MAPS Public Benefit Corporation
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17 March 2022

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Director, Division of Psychiatry Products
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
5901-B Ammendale Road
Beltsville, MD 20705-1266

CLINICAL HOLD COMPLETE RESPONSE

RE: IND#063384; Serial No. 0200, MPG1 Partial Clinical Hold Response Letter

Dear Division of Psychiatry Products,

Please see below the complete response to the Agency's Clinical Hold Letter dated 28 February 2022 for the MAPS-sponsored protocol MPG1 entitled, "*An Open-Label Feasibility and Safety Study of MDMA-Assisted Group Therapy for the Treatment of Posttraumatic Stress Disorder in Veterans*," submitted to the Agency on 08 November 2021 under IND# 063384 (Serial No. 0191).

Hold Issue: 21 CFR 312.42(b)(2)(i): Unreasonable and significant risk of illness or injury to human subjects

FDA communication: *"An overnight stay must be required for Protocol MPG1. You have not yet provided sufficient safety data from your no-overnight stay substudies to allow this study to proceed without an overnight stay.*

You may not legally initiate or resume Protocol MPG1 until you have submitted the required information and we notify you that you may initiate or resume clinical studies."

Sponsor Response: MPG1 is a small proof-of-concept study of up to 18 participants, consisting of 3 cohorts of 6 participants each, wherein participants will undergo the first treatment session individually and the second treatment session in a group setting of six participants receiving MDMA. In light of the absence of data indicating a safety risk in returning home following dosing sessions in the substudy data, the small study sample in MPG1 (n=18), and the potential risks of requiring an overnight stay in a group therapy setting of this study described below, the sponsor retains the position that allowing participants to return home would be the best for their physiological and psychological health.

As outlined in the original protocol submission cover letter, the sponsor is raising this issue in the context of Study MPG1 due to its unique differences that impact the safety assessment: 1) MPG1 will be conducted in a significantly smaller sample than other trials (n=18), 2) Overnight stays in the context of a group study may compromise the participant's psychological processing, 3) the introduction of overnight stays into MPG1's group therapy design would make the study impracticable to execute, and 4) available data provided to the Division from the Phase 3 MAPP1 no-overnight stay substudy and the substudy data in the CSR from Study MP16. **The sponsor believes that the exclusion of participant overnight stays following the group treatment session in study MPG1 does not present any unreasonable or significant risk to participants.**

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As the hold letter from the Agency did not address any of the concerns or rationale posed in the MPG1 original protocol submission, we include them again here with a request for the Division's feedback on these points to help the sponsor better understand the risks identified by the Agency:

- **The sponsor requests clarification from the Division whether any portion of the no-overnight-stay substudy data prior to completion would be sufficient for reconsideration of the overnight stay requirement in the setting of group treatment sessions**. The sponsor acknowledges the Division's position that overnight stays remain required until submission of complete data from the no-overnight-stay substudy in n=50 participants in the Phase 3 program (MAPP1, MAPP2, MAPPUSX). However, as requested by the Division, no-overnight-stay data from MP16 (n=4) was submitted to the Agency on 12 March 2021 (SN 0171) in the MP16 CSR and no-overnight-stay data from MAPP1 (n=15) was submitted with the sponsor's original protocol submission for MPG1 on 08 November 2021 (SN 0191) and provided again in the below Appendix. These data demonstrate no serious safety signals overall and specifically no increased incidence of adverse events in the non-overnight stay group.
- **The sponsor requests clarification from the Division on the nature of the unreasonable and significant risk of illness or injury posed by the removal of the overnight stay requirement in the setting of group treatment sessions.** It is significant to note that the sponsor's early Phase 2 studies included an overnight stay as an opportunity for rest and integration in a relaxed and comfortable environment away from the distractions of home and to ease logistics of data collection and arrival for the integrative psychotherapy session on the following day. There has never been any evidence or data to suggest that this was required to ensure safety. However, due to this precedent, it has been communicated by the Agency that overnight stays are a required safety component to mitigate a potential theoretical risk until demonstrated otherwise via the no-overnight-stay substudy. The sponsor seeks to understand the nature of the perceived risk so that we may best address it on submission of the substudy data.
- **The sponsor requests clarification on the Division's view of safety in a group overnight stay**. In the context of a group visit, it is the sponsors view that the overnight stay may compromise the participants' psychological processing. Requiring an onsite overnight stay for six participants following simultaneous treatment may impede the participants' ability to individually process their reflections and feelings during this initial period where their integration is more open to external inputs. Following the MDMA-assisted individual therapy sessions, participants are asked to quietly reflect on their experience and their support persons are instructed to help create space for individual processing. This protective space respects and holds the experience of the participant allowing them to contain and process their emergent emotions and dynamics. As described in the submission letter, this process and environment may be better achieved at home (or another suitable location), instead of at the facility with all the other participants present after spending a day-long treatment session together. Requiring six veterans to remain on site concurrently may negatively impact integration and treatment outcomes by not allowing the psychological space needed following treatment sessions. Further, it would not be feasible or appropriate in this treatment model for all six veterans to sleep in the group treatment room nor to confine them each to a room, even if six such rooms were available.

The importance of piloting a group administration paradigm is essential for developing the evidence base for broader patient access to MDMA-assisted therapy. The Agency granted MDMA-assisted therapy for PTSD a Breakthrough Therapy designation due to its potential to substantially improve treatment for a serious condition over available medications. However, if the marketing application for this treatment is successful, a critical factor in the ability of this treatment to impact the unmet need for treating PTSD will be accessibility. If this treatment is approved, supporting its ability to be accessible is a critical goal of the sponsor, and the administration of MDMA-assisted therapy in a group treatment model is key to supporting accessibility. We hope that the agency will recognize the importance of this goal.

Proposal:
Given the unique design of MPG1, the sponsor proposes to modify the protocol such that an overnight stay be required of all participants following the first individual treatment session. This will allow for an individual session and an overnight stay at the site for the first session. Then, for participants who complete the first session without safety concerns arising, an overnight stay following the subsequent group treatment session would *not* be required. If a safety concern arose for an individual participant (either during their individual session and overnight stay or during the group session), that individual participant would stay overnight following the group session. Participants without safety concerns would instead be dismissed from the group setting following procedures specified in Section 8.3.1.3 End of Experimental Session of the MPG1 protocol, which are similar to those utilized in the no-overnight-stay sub-studies in the sponsor's Phase 3 program.

> Participants would be required to identify an appropriate support person who would commit to ensuring the participant is safely transported from the study site and would stay with the participant overnight on the evening of the second Experimental Session at the participant's home or other suitable location. The designated support person would be required to meet a member of the therapy team in person and engage in a conversation with the therapy team regarding the primary responsibilities of the support person role in advance of the Experimental Sessions. Full details of the intended support person responsibilities can be found in Section 8.2.4.1 Orienting the Support Person of the study protocol. Additionally, the site physician and each participant's therapist would remain on call overnight following the Experimental Session.

Importantly, the study site investigator relied on a similar process of support persons accompanying participants home with no overnight stay following dosing sessions in a previous psilocybin group therapy study approved by the Agency without safety issue reported due to the absence of overnight stay (Anderson, B.T., Danforth, A., Daroff, R., et al., *Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study*. Eclinical Med. 2020.).

Taking into account the small number of participants in this proof-of-concept study, the nature and importance of piloting this treatment model, and the infeasibility of requiring overnight stays in the context of a group visit, which will effectively impede the progress of the study, the sponsor asks for the Division's consideration on the inclusion of an overnight stay for the first individual session and removal of the overnight stay requirement for the group therapy treatment session in MPG1.

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If you have any questions or requests regarding this submission, please do not hesitate to contact sponsor Designee, Amy Emerson, at [redacted] or Associate Director of Regulatory Affairs, Allison Coker, at [redacted]

Sincerely,

Amy Emerson

Electronically signed by: Amy Emerson
Reason: I am the approver of this document
Date: Mar 17, 2022 15:03 PDT

Amy Emerson
Chief Executive Officer
MAPS Public Benefit Corporation

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MAPP1 No Overnight Stay vs Overnight Stay AE data

The table below presents treatment-emergent adverse events with twice the prevalence in the MDMA group by overnight stay or no overnight stay. In the MDMA group, subjects in the overnight stay and no overnight stay group reported a similar percentage of muscle tightness and decreased appetite. In the MDMA group, a higher percentage of subjects in the overnight stay group reported feeling cold, bruxism, dry mouth, mydriasis, dizziness postural, non-cardiac chest pain, blood pressure increased, feeling jittery, nystagmus, pollakiuria, musculoskeletal pain, pyrexia, vision blurred, chills, micturition urgency, muscle twitching, nervousness, somnolence, and substance use than subjects in the no overnight stay group. Among MDMA subjects who had no overnight stay, there was a higher percentage of decreased appetite, nausea, hyperhidrosis, restlessness, intrusive thoughts, stress, and vomiting. While there was only one subject who reported intrusive thoughts, stress, or vomiting in the no overnight stay group, the percentage of prevalence of these AEs was higher because the sample size was only nine subjects, causing each subject's AE to be disproportionally weighted.

Treatment-emergent AEs with Two-Fold Prevalence in MDMA Group over Placebo, by Overnight Stay

Preferred Term	MDMA-assisted therapy (N=46)		Placebo with therapy (N=44)	
	Overnight (N=37) n (%)	No Overnight (N=9) n (%)	Overnight (N=38) n (%)	No Overnight (N=6) n (%)
Muscle tightness	23 (62.2)	6 (66.7)	3 (7.9)	2 (33.3)
Decreased appetite	18 (48.6)	6 (66.7)	4 (10.5)	1 (16.7)
Nausea	9 (24.3)	5 (55.6)	5 (13.2)	0 (0.0)
Feeling cold	9 (24.3)	0 (0.0)	2 (5.3)	1 (16.7)
Bruxism	6 (16.2)	0 (0.0)	1 (2.6)	0 (0.0)
Dry mouth	5 (13.5)	0 (0.0)	2 (5.3)	0 (0.0)
Mydriasis	7 (18.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness postural	4 (10.8)	2 (22.2)	2 (5.3)	0 (0.0)
Hyperhidrosis	6 (16.2)	3 (33.3)	0 (0.0)	1 (16.7)
Non-cardiac chest pain	5 (13.5)	0 (0.0)	1 (2.6)	0 (0.0)
Blood pressure increased	5 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling jittery	5 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nystagmus	5 (13.5)	1 (11.1)	0 (0.0)	0 (0.0)
Pollakiuria	4 (10.8)	0 (0.0)	1 (2.6)	0 (0.0)
Restlessness	5 (13.5)	2 (22.2)	0 (0.0)	0 (0.0)
Musculoskeletal pain	4 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	3 (8.1)	0 (0.0)	1 (2.6)	0 (0.0)
Vision blurred	4 (10.8)	0 (0.0)	0 (0.0)	1 (16.7)
Chills	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Intrusive thoughts	3 (8.1)	1 (11.1)	0 (0.0)	0 (0.0)
Micturition urgency	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)

Muscle twitching	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervousness	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stress	3 (8.1)	1 (11.1)	0 (0.0)	0 (0.0)
Substance use	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	3 (8.1)	1 (11.1)	0 (0.0)	0 (0.0)

These data will be included in the complete Clinical Study Report for Study MAPP1 which is in preparation.