Study MT-1.

(c) Contribution of Data Relevant to Psychiatric Illness

The Original Clinical Hold noted that the primary endpoint in Study MT-2 is measured by the SCS Scale and stated, "[l]ack of self-compassion is not a recognized psychiatric illness," and "[y]ou must justify how the data obtained from [Study MT-2] will contribute to your development program for MDMA in psychiatric illness."

In response, CR1 clarified that Study MT-2 was not intended to be a registration study and the information obtained was to be used for research purposes.[10] CR1 also noted that

[10] Note that, in light of the applicability of Study MT-2 to a variety of potential indications and its potential to provide useful publication data, MAPS originally submitted the protocol for Study MT-2 to a new IND 142908, under which it intended to conduct more general MDMA-related research. On 11 April 2019, the Division indicated via e-mail that it believed a study in healthy normal volunteers was "inappropriate" in light of the open IND for the study of MDMA in the treatment of PTSD. The Division advised that the protocol could be submitted to PTSD IND 63384, but that it would most likely be placed on a clinical hold due to unspecified safety concerns. MAPS updated the protocol based on experiences in MT-1 and submitted Study MT-2 to IND 063384 on 21 May 2019 (SN 0117) upon which the Division promptly issued the Original Clinical Hold. MAPS takes no position regarding which IND should house Study MT-2

MDMA's ability to enhance self-compassion is germane to PTSD as evidenced by endpoints included in the Phase 3 PTSD trials, MAPP1 and MAPP2, which are designed to explore the relationship between PTSD symptom severity and self-compassion. As described in CR1, other studies have found that patients with PTSD may improve by combining elements of self-compassion into their treatment plans (Thompson et al., 2008).

(2) Clinical Investigator Qualifications

As a second reason for imposition of the clinical hold, the Original Clinical Hold correctly set forth the required minimum qualifications of Facilitators:

> all psychotherapy sessions will be conducted by at least one trained, qualified, and licensed therapist, who will be accompanied by an observer. The observer may be a second licensed therapist or a trainee who is enrolled in or has completed a therapy training program under the auspices of the sponsor (if both the therapist and participant agree). Each licensed therapist will hold a certificate from the MAPS Therapy Training Program specifying their approved status

followed by an incorrect assertion that the requisite qualifications were lower than those in the Phase 3 studies. Specifically, the letter stated,

> You must explain why the therapists' requirements will be safe for healthy volunteers when the proposed therapists are less qualified than in your phase 3 trials.

In CR1, MAPS provided detailed information about the qualifications of the Clinical Investigators, Site Physicians, and Facilitators conducting Study MT-2. CR1 also noted that the protocol for Phase 3 Study MAPP1 does not require any higher level of Facilitator education or licensure than is required for Study MT-2. It requires that all members of the two-person therapy team have the "proper background, education, and experience," and that at least one of the Facilitators be licensed to provide psychotherapy according to applicable law. If one of the two is unlicensed, the unlicensed Facilitator will work under the direct supervision of the licensed Facilitator.

b. Continue Partial Clinical Hold Letters And Responses

On 27 September 2019, MAPS received a Continue Partial Clinical Hold Letter documenting the Division's view that the issues had not been resolved. In that letter the Division requested additional justification that the benefits of MDMA outweigh the risks for healthy individuals, again noting a prior suicidal ideation event (but not mentioning blindness or suicidal

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and would move the protocol to a research specific IND if that would better serve the FDA's regulatory needs.

behavior) and juxtaposing the Phase 2-derived suggestion of direct clinical benefit to PTSD subjects with the lack of similarly demonstrated benefit to healthy volunteers.

In addition, the September 2019 Continue Partial Clinical Hold Letter, for the first time, set forth requirements for Study MT-2 to have a physician on site during Experimental Sessions, and a doctoral-level Lead Facilitator. As with its previous assertions regarding Facilitator licensing, the Division incorrectly asserted that these educational requirements were in place for the Phase 3 studies and stated that Study MT-2 should have identical requirements to those Phase 3 studies. These comments are in direct opposition to the SPA-agreed protocol for Study MAPP1 which does not include such language.

MAPS responded on 11 October 2019, again correcting the Division's error, providing the additional requested information and justifications and requesting reconsideration by the Division in accordance with 21 C.F.R. §§ 312.42(f) and 312.48(c) (SN 0126). Having received no reply to its reconsideration request in two and a half months, on 31 December 2019, MAPS submitted a second Clinical Hold Complete Response (CR2) (SN 0136) in an effort to engage the Division in a scientific discussion. CR2 included new supportive data, an amended protocol restricting study eligibility criteria, and an analysis of the risk:benefit balance for healthy individuals in Study MT-2.

The Division issued a second Continue Partial Clinical Hold Letter on 30 January 2020 which, with remarkable brevity, indicated the issues had not been resolved to its satisfaction. This letter included no further articulation of the Division's rationale or any response to the specific arguments or data in either the Sponsor's 11 October 2019 or its 31 December 2019 submissions, including the protocol amendment.

Having reached an apparent impasse with the Division, the Sponsor submitted a Type A Meeting Request which included a succinct 18-page Briefing Document on 20 April 2020 (SN 0146). The meeting questions sought to further understand the Division's views of the data, amendments, and justifications previously submitted with the objective of reaching agreement on a path forward. Each question was supported by a concise summary of the relevant information from the prior submissions in an effort to streamline the Division's review. Ten days later, on 30 April 2020 FDA, DP denied the meeting request, "because the meeting package is not submitted with the meeting request and the meeting request does not propose discussion of new information." In a 01 May 2020 email, MAPS clarified that the meeting request itself included all information intended to be provided for the meeting. The Division did not respond to this email.[11]

[11] Via email to Counsel, JM Torrente, dated 7 May 2020, Melissa Sage, CDER Formal Dispute Resolution Project Manager, confirmed that the Division's refusal to grant the meeting would meet the threshold for requested reconsideration to allow adjudication of the issues via formal dispute resolution.

III. Regulatory Standard For Imposing A Clinical Hold

The Food, Drug, and Cosmetic Act (FDC Act) provides that the Agency may place a clinical trial on clinical hold if the Agency determines that,

> the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; …[or] for such other reasons as [FDA] may [issue a determination] by regulation. (FDC Act § 505 (i)(3)(B))

FDA's implementing regulations provide that the following findings by FDA are grounds for imposing a clinical hold of a proposed or ongoing Phase 1 study under an IND:

> (i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
> (ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;
> (iii) The investigator brochure is misleading, erroneous, or materially incomplete; or
> (iv) The IND does not contain sufficient information required under § 312.23 to assess the risk to subjects of the proposed studies. (21 C.F.R. § 312.42(b)).

The first two of these criteria were cited by the Division in imposing and continuing the Clinical Hold.

IV. Argument

The Division maintains that Study MT-2 may not proceed because benefits to healthy study subjects do not outweigh the risks of suicidal ideation/behavior to those subjects, psychotherapy Facilitators are not required to have doctoral degrees, and physicians are not required to be on site during MDMA-assisted psychotherapy sessions. MAPS disagrees with each of these positions. Regarding the risks and benefits, Section IV.A will establish that (1) there is no meaningful risk of suicidal ideation/behavior from MDMA exposure in the Study MT-2 population, (2) Study MT-2 is designed to capture important safety information that cannot be obtained in a PTSD population, and (3) the benefits to subjects in Study MT-2 are consistent with or greater than the sorts of benefits typically seen in Phase 1 studies. Regarding

investigator qualifications, Section IV.B will establish that neither doctoral degrees for the Lead Facilitator nor on-site physicians are necessary to ensure subject safety.

A. Study MT-2 Would Not Expose Subjects To An Unreasonable And Significant Risk Of Illness Or Injury

1. No Signal Of Increased Risk Of Suicidal Ideation Or Behavior Has Been Identified In The MDMA Clinical Development Program

To support its statement that MT-1, "appears to reveal the potential for serious risk," the Original Clinical Hold cites "a case of blindness, severe suicidality, and intentional self-harm in a population of 76 healthy subjects."[12] The 27 September 2019 Continue Partial Clinical Hold Letter goes on to note the Division's "concerns about an adverse event (i.e., de novo suicidal ideation) occurring in a healthy subject in trial MT1." The 30 January 2020 Continue Hold Letter does not expressly mention AEs, but states that the Division disagrees with Sponsor's justification of scientific benefit for MT-2.

Contrary to the Division's assertion, there have been no (zero) de novo instances of suicidal ideation or behavior reported in the 122 heathy normal volunteers who have received MDMA in the clinical development program and there have been no instances of suicidal behavior in heathy normal volunteers. A single instance of suicidal ideation was reported in a healthy normal subject (Subject [redacted]) that occurred and resolved during a blinded Experimental Session with either MDMA or placebo in Study MT-1. The event was not de novo. Specifically, Subject [redacted]'s medical history includes a previous report of suicidal ideation and behavior 11 years prior to enrollment in Study MT-1. In addition, the lifetime C-SSRS administered to the subject during screening reflected a positive score of lifetime suicidal ideation (5), intensity of 10/25, and a positive for lifetime history of suicidal behavior. MAPS has provided additional information about the subject's history to the Division on several occasions but has not been able to ascertain whether the Division agrees that the case was not de novo. [13]

Moreover, the event in Subject [redacted] did not involve suicidal behavior. As reported in the 06 November 2019 IND Safety Report (SN 0129), during the second blinded Experimental Session, the subject engaged in non-suicidal self-injurious behavior, including putting her hand near a candle flame and hitting her head against a couch and with a foam bat. None of these actions posed the risk of serious injury and none resulted in injury. The subject expressed suicidal ideation in the form of a desire to run out into traffic while she was walking around the therapy room. One of the Facilitators stood in front of the exit door as a precautionary measure,

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[12] The Division has not mentioned "blindness" again since the 5 August 2019 Original Clinical Hold. As explained in CR1, the case of blindness to which FDA referred was incorrectly coded. We have assumed that the Division agrees that MDMA does not present an unreasonable and significant risk of blindness to Study MT-2 participants, but have not received any confirmation from the Division.

[13] This distinction is important. Prior suicidal ideation and behavior are the strongest predictors of suicidal ideation or behaviors (Franklin et al., 2017).It is noteworthy that an additional four healthy normal subjects in Study MT-1 reported lifetime suicidal ideation or behavior at study entry but did not suffer any ideation or behavior during the treatment period.

for the subject's safety. The subject did not try to move past her. Suicidal ideation decreased from active (with method and some intent) to passive by the end of the Experimental Session. The emergence of the suicidal ideation during Subject [redacted]'s therapy session was promptly and fully managed by the Facilitators consisting of a licensed therapist (Lead Facilitator) and nurse (Co-Facilitator), and resolved during the therapeutic session without involvement of the on-call physician.[14] Three days following the session, the subject's remaining passive suicidal ideation resolved with a C-SSRS Score of 0-0-No.

In light of Subject [redacted]'s pre-enrollment history of suicidal ideation, and in response to the Division's concerns, the Sponsor revised eligibility criteria for Study MT-2 in a protocol amendment submitted with CR2 (SN 0136) in an effort to minimize exposure of subjects at some increased risk for such ideation. As discussed in Section II.C.1.b(2), the revised criteria exclude subjects with a history of a suicide attempt in the last ten years, suicidal ideation within the past year, or any psychiatric diagnosis requiring chronic medication except ADHD or insomnia.

Additional protocol revisions were made to require that eligible subjects have previously undergone personal psychotherapy and to require, as an additional precaution, that eligibility for enrollment in Study MT-2 be confirmed by the Site Physician and Sponsor medical monitor after a review of medical history, MINI results ascertained by the independent raters, concomitant medications, physical exam, and laboratory testing results. The Division has not provided its view on the extent to which these modifications address its concerns regarding risk to subjects.

Further evidence that the Division's concerns regarding a risk of suicidal ideation in the proposed healthy volunteer population of Study MT-2 are misplaced comes from the data in PTSD patients. A highly significant positive association between a PTSD diagnosis and suicidality has been confirmed via a published meta-analysis of PTSD studies that analyzed different measures of suicidality, current and lifetime PTSD, psychiatric and nonpsychiatric samples, and PTSD populations exposed to different types of traumas (Panagioti et al., 2012). Consistent with this known association, there have been reports of suicidal ideation and behavior in MAPS' Phase 2 studies which involved subjects with PTSD, but with no signal implicating MDMA. That is, the unblinded Phase 2 data show no imbalance between groups in positive or serious responses to the C-SSRS or other signal of MDMA-related suicidality risk during or after Experimental Sessions despite the heightened risk threshold associated with PTSD.[15] C-SSRS data from the recently unblinded pivotal Phase 3 PTSD trial, Study MAPP1, confirm the absence of safety findings seen in Phase 2 data but are not included here because they were not submitted to the IND at the time of the clinical hold. At the last independent Data Monitoring Committee (iDMC) review of unblinded aggregate data of the MAPP1 Study (data as of 05 May 2020), with

[14] The subject, herself a licensed therapist, described the experience as follows: "[m]y therapists did an amazing job keeping me safe during my MT1 experience. I did experience some suicidal thoughts; however, the thoughts eventually passed. I did not engage in self-harm behaviors."

[15] Data from Studies MP-4, MP-8, MP-9, MP-12, MP16, MP17, and MPVA-1 are reported in the Investigator's Brochure (11th Edition 2019, dated 10 July 2019 SN 0120; 12th Edition 2020, dated 17 August 2020 SN 0154). Data from Studies MP-1 and MP-2 are not included because suicidal ideation and behavior were not formally measured in those studies. Data from Study MP-3 are not included because that study terminated early.

91 subjects randomized in Phase 3 and a total of 11 IND Safety Reports[16] related to suicidal ideation or behavior in seven subjects across all treatment groups in the program, the iDMC expressed no concerns regarding suicidality.[17]

To recap, the MDMA development program includes a single event of suicidal ideation in a healthy volunteer. The event occurred and resolved during a blinded Experimental Session in which the subject was administered either MDMA or placebo. The subject had a prior history indicative of increased risk independent of drug exposure. Phase 1 study protocols have since been amended to exclude subjects with this or similar risk profiles. The Phase 2 and 3 programs in PTSD similarly reveal no increase in the risk of suicidal ideation or behavior between groups despite the expected incidence of such events in this population.[18] Not only has MDMA shown no positive signal of risk in either MAPS-sponsored or independently conducted MDMA studies reported in the literature, the conduct of Study MT-2 in a population without PTSD lowers the baseline (non-drug associated) risk. MAPS disagrees that there is any signal of potential MDMA-associated suicidal ideation (or blindness or suicidal behavior), much less a signal sufficient to justify a clinical hold, the standard for which is "unreasonable and significant."

2. The Benefits Inherent In Study MT-2 Are Sufficient To Offset The Risks To Study Subjects

The Clinical Hold asserts that MAPS has not justified a potential benefit to healthy subjects that could offset the identified risk. Having established that there is effectively no signal of risk for subjects who will participate in Study MT-2, we now turn to the benefits of the study which, like all Phase 1 research, accrue in large part to society, as well as the unique potential benefits to Study MT-2 participants themselves.

a. The Benefits Of Study MT-2 Are Consistent With, Or Greater Than, Those From Other Phase 1 Studies In Healthy Volunteers

The Clinical Hold suggests that Phase 1 MDMA research is de facto objectionable because Phase 1 subjects (who by definition do not suffer from PTSD) do not have the potential for the direct clinical benefit that was seen in the Phase 2 program ("Your phase 2 data suggest that patients with PTSD have the potential for direct clinical benefit in the context of these ongoing phase 3 trials. However, healthy subjects have no such potential benefit; you have not

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[16] We note for completeness that several of these IND Safety Reports were submitted retrospectively in response to a request from the Division on 01 Nov 2019. As described in MAPS' response to the inquiry (SN 0129, resubmitted with correction as 0132), the Sponsor's original assessment of the events concluded that they did not warrant expedited reporting in light of language in the Investigator's Brochure highlighting the high incidence of suicidal ideation and behavior in populations of people with PTSD. Following the Division's request, MAPS updated its understanding of reportability and amended protocols for ongoing studies accordingly.

[17] As of 01 August 2020, a total of 16 IND Safety Reports (all of which related to suicidal ideation or behavior in 11 subjects) have been submitted. As of that same date, a total of 122 healthy subjects and 281 subjects with PTSD or other diagnosis had been exposed to MDMA in the clinical development program.

[18] The Phase 2 data, in fact, show an imbalance in both non-serious and serious suicidal ideation with more events occurring in Experimental Session with placebo than with MDMA.

provided a valid scientific rationale to justify the potential risks to these individuals" (Continue Clinical Partial Hold Letter, 27 September 2019). "[It] is not clear what, if any, potential benefit healthy volunteers may expect to experience" (Continue Partial Clinical Hold Letter, 30 January 2020).).

Phase 1 studies often do not, and are not required to, provide a direct benefit to healthy volunteer subjects. Many Phase 1 studies of drugs with serious or unknown safety risks are conducted in healthy volunteers and assess the effects of a drug without offering any potential direct benefit to subjects. The benefits that permit Phase 1 research are typically the benefits to society and not those to the individual subjects. FDA and the Department of Health and Human Services have long recognized that the benefits to society from Phase 1 studies are substantial and that such studies permit improved knowledge and development of novel medical, psychotherapeutic, and social procedures. The Informed Consent regulations expressly acknowledge that there may be studies that do not provide direct benefit to study subjects but rather that the benefits may accrue to others (21 C.F.R. § 50.25(a)(3)).

Study MT-2 will provide additional safety and pharmacodynamic information for use of MDMA in a therapeutic setting. As described above in Section II.C.2.a.(1), MAPS has not studied and does not have access to, or a right of reference to, the underlying data from the 1286 healthy volunteers reported in the medical literature as asserted in the Original Clinical Hold. Further, those data are not derived from MDMA administered in a therapeutic setting relevant to PTSD. While efficacy and safety of MDMA in PTSD will be principally derived from the data and AE collection in the controlled Phase 3 clinical program, Phase 1 and 2 studies, including single-arm studies such as MT-2 also play a significant role in understanding product safety and pharmacodynamics. Study MT-1, in healthy normal volunteers at relatively low risk for intrinsic psychological complications, provided important information regarding safety as well as changes in the Profile of Mood States, Interpersonal Closeness, and the NEO Personality Inventory between Baseline and 60 days after Experimental Sessions. Study MT-2 is designed to augment the Study MT-1 data with information from a larger (n=150) cohort of subjects. From a safety perspective, all subjects will have psychotherapy training or education germane to reporting of suicidal ideation and behavior. In terms of pharmacodynamics, subjects will be assessed using different instruments than were used in MT-1, including the SCS, Acceptance and Action Questionnaire, Positive and Negative Affect Scale, and Professional Quality of Life Scale, and followed for a 60-day safety observation period after Experimental Sessions.

Study MT-2 is designed to produce actionable information about the psychological effects of MDMA when administered in a therapeutic setting from subjects who, unlike those who participate in Phase 3 trials, do not have an active diagnosis for a mental condition that may confound the experience and make it more difficult to isolate the effects of the drug alone. The subjects in Study MT-2 are better positioned to provide more insight into those psychological experiences by virtue of their education or training as mental health professionals. The information gathered from Study MT-2 will augment, rather than duplicate, the information available in the published literature and the safety data MAPS has generated through its previous and ongoing clinical trials.

b. Study MT-2 Subjects May Experience Positive Personal And Professional Benefits From Study Participation

As in Study MT-1, subjects in Study MT-2 will participate in an initial psychotherapy Preparatory Session before receiving MDMA in an Experimental Session and will also participate in a final psychotherapy Integrative Session. Although the possibility of direct personal benefit to study subjects is not a requirement for Phase 1 research, Study MT-2 subjects may benefit personally from the therapy sessions that are part of the trial. Psychotherapy can have a positive impact on emotions and behaviors, increasing emotional regulation and personal understanding. Consistent with this, of 79 heathy normal volunteers enrolled in Study MT-1 who responded to a survey (96.3% response rate), the majority reported personal benefit from study participation. On a 7-point Likert-scale ranging from 0 (Not at all) to 6 (Greatly), study subjects reported an average of 5.6 out of 6 to the question "*How personally beneficial was your experience participating in the MT-1 clinical trial where you received MDMA-assisted psychotherapy in a clinical therapeutic setting?*"

Additionally, practitioners of psychotherapeutic methods such as trauma-focused cognitive behavioral therapy, prolonged exposure therapy, and psychoanalysis consider their personal experience with those modalities to be a beneficial part of their training (Grimmer et al., 2001; Rake et al., 2009). Because all Study MT-2 subjects have education or training in psychotherapy with an expressed interest in MDMA-assisted therapy, they may benefit from becoming familiar with the patient experience in MDMA-assisted therapy. While this potential benefit is not able to be assessed directly, to the extent that subjects in Study MT-2 go on to treat PTSD patients with MDMA-assisted psychotherapy in future clinical trials or the post-approval setting, their experience in Study MT-2 may improve their skills in treating future patients. Consistent with this, on the same survey, MT-1 subjects reported an average of 5.8 out of 6 to the question, "*Do you think your MT1 experience increased your qualifications to provide MDMA-assisted psychotherapy?*"

3. The First Clinical Hold Criterion Is Not Supported By The Data, Study Design, Or Precedent

In summary, the level of risk of illness or injury necessary to impose a clinical hold is "unreasonable and significant." The risk of suicidal ideation in heathy normal volunteers generally, and certainly in those healthy normal volunteers who meet the revised study entry criteria, does not meet either prong of this test. That is, the level of risk is neither unreasonable nor significant as there is no evidence whatsoever of MDMA-associated suicidal ideation or behavior risk in this population. The benefits inherent in Phase 1 research, the opportunity to collect additional valuable information about the safety and effects of MDMA in a therapeutic

setting, and the potential for direct benefit to study subjects far outweigh the theoretical risk, taking it even farther from the requisite "unreasonable and significant" standard.

B. Study MT-2 Investigators Are Qualified By Reason Of Their Scientific Training And Experience To Conduct The Study

The Study MT-2 Protocol requires that a medical physician (i.e., the Site Physician) be on-call and able to respond in case of a medical emergency during the Experimental Session and that two Facilitators be present for each Experimental Session: a Lead Facilitator licensed to practice psychotherapy according to state and local requirements and a Co-Facilitator who, if not qualified as a Lead Facilitator, has a bachelor's degree and training in mental health.

The Clinical Hold maintains that the proposed investigator qualifications are unacceptable and the following are required: (a) the medical physician must be physically on site during each Experimental Session during which MDMA is administered and cannot be on call, and (b) the Lead Facilitator of the two-person therapy team must be a doctoral (Ph.D./M.D.)-level psychotherapist.[19] There is no evidence to support the Division's position that either of these requirements is necessary to prevent unreasonable risk in Study MT-2 and, contrary to assertions in the Clinical Hold, neither is included in the Phase 3 studies.

1. Study MT-2 Investigator Qualification Requirements Are Not Materially Different Than Phase 3 Qualification Requirements

With respect to the availability of a physician during an Experimental Session, the Phase 3 Study MAPP1 Protocol provides the following:

> In the event of a medical emergency or any other medical problem during an Experimental Session, the site physician will be immediately available by telephone, and based on assessment of the situation, they will make the decision to either evaluate the participant themselves at the site, have the therapy team call EMS to transport the participant to the ED, or instruct the therapy team to take the participant to the ED**.**

The Study MAPP1 Protocol also provides that the Site Physician will approve or deny the administration of the supplemental dose, an activity that does not require in-person review. In both Studies MT-2 and MAPP1, a physician must be on call but need not be physically present during Experimental Sessions.

With respect to Facilitator requirements, the Sponsor-proposed qualifications for Study MT-2 are essentially the same as those in the Phase 3 Study MAPP1. For both Study MT-2 and Study MAPP1, two-person therapy teams are required for all therapy sessions (Preparatory, Experimental, and Integrative). In both studies, at least one member of the two-member team

[19] We note that the regulations do not specify minimum requirements or qualifications such as a particular educational pedigree for a clinical investigator or other study personnel to be considered qualified by training and experience to conduct a clinical investigation (21 C.F.R. §312.53).

must be licensed as required by applicable law to provide psychotherapy (the Lead Facilitator), and, if the other person on the therapy team is unlicensed, they will work under the direction of the Lead Facilitator.

The requirements for Study MT-2 set forth in the Clinical Hold are a wholly new set of criteria and are not consistent with previously agreed upon Site Physician and Lead Facilitator qualifications for Phase 3 trials in which the subjects suffer from chronic severe PTSD. The Division has not responded specifically to this point or explained its position that Study MT-2 in healthy normal volunteers warrants more stringent requirements for the physician to be on site or for the Lead Facilitator to have earned a higher educational degree.[20]

2. Doctoral Degrees Are Neither Necessary Nor Sufficient To Ensure Subject Safety

Depending on the licensure requirements of the state in which a particular study site is located, Lead Facilitators (who must be licensed psychotherapists) could be a master's level psychotherapists or registered nurses as well as Ph.D./M.D.-level psychotherapists. The Division has stated regarding Study MT-2 that "[g]iven the known medical risks of the study drug, including previously reported adverse events from your own program, we continue to require the following [Clinical Investigator] requirements to ensure patient safety… Lead Facilitator should be a doctoral-level Ph.D./M.D.-level psychotherapist (or equivalent)" (Continue Partial Clinical Hold Letter, 30 January 2020).

The Division has provided no rationale or literature references for its stated view that educational degree, rather than licensure as a psychotherapist, is the critical requirement to minimize risks to subjects in Study MT-2.[21] We know of no reason to believe that a doctoral degree is necessary or important to ensure the safety of trial subjects during MDMA-assisted psychotherapy sessions. Such credentials are not an indication of more extensive training or experience in the practice of psychotherapy as compared to master's level psychologists and clinical social workers. Indeed, a search of relevant literature provided no evidence that a Lead Facilitator with advanced academic credentials (an Ph.D. or M.D. or equivalent) would ensure

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[20] We note for completeness that the Division has required a doctoral level facilitator in the two studies submitted after Study MT2 (i.e., Study MED1 in eating disorders which is being conducted under a separate IND, and Study MPVA6 in PTSD).

[21] With respect to Lead Facilitator qualifications, the Sponsor has obtained an indirect signal that the Division may have softened its position. Specifically, on 16 June 2020, the Division issued a Partial Clinical Hold letter to the Sponsor for Study MPVA-6 (a Phase 2 study in military veterans with chronic PTSD) in which it provided "updates with [the Division's] current thinking" for requirements for clinical staff: Lead Facilitator must be either a doctoral (Ph.D./M.D.)-level psychotherapist (or equivalent) with active licensure *or a master's level psychotherapist with active licensure*, Co-Facilitators should have a bachelor's degree and be trained in mental health, and an on-site physician (i.e., in the same building as the patient) during the Experimental Sessions. The Division has not, however, provided the Sponsor with any updated view of the Facilitator qualification requirements as they apply to Study MT-2.

patient safety more than a Lead Facilitator with relevant therapeutic competence with a master's level degree.[22]

To the contrary, evidence suggests that training in psychotherapy is the most critical component for ensuring the psychological well-being of subjects (Nielson et al., 2018). Lead Facilitator qualifications for Study MT-2 are appropriately focused on ensuring extensive psychotherapeutic training and experience, including completion of the MDMA Therapy Training Program which provides specific training in the MDMA-assisted psychotherapy method. Training consists of course reading, an online training module, and a week-long live training program that includes watching and discussing videos of Experimental Sessions. Finally, the trainee's skills as a facilitator are evaluated in at least one MDMA-assisted therapy session with oversight and under supervision, generally in an open-label study, such as Study MP16 or Study MP17.

A comparison of the AEs reported for therapy pairs that did and those that did not include a doctorate level psychotherapist as Lead Facilitator in the Sponsor's development program reveals very little difference. As of 03 March 2020, across subjects enrolled in Phase 2 or Phase 3 PTSD studies, 44 subjects participated in Experimental Sessions conducted by a Lead Facilitator with a master's degree while 234 subjects had participated in Experimental Sessions conducted by a Lead Facilitator with a doctoral degree.[23] Event-level AE data show that subjects who participated in Experimental Sessions conducted by teams in which the Lead Facilitator had a master's degree averaged a total of 7.95 AEs (including 2.82 psychiatric AEs) per enrolled subject while subjects who participated in Experimental Sessions conducted by teams in which the Lead Facilitator had a doctoral degree similarly averaged a total of 7.75 AEs reported (including 2.59 psychiatric AEs) per enrolled subject. Determinations of "seriousness" and "severity" of AEs were also similar across subjects regardless of whether their psychotherapy sessions were conducted by doctoral-level teams or by master's level teams. Master's level teams reported an average of 0.07 serious and 0.23 severe AEs per enrolled subject while doctoral-level teams reported an average of 0.05 serious and 0.22 severe AEs per enrolled subject.

3. An On-site Physician Is Not Necessary To Ensure Subject Safety

The Clinical Hold Letter states that the

> current description of the Clinical Investigator (CI) Qualifications in your Protocol MT-2 remains unacceptable: The CI and the medical physician are allowed to be off-site and delegate duties to less qualified staff (under 21 C.F.R. §312.42(b)(1)(ii)) to prescribe and monitor the use of an unapproved, Schedule I substance. We do not agree with your justification. Given the known medical risks of the study drug,

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[22] The sponsor has previously submitted over 20 letters from experts in the field speaking against the requirement for therapists to hold doctoral level degrees (SN 0136).

[23] At the time of this data collection, some subjects with AE reports may have participated only in Preparatory Sessions but are nonetheless included in this analysis.

> including previously reported adverse events from your own program, we continue to require the following CI requirements to ensure patient safety … on-site physician (not on-call). (30 January 2020 Continue Clinical Hold Letter)

To be clear, the Study MT-2 protocol does not permit a Site Physician to delegate the duty to prescribe to staff who are not qualified to prescribe a Schedule I substance. Each Study MT-2 site is required have a Schedule I License Holder who fulfills DEA Schedule I license requirements, and a Site Physician who fulfills medical oversight requirements. Consistent with DEA regulations, the DEA registered practitioner may authorize a delegate to administer drug under their DEA registration (21 C.F.R. § 1301.22). The Study MT-2 protocol specifically calls for "appropriately qualified personnel who will be licensed to manage and administer Schedule I controlled substances and may authorize a delegate (per DEA requirements) to administer drug under their license" (MT-2 Protocol Section 4.2.1). All DEA requirements for administration under the license of the Schedule I License Holder must be fulfilled. Such requirements do not include the presence of the prescriber or a physician on site at the time of drug administration.

The duty to monitor the subjects while under the effects of MDMA is shared by both the Facilitator/Co-Facilitator team on site during an Experimental Session and the Site Physician who remains available on-call at all times during the Experimental Session. As noted above, MAPS' Phase 3 Study, MAPP1, which is a study in PTSD patients—a more vulnerable population—also provides that the Site Physician must be on-call. While MDMA is a Schedule I controlled substance, its known potential adverse effects, as described below, are not of the sort that would be better monitored by a physician or that would require immediate physician involvement.

The Sponsor conducted a risk assessment based on Phase 2 data utilizing a Risk Assessment and Categorization Tool. This analysis, including a review of study eligibility criteria and procedures for managing identified risks, was set forth in the protocol for Study MAPP1. Upon review, the Division stated that it agreed with Sponsor's risk assessment and proposed risk management measures which did not include the presence of an on-site physician (4 April 2017 Type A Meeting SPA Non-Agreement Discussion (SN 0077)). A short summary follows.

No high-level risks of MDMA were identified in MAPS' clinical trials to date. The medium level risks identified were cardiovascular/cerebrovascular risk (CV Risk) and psychological distress. Psychological distress has been addressed infra and we note that psychotherapy teams are particularly skilled at monitoring and handling psychological risks. CV Risk is managed primarily by excluding subjects with pre-existing uncontrolled hypertension, a history of myocardial infarction or cerebrovascular incident or aneurysm, among other specific medical histories, and by monitoring blood pressure, body temperature, and pulse. This monitoring is standardized through the use of equipment that does not require physician involvement. The same monitoring is incorporated into Study MT-2.

The risk assessment identified a low-level risk of slight increase in body temperature, which is monitored during Experimental Sessions. Minimal risks identified through the risk

assessment include common expected adverse effects which have been observed in Experimental Sessions to be transient and diminish as MDMA effects wane during the Experimental Session and over the 72 hours after dosing. The most common acute reactions at any severity in MAPS' clinical trials were tight jaw, lack of appetite, dizziness, nausea, and reactions related to thermoregulatory and osmoregulatory effects. Adverse effects that occurred at a higher rate than placebo were sensitivity to cold, perspiration, dry mouth, and thirst. Most AEs reported in the clinical development program fully resolved or returned to baseline with minimal intervention. None of these AEs is of the sort that would require a physician to be present to avoid serious harm.

A comparison of AE reporting across study sites in the Sponsor's overall MDMA clinical program does not reveal a differential outcome based on presence or absence of an on-site physician.[24] As of 03 March 2020, across subjects enrolled in Phase 2 or Phase 3 PTSD studies, 180 subjects had participated in Experimental Sessions with a physician on site while 98 subjects participated in Experimental Sessions with a physician on-call.[25] Event-level AE data show that teams with a physician on site reported an average of 7.28 AEs per enrolled subject while teams with an on-call physician similarly reported an average of 8.67 AEs per enrolled subject. In both conditions, comparable rates around determination of "seriousness" and "severity" of AEs were reported. Physician on site averaged 0.06 serious and 0.21 severe AEs per enrolled subject and teams with an on-call physician averaged 0.04 serious and 0.24 severe AEs per enrolled subject.

Taking into consideration what is already known about the risks associated with MDMA, there is no reasonable basis to conclude that the presence of an on-site physician would reduce AE frequency, duration, or severity.

V. Conclusion

As the Sponsor has illustrated in its several responses to the Clinical Hold (including CR1, CR2 and the Meeting Request), Study MT-2 would not expose the healthy volunteer subjects to an unreasonable or significant risk of illness or injury and the Clinical Investigators and Facilitators conducting the study are qualified by reason of their training and experience, evidenced by licensure by applicable government authorities. The Sponsor does not have the benefit of the Division's substantive thinking about the corrections the Sponsor has provided to misstatements of fact or to the modifications the Sponsor has made to the study protocol. The information provided demonstrates that there is no credible basis for continuing the Clinical Hold.

We request that ON find that Study MT-2, as currently designed, may proceed and direct the Division to remove the Clinical Hold.

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[24] Because the MDMA study protocols under IND 063384 do not require an on-site physician, the analysis considered cases in which a facilitator was also a physician as having an physician "on site."

[25] At the time of this data collection, some subjects with AE reports may have participated only in Preparatory Sessions but are nonetheless included in this analysis.

* * * * *

All of the documents necessary for resolution of these issues are part of the FDA's administrative file for MDMA under IND 063384 or IND 142908 or matters of public record. The Division has had an opportunity to review all the documents and information listed and described above and to discuss these issues with Sponsor.

MAPS is eager to resolve the issues raised in this FDRR and would be pleased to provide ON with any additional information it may need during its review. MAPS is requesting a meeting with the appellate officer of ON prior to their rendering a decision on this appeal.

Attachment 1

Table 1 Ongoing and Completed Clinical Studies

Study Number	Phase	Population	Design	No. of Subjects (Enrolled/Planned)	Status
MT-1	1	Healthy volunteers	Multicenter, Placebo-controlled, Randomized, Blinded, Crossover	89/120	Ongoing
MT-2	1	Healthy volunteers	Multicenter, Single Arm	N/A	On clinical hold
MPVA-4	1	Healthy volunteers with previous MDMA experience	Single center, Placebo-controlled, Randomized	34/30	Completed
MPVA-6	2	PTSD in veterans	Single center, Single Arm, Open-label	0/60	Ongoing
MP-1	2	PTSD in crime victims, veterans	Single center, Placebo-controlled, Randomized, Blinded, Open label crossover to MDMA	23/21	Completed
MP-2	2	PTSD	Single center, Active-controlled, Randomized, Blinded, Open-label crossover to MDMA	14/12	Completed
MP-3	2	PTSD	Single center, Active-controlled, Randomized, Blinded, Open-label crossover to MDMA	5/12	Terminated early
MP-4	2	PTSD	Single center, Placebo-controlled , Randomized, Blinded, Open-label crossover to MDMA	6/12	Terminated early
MP-8	2	PTSD in veterans, firefighters, police	Single center, Active-controlled, Randomized, Blinded, Open-label crossover to MDMA	26/24	Completed
MP-9	2	PTSD	Single center, Active-controlled, Randomized, Blinded, Open-label crossover to MDMA	10/10	Completed
MP-12	2	PTSD	Single center, Active-controlled, Randomized, Blinded, Open-label crossover to MDMA	28/23	Completed
MP16	2	PTSD	Multicenter, Single arm, Open label	38/60	Completed
MP17	2	PTSD	Multicenter, Single arm, Open label	4/5	Completed
MPVA-1	1/2	Dyads - 1 w/ PTSD ; 1 w/o PTSD	Single center, Open label	12/20	Terminated early
MAA-1	2	Autism w/ social anxiety	Single center, Placebo-controlled, Randomized, Blinded, Open label crossover to MDMA	12/12	Completed
MDA-1	2	Anxiety related to life-threatening illness	Single center, Placebo-controlled, Randomized, Blinded, Open label crossover to MDMA	21/18	Completed
MP1-E2	2	Relapse after MDMA-assisted psychotherapy	Single center, Open-label	3/3	Completed
MAPP1	3	PTSD	Multicenter, Placebo-controlled, Randomized, Blinded	130/100	Completed
MAPP2	3	PTSD	Multicenter, Placebo-controlled, Randomized, Blinded	0/100	Ongoing

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