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23 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

RESPONSE TO NON-HOLD COMMENTS

RE: IND#063384; Serial No. 0201, MPG1 Non-Hold Issues Response Letter

Dear Division of Psychiatry Products,

Please see below a response to the Agency's non-hold issues from the Partial 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).

Non-Hold Comment 1: *"Please provide an explanation for changing the description of MDMA doses from the MDMA HCl equivalents (e.g., 120 mg initial dose, 40 or 60 mg supplemental dose) as in your other many protocols dating back almost two decades to MDMA (101 mg, 34 mg, or 50 mg). This change creates the appearance of new and different dosing in MPG1, especially in Table 6, and can be confusing."*

Sponsor Response to Non-Hold Comment 1: The dosing in our clinical trials has not changed. The sponsor updated the language surrounding the expression of dosage strength to be reported as active moiety with HCl equivalent for MAPS-sponsored clinical trials, per USP Salt Policy. The sponsor had previously received notification via email from the Agency on February 12th, 2019 requesting the sponsor comply with the USP Salt policy at the time of NDA submission:

"Per USP salt policy, for drug products that contain an active ingredient that is a salt, USP will use the name of the active moiety (or neutral form), instead of the name of the salt. Furthermore, the drug product strength must be expressed in terms of the active moiety. Therefore, you must express the strength of the drug product in terms of 3,4-methylenedioxymethamphetamine free base."

Though this instruction indicated that the sponsor should address this comment "at the time of NDA submission," there was concern that making this transition only at the time of the NDA meant that clinicians may not recognize the new dosing expression. Therefore, in preparation for the NDA submission, the sponsor decided in October 2021 to express dosage strength in terms of the active moiety while still providing the equivalent dosage strength in terms of the hydrochloride (HCl) salt for all new clinical trials to ensure that clinical investigators recognize the investigational medical product is unchanged in all key characteristics and avoid confusion during commercial launch. As such, the MPG1 protocol was submitted on 08 November 2021 listing the dosage strength of MDMA as the active moiety and the salt equivalent.

In response to this Partial Clinical Hold letter, the sponsor sought additional clarification and received updated guidance via email, indicating:

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"We acknowledge that inclusion of the base form dosage of MDMA in your protocols, annual report, and to-be-updated IB were in an effort to move toward compliance with the USP Salt Policy. However, during the IND phase of IND 063384, you may keep the dose strengths in terms of MDMA HCl and this is the preference of the Division. You may consider adding conversion language or a table with the salt to free form dose conversion in one place in those documents."

In keeping with this agreement, the sponsor will revise the dosage strength expression of MDMA as a HCl salt throughout the protocol with equivalent listing as the active moiety in one location, Section 4.3 Justification for Dose. This update will be included in the next protocol amendment following resolution of the clinical hold.

Non-Hold Comment 2: *"Please explain why the MDMA dosing is 120 mg followed by a supplemental dose of 40 or 60 mg in the MPG1 protocol submitted November 11, 2021. In your protocol (MPVA6 Amendment 5) submitted September 17, 2021, we note that you changed the MDMA dose to 120 mg followed by 40 mg based on new CMC information."*

Sponsor Response to Non-Hold Comment 2: The standard protocol for supplemental doses in sponsor protocols dating back two decades is to use a half dose of the initial dose. The drug product is manufactured in two dosages, 40 mg and 60 mg capsules, permitting doses of 80 mg and 120 mg plus the respective supplemental half-doses. While 60 mg is the preferred supplemental dose for an initial dose of 120 mg, the sponsor has administered 40 mg as the supplemental dose due to drug supply availability issues in previous protocols, such as MPVA6. In order to ensure consistency, a single supplemental dose was selected for MPVA6 once the drug supply was determined. The study is underway and was supplied with 40 mg capsules, supporting a 120 mg initial and 40 mg supplemental dose. The drug supply availability of 40 mg or 60 mg capsules for the start of MPG1 is currently unknown, therefore both were included in the initial protocol. Strength of the supplemental dose will be the same for all participants and determined by drug supply availability at the start of the trial and will always be a half dose of the initial dose if supply permits. If 60 mg capsules are available for the study, a 60 mg supplemental dose will be used following the 120 mg dose.

Non-Hold Comment 3: *"Further, please explain the dosing discrepancies in the initial dose of MDMA in your current protocol. If all supplemental doses will be the same for participants based on what is available, does the supplemental dose change between cohorts? If there is no efficacy difference in the 40 or 60 mg supplemental dose (assuming the second dose is tolerated) why is the manufacturing not consistent with the lower dose?*

a. In one place in the protocol it says, 'Initial doses per Experimental Session include 101 mg MDMA, followed 1.5 to 2 hours later by a supplemental dose of 34 or 50 mg MDMA (equivalent to 120 mg followed by 40 or 60 mg MDMA HCl).'

b. In another place it says, 'This open-label study will examine the effects of a divided-dose of 134 mg to 150 mg of MDMA (equivalent to 160 mg to 180 mg MDMA HCl) administered in two Experimental Sessions. Participants will receive an initial dose of 100 mg and a supplemental dose of 34 mg or 50 mg MDMA (equivalent to 120 mg and a supplemental dose of 40 mg or 60 mg MDMA HCl) at 1.5-2 hours after initial ingestion, unless tolerability issues emerge with the initial dose or the participant declines. Strength of supplemental dose will be the same for all participants and will be determined by drug supply availability at the start of the trial.'"

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Sponsor Response to Non-Hold Comment 3: The supplemental dose will not change between cohorts and will be determined at the start of the trial based on drug supply availability for the entire study. The sponsor is conducting various studies with requirements for both 40 mg and 60 mg capsules, distinct from the supplemental dose in MPG1, but drug supply availability for MPG1 is unknown as the study start date has not yet been determined.

The initial dose is incorrectly listed in Table 1 as "101 mg MDMA." This is a typographical error. It should be "100 mg MDMA" as it is listed elsewhere in the protocol. However, in keeping with Non-Hold Comment 1, this will be corrected in the next amendment to only reflect the salt weight, 120 mg MDMA HCl.

Non-Hold Comment 4: *"We acknowledge that MPG1 is a feasibility study. Please clarify if you intend on further evaluation of the group MDMA-assisted therapy model. As MPG1 is currently designed, we consider this study to be strictly exploratory. Your current design will not provide an adequate comparison of efficacy between individual and group Experimental and Integrative sessions."*

Sponsor Response to Non-Hold Comment 4: MPG1 is designed to examine the feasibility and safety of the MDMA-assisted group therapy model for treatment of PTSD. We recognize that it is not statistically designed to compare efficacy between individual and group Experimental and Integrative sessions. This study will provide important safety information in the context of a group setting and an initial signal on effectiveness in the context of a group setting.

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 23, 2022 14:41 EDT

Amy Emerson
Chief Executive Officer
MAPS Public Benefit Corporation