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11 October 2019

We acknowledge receipt of the MT2 Continued Partial Clinical Hold Letter dated Sep 27, 2019 for protocol MT2, titled "A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers." Thank you for this timely response.

INTRODUCTION AND REQUEST

We request that the Agency reconsider the regulatory action of the continued clinical hold for MT2 per FDA guidance on formal dispute resolution, in light of inconsistencies between previous correspondence and the continued hold letter, and related concerns briefly mentioned below. If the division is not open to reconsidering, our intent is to submit a formal dispute resolution request. There are two continued hold issues considered by the agency to be unresolved:

- **Issue #1**: 21 CFR 312.42(b)(1)(i): Unreasonable and significant risk of illness or injury to human subjects
- **Issue #2**: 21 CFR 312.42(b)(1)(ii): Unqualified clinical investigators

Our observed inconsistencies and questions are related to FDA's evaluation in

- **Issue #1** a) risks to subjects in MT2, and b) the supposed lack of benefits to MT2 subjects
- **Issue #2** a) the appropriate qualifications of the two-person teams administering MDMA in MT2, and b) a newly introduced requirement for an on-site physician

ISSUES TO BE RECONSIDERED

Issue #1: Unreasonable and significant risk of illness or injury to human subjects
Issue #1 a) Risks to subjects in MT2

Background

In evaluating the benefit:risk balance of study MT2, the Agency has erroneously characterized an adverse event from study MT1 as "de novo" suicidal ideation, with the implication that the adverse event may be drug-induced.

> *AE clarification letter dated 8 August 2019, Serial No. 0121*
> A sponsor clarification was promptly submitted to the IND indicating that of the 76 MT1 subjects treated at the time, this adverse event was the only one of its kind and did not meet protocol-defined criteria for a serious adverse event. Furthermore, MT1 participant [redacted] had previously reported suicidal ideation and behavior prior to the study, as revealed in the medical history and hence the adverse event of transient suicidal thoughts would not qualify as "de novo." Rather, the emergence of the suicidal thoughts and emotions during the experimental session and their resolution by the end of the experimental session with lasting benefits demonstrate the healing process of MDMA-assisted psychotherapy in a person with pre-existing trauma exposure. The

suicidal ideation was promptly well-managed by a therapy team consisting of a licensed therapist and a nurse, with a physician on call who didn't need to be called.

Since the sponsor submitted this clarification, the total count of subjects treated in the MT1 study has risen to 82 with no similar adverse events. The MDMA Investigator's Brochure 11th Edition dated 10 July 2019 also supports the absence of suicidal ideation and behavior among published reports of mortality and morbidity associated with ecstasy use in epidemiological settings, and in all scientific publications from Phase 1 and Phase 2 clinical trials with MDMA conducted in controlled settings. Thus, this instance of emergent suicidal ideation in the context of MDMA assisted psychotherapy was an isolated event for which there is no other corroborating evidence that the event was drug induced. In fact, it was the type of event that might occur in the context of any intensive uncovering psychotherapy in an individual with prior traumatic experiences, and there is no reason to believe it was specifically induced by drug. The MT1 study remains blinded, so it is theoretically possible that this subject had received placebo in the specific experimental session where this adverse event was reported. The safety data demonstrates that any potential safety risk to subjects in the MT2 study can be well-managed under the proposed MT2 protocol and there is no evidence of unreasonable and significant risk of illness or injury to healthy participants.

Request to Reconsider:

MT2 Continued Clinical Hold Letter, dated 27 September 2019
Please confirm review of the AE clarification letter dated 8 August 2019, submitted under Serial No. 0121 to this IND, and reconsider the characterization of the adverse event from study MT1 as "de novo" suicidal ideation. Please inform us if any further action for the IND is needed related to the clarification of this adverse event. In light of this recharacterization and stricter eligibility criteria in the MT2 protocol, please reconsider the benefit:risk ratio of the MT2 study.

Issue #1b) Supposed lack of benefits to MT2 subjects and lack of scientific benefit

Background
The MT1 protocol has provided 82 trainees in the MDMA Therapy Training program with an MDMA and placebo experience in the same blinded clinical setting in which they will administer MDMA or placebo to PTSD patients.

MT2 Complete Response to Partial Clinical Hold, dated 28 August 2019, Serial No. 0123
We consider the opportunity to volunteer to receive MDMA and placebo in a clinical trial under US-IND to be a vital part of the MDMA Therapy Training Program. Many therapists who have participated in MT1 consider the experience to have been an invaluable part of their training. Furthermore, the benefit of the MT2 study must be viewed in the broader context of the sponsor's entire MDMA clinical development program. We hypothesize that study participants will achieve enhanced self-compassion, professional quality of life, and reduced burnout. We are persuaded by reports of our trainees that experiencing the psychological effects of MDMA is a valuable enhancement of their therapist qualifications in delivering effective care. The benefit of the MT2 study begins at the individual level and bridges to the clinical and societal level.

Training in MDMA-assisted psychotherapy presents a unique situation for a psychopharmacology program. As psychopharmacology is combined with psychotherapy in this treatment method, it is very helpful for facilitators to actually have experience with MDMA, since their primary role will be to help future patients process their experiences with MDMA. This is not a typical requirement for a psychiatric drug trial, but it is appropriate for psychedelic-assisted psychotherapies. In

psychedelic-assisted psychotherapy, the therapeutic setting and the mindset of the facilitators make critical contributions to the administration of the treatment, which is an inherently variable process. This differentiates the training needs for psychedelic-assisted therapies from other medications that are not prone to operator effects.

We have initiated a brief survey of MT1 participants regarding benefits, harms and qualifications and will submit the results to FDA in a week or two.

MT2 Complete Response to Partial Clinical Hold, dated 28 August 2019, Serial No. 0123
The primary endpoint of the MT2 study is the Self-compassion Scale. Although lack of self-compassion is not a recognized psychiatric illness, it contributes to resistance to treatment and also to therapist burnout. MT2 is not a registration study and the information obtained is for research purposes only. MT2 is for training therapists, to gather additional safety data (even though FDA has indicated that no additional safety data other than from Phase 3 is necessary), and in addition is a feasibility study intended to study the development of self-compassion associated with the administration of MDMA to qualified trainees enrolled in the MDMA Therapy Training Program. This research study will collect data from participants to measure changes in self-compassion with a validated measure as the primary endpoint. Data from a healthy population of treatment providers may contribute to the sponsor's understanding of psychological mechanisms of action of MDMA- assisted psychotherapy and allow comparison of differences in self-compassion between treatment providers and PTSD patients. MT2 is hypothesized to demonstrate the benefit of exposure to MDMA in a treatment provider population, and potential correlations with professional quality of life and burnout.

Self-compassion is being measured in the Phase 3 PTSD trials of MDMA-assisted psychotherapy to continue to explore the relationship between PTSD symptom severity and self-compassion. Research supports the role of several components of self-compassion in recovery from PTSD, and recommends facilitating decrease in self-judgment, isolation, and over-identification and increase in self-kindness in PTSD patients as important contributors to the treatment of PTSD (Hoffart, Oktedalen et al. 2015). In a study examining the relationship between PTSD symptoms and components of self-compassion, PTSD symptoms ranked higher when initial self-judgement existed. Other studies have found that patients with PTSD may improve by combining elements of self-compassion into their treatment plans (Thompson and Waltz 2008). In an open trial, the addition of imagery re-scripting to prolonged exposure psychotherapy, with the goal of fostering self-compassion, was found to be helpful for PTSD patients who had previously not responded to standard prolonged exposure psychotherapy (Grunert, Weis et al. 2007). In pilot studies, both loving-kindness meditation and mindfulness-based stress reduction have shown promising results in the treatment of veterans with PTSD (Kearney, Malte et al. 2013, Kearney, McManus et al. 2014). Since neurobiological effects of MDMA increase compassion (see Section 5.2.3.2 Behavioral and Neuropsychological Effects of the MDMA Investigator's Brochure), the Sponsor hypothesizes that self-compassion will also increase in trainees as well as in PTSD patients.

The primary and exploratory outcome measures from the MT2 healthy volunteer study will provide important and relevant data which are not being captured in the MT1 study. Changes to professional quality of life and burnout can impact the quality of care patients receive. Recently, the World Health Organization classified burn-out as an occupational phenomenon deriving from workplace stress left unsuccessfully managed, which is classified in the International Statistical Classification of Diseases and Related Health Problems (ICD-11) under the diagnosis code of Z73.0. Burn-out is a syndrome conceptualized as resulting from chronic workplace stress that has

not been successfully managed. It is characterized by three dimensions: 1) feelings of energy depletion or exhaustion; 2) increased mental distance from one's job, or feelings of negativism or cynicism related to one's job; and 3) reduced professional efficacy. The data gathered with the MT2 study is designed to measure possible changes in the study participants that would be likely to correlate with professional effectiveness and satisfaction.

The MT2 study will gather scientific data on the unique challenges experienced by treatment providers who are learning to deliver MDMA-assisted psychotherapy to PTSD patients and has the potential to improve the quality of care that PTSD patients will ultimately receive. Managed care providers such as Kaiser Permanente, institutions such as the University of California at San Francisco (UCSF), and the rehabilitation division of the Veterans Administration are investing heavily in the exploration of the impact of burnout on care delivery. This is an imminent concern that has broad impact on the healthcare system and the MT2 study is designed with the goal of supporting the future implementation of MDMA-assisted psychotherapy in this context.

Request to Reconsider:

MT2 Continued Clinical Hold Letter, dated 27 September 2019

Our main point for reconsideration is the unique importance for this type of treatment package that the therapists delivering this care have actually experienced MDMA so that they can better empathize with the patients who are undergoing this experience. The opportunity to process past suicidal ideation or normal accumulated traumas with a qualified, experienced therapy team can provide lasting individual benefit for MT1 and MT2 study participants who do not qualify for a current psychiatric diagnosis. Please reconsider the conclusion that there is no evidence of potential benefit in the MT2 study. Our justification for the initiation of MT2 rather than for the continued clinical hold is based on the data demonstrating minimal risk in our controlled setting with a two-person therapy team, as well as on the scientific benefit described above, the potential individual benefit and the enhanced and uniquely valuable training opportunity provided.

Issue #2: Unqualified clinical investigators

Background

We understand Title 21 CFR 312.42(b)(1)(ii) is not typically used as justification for a clinical hold. We also understand that FDA has no prior experience trying to regulate the psychotherapeutic portion of a novel combination of psychopharmacology and psychotherapy. There is no clear objective standard for what makes a qualified investigator (at the sub investigator level for this study) for a novel treatment. Each site has an appropriately qualified Clinical Investigator listed on the 1572 in place at each site who bears overall responsibility for conduct of the clinical trial.

In the review group's latest response to our MT2 protocol, it is requiring a wholly new set of criteria for the qualifications for Sub-investigator therapists working under oversight of the Clinical Investigator through appropriate delegation of responsibility. In the view of the sponsor, these new requirements that the lead therapist be either an MD or Ph.D. (or equivalent) mistakenly confuses credentials with specific competence. This requirement does not fit with the clinical practice requirements for psychotherapy in the United States as it effectively precludes masters' level psychologists and clinical social workers yet assumes that psychiatrists are trained in and practice psychotherapy. Medical degrees, even in psychiatry, do not require any courses or experience in psychotherapy. People with Ph.D. degrees in psychology are trained primarily for research. The PsyD program was created to train psychologists with greater emphasis on clinical work than PhD psychology programs whose graduates often knew little about psychotherapy. People with post-graduate and/or master level licenses to conduct therapy are usually

more experienced in providing psychotherapy than either MDs, Ph.D.s or even PsyDs who also are trained to conduct research. Requiring an MD or Ph.D. or equivalent as the lead person in the two person therapy team increases costs and limits access without any evidence of significant benefit or risk reduction, and can actually increase risks and reduce benefits by requiring psychotherapy to be provided by some MDs, Ph.D.s or equivalent who have less experience as psychotherapists than others licensed to provide psychotherapy.

The current minimum qualifications for credentials of Sub-Investigator therapists who provide psychedelic-assisted therapy were developed by the sponsor and previously approved by the FDA. They were based on data collected from our Phase 2 and Phase 3 MDMA/PTSD clinical trials. To date, 32 of 198 participants with PTSD were treated by 14 teams that did not include an MD or PhD-level psychotherapist, with physicians on call but not present full-time at the site. Those teams did not present any new safety concerns and generated promising outcomes.

Issue #2 a) Appropriate qualifications of the two-person teams administering MDMA in MT2

In the MT2 study for healthy volunteers the sponsor is following the precedent for qualifications set by Phase 3 clinical trials and agreed upon by SPA and those same qualification were reiterated in Expanded Access communications by the agency.

> *SPA Agreement and most recently approved MAPP1 Phase 3 Protocol Amendment 1 Version 1, dated 26 February 2018, Serial No. 0102*
> MAPP1 Phase 3 Protocol Amendment 1 Version 1 Section 6.2 below, states each investigative site will include:
> - "One person licensed to manage and administer controlled substances for each site
> - A physician to assess participant safety at Screening
> - One or more male/female therapy teams
> - One person per therapy team is required to be licensed to provide psychotherapy according to state and local requirements
> - If one person on the therapy team is unlicensed, they will work under the direct supervision of the licensed team member"
>
> *IND 142690 Full Clinical Hold Letter dated 15 March 2019 –Protocol EAMP1*
> The agency provided the following two options:
> "Please amend the teams' qualifications to be consistent with the qualifications specified in your Phase 3 clinical development program for MDMA
> - One person licensed to manage and administer controlled substances for each site
> - A physician to assess participant safety at Screening
> - One or more male/female therapy teams
> - One person per therapy team is required to be licensed to provide psychotherapy according to state and local requirements
> - If one person on the therapy team is unlicensed, they will work under the direct supervision of the licensed team member"
>
> OR
>
> "Alternatively, please revise your teams' therapists' qualifications to adhere to our minimum requirements; our current thinking with the set and setting model of psychedelic-assisted psychotherapy is that the lead facilitator should have the qualifications of a doctoral level

(PhD/MD-level) psychotherapist (or equivalent). The second therapist should, at a minimum, hold a bachelor's degree and be trained in mental health."

The sponsor agreed to follow the existing Phase 3 qualifications for EAMP1 rather than the new option of a doctoral level (PhD/MD-level) psychotherapist (or equivalent), and this choice was submitted to the agency as part of the EAMP1 complete response.

Request to Reconsider:

MT2 Continued Clinical Hold Letter, dated 27 September 2019
The continued hold letter states "the clinical investigator requirements for conducting research with MDMA-assisted psychotherapy in healthy volunteers must not be less stringent than those required for your ongoing Phase 3 studies."

To reiterate our confusion, we restate the therapy team requirements per the MT2 protocol Amendment 1 Version 1 dated 27 August 2019:

- Staff at each site will work under the supervision of an MD (or equivalent) Clinical Investigator, who will oversee eligibility determinations and review safety data throughout the study.
- Licensed MT2 facilitators are required to be a physician or a mental health professional licensed to practice psychotherapy according to state and local requirements.
- Co-facilitator-trainees are required, at a minimum, to have a bachelor's degree and training in mental health, which includes students in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments, or 1000 hours of behavioral health experience in addition to the MDMA Therapy Training Program.

Please reconsider this as we feel the qualifications proposed are consistent with the agency's request described in the continued clinical hold letter as well as Phase 3 requirements.

Issue #2 b) a newly introduced requirement for an on-site physician
As previously agreed with the Agency, in Phase 3 the Clinical Investigator (if an MD) or site physician (if the CI is not an MD) assess eligibility and oversee collection of safety data throughout the study. This oversight is conducted during the study through periodic on-site reviews of safety data. In between these reviews, the physician is on call and available to the therapy teams as needed for safety questions but is not on site. Through this method substantial safety data on blood pressure and temperature has been gathered which, along with our track record of physiological safety, indicates no need for a physician on site in subjects pre-screened in accordance with our inclusion/exclusion criteria.

MT2 Complete Response to Partial Clinical Hold, dated 28 August 2019, Serial No. 0123
Investigative site staff will work under the supervision of an MD (or equivalent) Clinical Investigator, who will oversee eligibility determinations and review safety data throughout the study.

Request to Reconsider:

Please consider MT2 sites, as in Phase 3, will work under the supervision of an MD (or equivalent) Clinical Investigator, who will oversee subject eligibility determinations in line with the protocol and review safety data throughout the study.

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We look forward to the agencies response to our request to reconsider the regulatory action of the continued clinical hold for the MT2 protocol.

Sincerely,
Amy Emerson

Amy Emerson
Electronically signed by: Amy Emerson
Reason: I am the author of this document
Date: 2019-10-11 13:59:05-07:00

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