



IND 063384

APPEAL GRANTED

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Amy Emerson
Chief Executive Officer
3141 Stevens Creek Blvd #40563
San Jose, CA 95117

Dear Ms. Emerson:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 3,4-methylenedioxymethamphetamine (MDMA).

I also refer to your request for formal dispute resolution request (FDRR) dated and received on December 1, 2020. The appeal concerned the partial clinical hold on Study MT2, entitled *“A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers.”*

I also refer to the meeting held between FDA and MAPS on January 15, 2021, where the issues raised in your request for formal dispute resolution were discussed.

Dr. Billy Dunn has delegated your Office of Neuroscience level appeal to me, the Deputy Director of the Office of Neuroscience.

I have carefully reviewed the materials you submitted in support of your appeal, as well as reviews prepared by FDA staff and the partial clinical hold letters. I have also consulted with staff in the Division of Psychiatry.

I have completed my review of your request for formal dispute resolution and grant your appeal. I describe below the basis for my decision.

The partial clinical hold issues identified by the Division of Psychiatry are presented below in **bold font and italicized**, followed by my responses.

21 CFR 312.42(b)(1)(i): Unreasonable and significant risk of illness or injury to human subjects

Based on the study design of MT2 Amendment 2 and safety information submitted in your cover letter, the benefit:risk profile for MDMA in healthy subjects is unacceptable.

Lack of scientific benefit:

a. You describe Protocol MT2 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.

Information Needed to Resolve Deficiency: You must justify the large number of healthy subject exposures in MT2 for an unapproved therapy when data already exists.

b. The overall objective of this study is to explore the safety and psychological effects of open-label, manualized, MDMA-assisted psychotherapy in healthy volunteers and to expand the knowledge of treatment providers who are learning to conduct MDMA-assisted psychotherapy or MDMA research. Your submission admits that the purpose of the study is to allow therapists to experience MDMA to aid in their training.

Information Needed to Resolve Deficiency: You must justify why MT2 is necessary when you already are currently conducting a similar study (MT1).

c. The primary endpoint is the Self-compassion Scale. Lack of self-compassion is not a recognized psychiatric illness.

Information Needed to Resolve Deficiency: You must justify how the data obtained from this study will contribute to your development program for MDMA in psychiatric illness.

Regarding hold issues a, b, and c listed by the Division of Psychiatry under “lack of scientific benefit,” you noted in your formal dispute resolution request that “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.” You further noted that “many standard Phase 1 studies, such as pharmacokinetic studies, provide no possibility of benefit to the subjects other than the opportunity to support research,” and that “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 regulation in 21 CFR 312.42(b) authorizes FDA to issue a clinical hold of a Phase 1 study under an IND when “[h]uman subjects are or would be exposed to an unreasonable and significant risk of injury or illness.” I agree with you that a possibility of individual benefits is not a requirement in Phase 1 studies. However, I believe the Division of Psychiatry’s statement that “[b]ased on the study design of MT2 Amendment 2 and safety information submitted in your cover letter, the benefit:risk profile for MDMA in healthy subjects is unacceptable” is meant to express the view that the study’s

scientific merit does not justify the risk to patients, and is not meant to address individual risk/benefit. The regulation in 21 CFR 312.22(a) describe that “FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.” This regulation also describes that “FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations.” The safety of an investigation, however, is always assessed in the context of the design of that investigation, even in Phase 1. A Phase 1 study so poorly designed that it would yield no interpretable information could certainly be viewed as placing patients at an unreasonable and significant risk of illness or injury. I view your proposed investigation as generally consistent with a Phase 1 study, although the sample size of the study, and the fact that you have already evaluated a large number of healthy subjects in your development program is unusual in Phase 1. I also find your objective of obtaining data about the safety and pharmacodynamic effects of MDMA reasonable in a Phase 1 study, albeit possibly redundant, at least in part, to studies you have already conducted. Overall, after reviewing the explanations in your FDRR, I do not find the lack of scientific benefit (as described in issues a, b, and c) as valid justification for imposing a partial clinical hold.

Safety risk:

d. The safety data submitted from MT1 appears to reveal the potential for serious risk. You state that the benefit:risk ratio of 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.

Information Needed to Resolve Deficiency: Given that the safety and efficacy of your proposed product has yet to be adequately characterized, you must 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.

Regarding hold issue d listed by the Division of Psychiatry under “safety risk,” I note your argument in the FDRR that “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.” You state that the single event of suicidal ideation in Study MT-1, which resolved during an experimental session, was in an individual who “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.” I also note your explanation that you have “amended the Study MT-2 protocol to exclude subjects who present similar risks at baseline.” In addition, you state 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” and that “[t]he blurred vision resolved after three to four hours and before the end of the blinded Experimental Session without treatment.”

I also note that Study MT-1, a “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”, has been ongoing since 2009, and has enrolled so far 89 patients of the planned 120 patients. MDMA dosage in Study MT-1 is a single dose of 125 mg (or placebo), followed by an optional supplemental half-dose of placebo or 62.5 mg MDMA administered one and a half to two hours later. MDMA dosage in Study MT-2, which is the object of the partial clinical hold, is no higher than that in Study MT-1: 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 patient population is also similar in both studies, consisting of “healthy volunteers who are trainees in the conduct of MDMA-assisted psychotherapy or MDMA research.” I could not find any differences between Study MT-1 and Study MT-2 that would make the acceptability of the safety risks of the drug any different between the studies, and therefore disagree with the Division of Psychiatry that the risk of MDMA is unreasonable and significant in Study MT-2, when the same risk was found reasonable in Study MT-1. Overall, based on your explanations of the safety risks and my assessment, I do not find that human subjects would be exposed to an unreasonable and significant risk of injury or illness that would justify imposing a partial clinical hold.

21 CFR 312.42(b)(1)(ii): Unqualified clinical investigators

Protocol MT2 states that 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.

Information Needed to Resolve Deficiency: 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. (We remind you that subjects taking MDMA are in a vulnerable state and that you already have reported safety compliance issues.)

The regulation in 21 CFR 312.42(b) authorizes FDA to issue a clinical hold of a Phase 1 study under an IND when “[t]he 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.” , I note that the qualification of investigators in Study MT-2 is similar to that of investigators in Study MT-1. Based on your explanation of the investigators’ qualification and my assessment, I believe that the Division of Psychiatry’s determination for Study MT-1 that the investigators’ qualification was acceptable also applies to Study MT-2, and that the qualification of investigators in Study MT-2 should not be a ground for clinical hold.

Conclusions and Recommendations:

I have completed my review of your FDRR and grant the appeal, for the reasons described above.

Please note that as safety information has been accruing in your development program, changes to your clinical study protocols may be needed to ensure that the risk to study participants remains reasonable. You should discuss with the Division of Psychiatry whether such changes are needed for some or all of your ongoing and future studies.

This constitutes the final decision at the Office of Neuroscience level. Any questions concerning your appeal should be addressed to Paul David at [REDACTED] or via e-mail at [REDACTED].

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
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