MAPS Public Benefit Corporation
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08 November 2021

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

RE: IND #063384, Serial No. 0191, Original Protocol Submission for MPG1

Dear Division of Psychiatry Products,

The Sponsor is writing to submit 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.*" The MPG1 protocol will serve to assess the feasibility, efficacy, and safety of MDMA-assisted group therapy in a Veteran population with at least moderate PTSD using an open-label, non-randomized study design in a sample of up to 18 participants, recruited into three group therapy cohorts of up to 6 participants each.

In keeping with the Agency's request to highlight potential issues that may require discussion within the cover letter of new protocol submissions per the End of Phase 2 Meeting Minutes dated 29 December 2016, the Sponsor notes that the End of Experimental Session procedures proposed for this novel group therapy protocol, MPG1, do not include participant overnight stays at the study site.

This is a small proof-of-principle feasibility study of 3 cohorts of up to 6 participants each. The proposed End of Experimental Session procedures in MPG1 will follow similar procedures to those utilized in the no-overnight stay substudies in the Sponsor's Phase 3 program. Participants will be required to identify an appropriate support person who will commit to ensuring the participant is safely transported from the study site and will stay with the participant overnight on the evening of Experimental Sessions at the participant's home or other suitable location. The designated support person will 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 Sessions. The study site investigator relied on a similar process of support persons accompanying participants following dosing sessions in a previous psilocybin group therapy study (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.).

It's significant to note that while MAPS' early Phase 2 studies included an overnight stay to allow for emotional space to support psychological processing, there has never been any evidence 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. In order to distinguish actual risk from theoretical risk, the Sponsor is conducting an ongoing no-overnight-stay substudy in n=50

participants in the Phase 3 program (MAPP1, MAPP2, MAPPUSX), as previously agreed upon with the Agency in the Sponsor's letter dated 22 December 2020 in response to the Agency's potential hold and non-hold comments regarding protocol MAPPUSX (SN 0162). The CSR for the Phase 2 Study MP16, which included no-overnight-stay substudy data, was submitted to the Agency on 12 March 2021 (SN 0171). The CSR for the first completed Phase 3 study MAPP1 is being prepared for submission and will include data from 15 additional no-overnight-stay substudy participants (MDMA group n=9, placebo group n=6, see Appendix below for final adverse event data). These data support that there were no serious safety signals demonstrated overall and specifically no increased incidence of adverse events in the non-overnight stay group.

Study MPG1 has a unique study design wherein participants will undergo the first treatment session individually and the second treatment session in a group setting of six participants receiving MDMA. In the context of a group visit, the overnight stay may actually compromise the participants' psychological processing. Requiring an onsite overnight stay for 6 participants following simultaneous treatment may impede the participant's 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 therapy sessions, participants are asked to quietly reflect on their experience and support people 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. This process and environment may be better achieved at home (or another suitable location), instead of at the facility with all of the other participants present after spending a day-long treatment session together. Requiring six veterans to remain on site concurrently may negatively impact group integration and participant 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 room, even if six such rooms were available.

The Sponsor recognizes that making participant overnight stays an optional element was previously proposed to the Agency in the original protocol submission for study MPVA6 (SN 0140). Following discussion with the Agency, and in accordance with the Agency's Partial Clinical Hold letter dated 16 June 2020, the Sponsor subsequently amended the MPVA6 study to include mandatory overnight stays. The Sponsor is raising this issue here given the unique differences in Study MPG1 that may impact the Agency's assessment: 1) MPG1 will be conducted in a significantly smaller sample than MPVA6 (n=18 versus n=60), 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 from the Phase 3 no-overnight stay substudy and the Clinical Study Report from Study MP16. The Sponsor believes that the exclusion of participant overnight stays in study MPG1 does not present any unreasonable or significant risk to participants and requiring this stay in the context of a group study would be impracticable.

The importance of piloting a group administration paradigm is essential for developing the evidence base for broader patient access to MDMA-assisted therapy. This Agency granted MDMA-assisted therapy for PTSD a Breakthrough Therapy designation due to its potential to improve treatment for a serious condition. 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 as

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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.

Given 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 which will effectively impede the progress of the study, the sponsor requests that the Division find it appropriate to approve this protocol with no overnight stays.

Please find the following documents enclosed in submission Serial No. 0191:

- FDA Form 1571, dated 08 November 2021
- FDA Form 3674, dated 08 November 2021
- MPG1 Original Protocol Version 1, dated 07 October 2021
- FDA Form 1572 Stauffer, dated 05 November 2021
- Clinical Investigator CV Stauffer
- MPG1 Informed Consent Form Template, dated 21 October 2021
- MPG1 Description of CRFs, dated 22 October 2021
- Cornell Services Index (CSI)
- Experiences in Close Relationships-Short Form (ECR-S)
- Group Questionnaire (GQ)
- Social Provisions Scale (SPS)

If there are any questions regarding this submission, please do not hesitate to contact Sponsor Designee, Amy Emerson, [redacted] or Regulatory Affairs Manager, Allison Coker [redacted]

Sincerely,

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, 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.