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CLINICAL HOLD COMPLETE RESPONSE

RE: IND#063384; Serial No. 0204, MPG1 Continue Partial Clinical Hold Response Letter

Dear Division of Psychiatry Products,

Please see below the complete response to the Agency's Clinical Hold Letter dated 15 April 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: "*Summarized below is the information needed to resolve these deficiencies. We acknowledge that you provided the no overnight stay safety data from MP16 (N=4) and MAPP1 (N=15). We have further questions about the safety data from the adverse event (AE) table from the substudy in MAPP1 (table below):*

[Sponsor note: The Treatment-emergent adverse event table provided in the 17 March 2022 response letter is provided again as an appendix to the current response for the Agency's reference.]

Sponsor General Response:

The treatment-emergent adverse event (TEAE) data provided as a table in the sponsor's response dated 17 March 2022 is representative of all TEAEs occurring in MAPP1 at any time period following initiation of treatment, irrespective of proximity to Experimental Sessions. In order to provide adverse event information more temporally relevant to dosing, the sponsor is additionally providing data on TEAEs occurring within two days of an experimental session by treatment and overnight stay group in Table 1 below.

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Table 1: Treatment-emergent AEs Occurring within Two Days following an Experimental Session with Two-Fold Prevalence in MDMA-AT Group over Placebo, by Overnight Stay

	MDMA-assisted therapy (N=46)		Placebo with therapy (N=44)	
Preferred Term	Overnight (N=37) n (%)	No Overnight (N=9) n (%)	Overnight (N=38) n (%)	No Overnight (N=6) n (%)
Muscle tightness	21 (56.8)	6 (66.7)	3 (7.9)	2 (33.3)
Decreased appetite	18 (48.6)	6 (66.7)	2 (5.3)	1 (16.7)
Nausea	8 (21.6)	5 (55.6)	3 (7.9)	0 (0.0)
Feeling cold	9 (24.3)	0 (0.0)	1 (2.6)	1 (16.7)
Bruxism	5 (13.5)	0 (0.0)	0 (0.0)	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	**3 (8.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Blood pressure increased	**3 (8.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Feeling jittery	4 (10.8)	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	3 (8.1)	1 (11.1)	0 (0.0)	0 (0.0)
Musculoskeletal pain	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vision blurred	4 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)
Chills	2 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
Intrusive thoughts	**1 (2.7)**	**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	**2 (5.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Somnolence	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stress	**1 (2.7)**	**1 (11.1)**	**0 (0.0)**	**0 (0.0)**
Substance use	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (5.4)	1 (11.1)	0 (0.0)	0 (0.0)

Only a portion of the TEAEs of interest outlined in the Agency's Clinical Hold Letter dated 15 April 2022 (non-cardiac chest pain, blood pressure increase, pyrexia, intrusive thoughts, nervousness, and stress) initiated within 48 hours following dosing, which corresponds to the end of systemic exposure of MDMA.

Three of the five (60%) TEAEs of non-cardiac chest pain initiated within 48 hours following dosing. Three of the five (60%) TEAEs of blood pressure increase initiated within 48 hours following dosing. None (0%) of the TEAEs of pyrexia initiated within 48 hours following dosing. Two of the three (67%) TEAEs of nervousness, two of the four (50%) TEAEs of intrusive thoughts, and two of the four (50%) TEAEs of stress initiated within 48 hours following dosing. However, the sponsor is providing the requested narratives for all of the AEs of interest for both those that initiated within and outside of the acute 48-hour post-dose window.

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FDA* Communication:** ***"1*. Provide the cutoff values of systolic and diastolic blood pressure used to determine the threshold for AE reporting. Provide detailed information, including the amount of rise of mm Hg, for the cases in the table. Provide narratives, if available."*

Sponsor Response 1:

Blood pressure readings were assessed by the site medical providers and determined to be adverse events if they were clinically significant in the context of any other signs or symptoms and the participant's medical history. There were no prescribed cutoff values of systolic and diastolic blood pressure used to determine a threshold for AE reporting. Per the agreed upon Special Protocol Assessment for the Phase 3 study protocols, vitals were taken for all participants and AEs were not identified based on elevation of blood pressure above cutoff values. Instead, clinical signs and symptoms were monitored by therapy teams to identify any potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction (AMI) during Experimental Sessions. Any symptoms such as chest pain, shortness of breath, neurological deficit or confusion, or other potential indicators of end organ effects that prompted additional vital sign measurements were tracked and assessed by the site physician for potential AEs.

Of the five participants with reported TEAEs of blood pressure increase, all occurred in the MDMA-assisted therapy (MDMA-AT) with overnight stay group. Three of these participants reported TEAEs of blood pressure increase that initiated within the 48 hours following dosing, and the narratives of these instances are described below:

- Participant [redacted] was a [redacted]-year-old [redacted] or [redacted] in the MDMA-AT overnight group. Their medical history included ADHD, generalized anxiety disorder, insomnia, major depression, alcohol abuse, and substance use. They did not have a history of hypertension. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). During Experimental Session 2 their pre-dose blood pressure was 131/82 mmHg at 9:17AM, which increased at interim following an initial dose of 120 mg blinded MDMA HCl to 173/94 mmHg at 11:01AM (42 mmHg increase in systolic blood pressure [SBP] and 12 mmHg increase in diastolic blood pressure [DBP]). An extra measurement was taken at 11:03AM which read 161/102 mmHg. They received the supplemental dose of 60 mg MDMA HCl. Their endpoint blood pressure reading was 149/92 mmHg at 5:01 PM. This TEAE was rated as moderate and resolved fully the same day without intervention.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group who had two TEAEs of blood pressure increase on Experimental Session days. Their medical history included insomnia, sleep apnea, nightmares, intrusive thoughts, flashbacks, hypervigilance, and suicidal ideation. They did not have a history of hypertension. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl).

    - During Experimental Session 1 on [redacted], [redacted] pre-dose blood pressure was 112/70 mmHg at 9:37AM, which increased to 160/101 mmHg at interim at

11:11AM following an initial dose of 80 mg MDMA HCl (48 mmHg increase in SBP and 31 mmHg increase in DBP). The PI contacted the medical monitor about the blood pressure reading and received approval to proceed with the supplemental dose of 40 mg MDMA HCl per the protocol and the PI's clinical judgement. Their blood pressure reading at endpoint at 6:09PM was 165/89 mmHg. This TEAE was rated as mild and resolved fully the same day without intervention.

  - During Experimental Session 3 on [redacted], [redacted] pre-dose blood pressure was 148/82 mmHg at 9:21AM, which increased at interim to 201/105 mmHg at 11:20AM following an initial dose of 120 mg MDMA HCl (53 mmHg increase in SBP and 23 mmHg increase in DBP). The study physician noted that the participant had just gotten up to use the restroom before the interim blood pressure reading was taken, so took a repeat reading 2 minutes later at 11:22AM, which read 162/87 mmHg. The supplemental dose of 60 mg MDMA HCl was administered. At endpoint at 4:53PM, their blood pressure decreased to 129/84 mmHg. This TEAE was rated as mild and resolved fully the same day without intervention.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group who had one TEAE of blood pressure increase. Their medical history included major depression, ADHD, alcohol abuse, suicide attempt, suicidal ideation, panic disorder, generalized anxiety disorder, social anxiety disorder, and suicidal ideation. They did not have a history of hypertension. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). During Experimental Session 1 they reported anxiety going into the session and their pre-dose blood pressure read 144/85 mmHg at 9:37AM. The therapists, both MDs, continued with the initial dosing of 80 mg MDMA HCl. Prior to supplemental dose administration, their interim blood pressure read at 11:17AM increased to 191/101 mmHg (47 mmHg increase in SBP and 16 increase in DBP), prompting the therapists to take a repeat measure at 11:18AM, which was 182/94 mmHg. Another reading 22 minutes later at 11:40AM was 169/96 mmHg. There were no concerning symptoms, so the therapists administered the supplemental dose of 40 mg MDMA HCl. At endpoint at 5:12PM, their blood pressure was 150/102 mmHg. A repeat measurement was taken at 5:40PM which read 151/89 mmHg. This TEAE was rated as moderate and fully resolved the same day without intervention.

The details of the remaining two participants who reported TEAEs of blood pressure increase that initiated more than 48-hours following dosing are as follows:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group who had one TEAE of blood pressure increase pre-dosing. Their medical history included erectile dysfunction, tobacco use, suicidal ideation, alcohol abuse, major depression, affect lability, insomnia, anxiety, flashbacks, anger, and suicide attempts. They had an ongoing medical history of hypertension, controlled with losartan and hydrochlorothiazide. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). The AE of increased

blood pressure occurred at 9:20AM before initial dosing (9:25AM) in Experimental Session 2 when their blood pressure reading was 158/100 mmHg. Two extra readings were taken at 9:20AM and 9:25AM and blood pressure had lowered to 142/92 mmHg and 143/89 mmHg, respectively. This AE was rated as mild and fully resolved the same day without intervention. The participant subsequently received an initial dose of 120 mg MDMA HCl and their interim blood pressure reading was 152/103 mmHg at 11:00AM, which further decreased at endpoint to 131/88 mmHg at 5:00PM following a supplemental dose of 60 mg MDMA HCl.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included muscle tightness, anxiety, insomnia, panic disorder, nightmares, major depression, migraines, intentional self-injury, fatigue, suicidal ideation, suicidal behavior, suicide attempts, and social anxiety disorder. They did not have a history of hypertension. Their Experimental Sessions were on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] (five days before their third Experimental Session and 23 days after their second Experimental Session), they were not feeling well and went to their doctor who took their blood pressure, which read 140/90 mmHg. They reported AEs of blood pressure increase, mild pyrexia, and mild anxiety all initiating on [redacted] and lasting three days, resolving on [redacted]. This TEAE was rated as mild and resolved fully without intervention. On the day of their third Experimental Session three days later on [redacted], their vitals were normal.

FDA Communication: "*2*. *Provide additional details for the cases of "non-cardiac chest pain." Provide narratives, if available."*

Sponsor Response 2:

Six participants reported TEAEs of non-cardiac chest pain, of which five were in the MDMA-AT group with overnight stay and one was in the placebo group with overnight stay.

Three of these participants, all receiving MDMA-AT and in the overnight stay group, reported TEAEs of non-cardiac chest pain that initiated within 48 hours following dosing:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included non-cardiac chest pain, anxiety, insomnia, major depression, bulimia nervosa, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). They reported non-cardiac chest pain on [redacted], two days after their first Experimental Session, which was rated as moderate. The participant was provided support from the therapy team and noted that their chest pain felt like tightness in their chest secondary to anxiety. This TEAE was recorded as fully resolved on 7 June 2019, 23 days later.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included generalized anxiety disorder, panic attacks, fear, a cardiac

murmur, aortic valve incompetence, mitral valve incompetence, and atrial septal defect. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl) and [redacted] (total dose 180 mg blinded MDMA HCl). They reported non-cardiac chest pain post-dosing on [redacted] on Experimental Session Day 2, which was rated as mild and resolved fully within one hour without intervention. The etiology was determined by the study physician to be due to anxiety rather than a cardiac event.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included anxiety, migraines, major depression, suicide attempt, insomnia, nausea, suicidal ideation, and headache. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). They reported non-cardiac chest pain during their second Experimental Session after dosing, which was described as lungs burning triggered by emotional processing during the session and rated as mild. It fully resolved the same day without intervention.

The remaining three participants with reported TEAEs of non-cardiac chest pain that initiated more than 48-hours following dosing are described below.

MDMA-AT participants:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included panic disorder as well as heart palpitations, anxiety, major depression, social fear, nightmares, intrusive thoughts, irritability, negative thoughts, cocaine use, ADHD, and selective eating disorder. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). They reported non-cardiac chest pain that was rated as mild on [redacted], the day prior to their second Experimental Session (and 28 days following their first Experimental Session), due to sadness with [redacted] illness and having to [redacted]. The AE fully resolved the same day without intervention.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their medical history included non-cardiac chest pain secondary to anxiety, depression, alcoholism, drug use disorder (cocaine and opiates), hypertension, insomnia, anxiety, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). They reported moderate non-cardiac chest pain secondary to anxiety on [redacted] (24 days after their second Experimental Session). This TEAE resolved on [redacted] (54 days later) without intervention. The participant reported that they experience chest pain when anxious. [redacted] described it as located in the center of [redacted] chest. The participant communicated with the site physician to monitor possible cardiac issues. [redacted] saw [redacted] cardiologist who was not concerned after performing an EKG. Episodes of anxiety-associated chest pains were confirmed by the study CI.

Placebo with therapy participants:

- Participant [redacted] was a [redacted]-year-old [redacted] in the placebo with therapy overnight group. Their medical history included generalized anxiety disorder, anxiety disorder, ADHD, headache, nausea, insomnia, major depression, emotional poverty, fatigue, substance use, and tinnitus. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded placebo), [redacted] (total dose 180 mg blinded placebo), and [redacted] (total dose 180 mg blinded placebo). They reported non-cardiac chest pain on [redacted], six days after their third Experimental Session, which was rated as mild. The participant reported worsening pain in chest, jaw, and back while doing a self-guided meditation on traumatic memories for two hours. It fully resolved the same day without intervention.

FDA Communication: ***"3****. Provide the quantitative temperature information, both absolute value and change from baseline, for the cases of pyrexia. Provide narratives, if available."*

Sponsor Response 3:

There were four participants who reported TEAEs of pyrexia, of which three occurred in the MDMA-AT group with overnight stay and one occurred in the placebo group with overnight stay. Of these TEAEs, all initiated more than 48 hours following dosing. These events are described below.

MDMA-AT participants:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). During their dosing sessions, their largest temperature increase was 0.4°C to 37.6°C, the highest recorded temperature in a session. No temperature increases in the session were recorded as pyrexia. Twenty days following their first Experimental Session, the participant reported mild pyrexia upon waking on [redacted] which lasted four days and resolved fully on [redacted] without intervention. On [redacted], they also reported an AE of dysuria. They took acetaminophen. There were no other concurrent AEs reported.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 120 mg blinded MDMA HCl). During their dosing sessions, their largest temperature increase was 1.2°C to 37°C, the highest recorded temperature in a session. No temperature increases in the session were recorded as pyrexia. Twenty-one days following their second Experimental Session, the participant reported mild pyrexia on [redacted], which lasted five days and was reported as resolved on [redacted]. They were prescribed paracetamol for the pyrexia, which they started on [redacted] and stopped on [redacted]. On [redacted], they reported ear pain. On [redacted], they also reported three other AEs: fatigue, dysphonia, and dizziness.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight group. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). During their dosing sessions, their largest temperature increase was 0.6°C to 37.5°C, the highest recorded temperature in a session. No temperature increases in the session were recorded as pyrexia. Twenty-three days following their second Experimental Session, the participant reported mild pyrexia on [redacted] which lasted three days and resolved fully on [redacted] without intervention three days prior to their third Experimental Session. AEs of blood pressure increase and anxiety were additionally reported on the same day as mild pyrexia.

Placebo with therapy participant:

- Participant [redacted] was a [redacted]-year-old [redacted] in the placebo with therapy overnight group. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded placebo), [redacted] (total dose 180 mg blinded placebo), and [redacted] (total dose 120 mg blinded placebo). During their dosing sessions, their largest temperature increase was 0.7°C to 36.8°C, and the highest recorded temperature in a session was 37.5°C. Four days following their most recent Experimental Session, the participant reported mild pyrexia on [redacted], that lasted three days and resolved fully on [redacted] without intervention. Oropharyngeal pain was also reported on the same day as mild pyrexia. On [redacted] they reported two additional AEs of cough and asthenia and were prescribed paracetamol for their pyrexia.

FDA Communication: ***"4.*** *Provide narrative for the cases of stress, intrusive thoughts, and nervousness and the definitions of these AE terms, if available."*

Sponsor Response 4:

Stress
There were four participants who reported TEAEs of stress that occurred in the MDMA-AT group, of which three were among participants who had an overnight stay. Of these, two participants reported TEAEs of stress that initiated within 48 hours following an experimental session.

Stress TEAEs within 48 hours of an experimental session:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT group with overnight stay. Their medical history included social anxiety disorder, insomnia, nightmares, anxiety, phobic avoidance, asthenia, and fatigue. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] (two days after their second Experimental Session), they reported mild stress that lasted 8 days, then fully resolved. The participant reported that the stress was related to an ongoing conflict where [redacted], where the participant lives.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT with no overnight stay group. Their medical history included insomnia, major depression, dissociation, neck pain, muscle spasms, anxiety, nightmares, fatigue, musculoskeletal pain, and suicidal ideation. Their Experimental Sessions were on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On the day of their third Experimental Session, the participant reported mild stress that resolved fully the same day.

TEAEs of "stress" that were initiated more than 48-hours following an experimental session are described below:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT group with overnight stay. Their medical history included hypervigilance, irritability, flashbacks, social fear, flat affect, exaggerated startle response, aggression, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] (11 days after their second experimental session), they reported mild stress which lasted eight days and resolved fully on [redacted]. The participant reported that this was due to their [redacted], resulting in their [redacted] being disrupted.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT group with overnight stay. Their medical history included depression, alcoholism, drug use disorder (cocaine and opioids), insomnia, anxiety, non-cardiac chest pain secondary to anxiety, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] (24 days after their first experimental session), they reported moderate stress that persisted until the end of the study. The therapist completed ongoing assessments of the participant's wellbeing for the duration of this event.

Intrusive Thoughts
There were four participants who reported TEAEs of intrusive thoughts, of which all were in the MDMA-AT group. Of these, two participants reported TEAEs of intrusive thoughts that initiated within 48 hours post-experimental session. Intrusive thoughts are defined as recurrent and persistent thoughts, urges or images that are experienced as intrusive, unwanted and that in most individuals, caused marked anxiety or distress.

Intrusive thoughts TEAEs that initiated within 48 hours following an experimental session:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT no overnight stay group. Their medical history included ADHD, major depression, panic disorder, insomnia, obsessive thoughts, and suicidal ideation. Their Experimental Sessions were on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). Sometime in early March (start date recorded as unknown), they reported that they began

experiencing mild intrusive thoughts which lasted until [redacted] when they fully resolved. An extra C-SSRS was administered on [redacted] during a mid-week call due to the intrusive thoughts. They reported a suicidal ideation score of 1 and suicidal intensity score of 15 with no suicidal behavior.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included intrusive thoughts, cannabis use, major depression, anxiety, flashbacks, anger, panic attack, emotional poverty, insomnia, hypervigilance, intentional self-injury, nightmares, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] following initial enrollment, before any Experimental Sessions had occurred, they reported worsening intrusive thoughts and images of hurting themselves without any desire or wish to do so that were rated as mild. Their C-SSRS score at Screening on [redacted] was1-13-No. The symptoms were not exclusionary; the site team assessed that the participant was not at increased safety risk continuing in the study. Their C-SSRS score at Baseline on [redacted] prior to dosing was 1-12-No. The adverse event was reported as resulted on [redacted], the day of the second experimental session. On [redacted] (two days after their second Experimental Session) they reported a TEAE of worsening intrusive thoughts of being abused, which were rated as mild. The intrusive thoughts resolved two days later on [redacted].

TEAEs of "intrusive thoughts" initiated more than 48-hours following an experimental session are described below:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included major depression, nightmares, anxiety, and suicidal ideation. They had one Experimental Session on [redacted] during which they received a total dose of 120 mg of blinded MDMA HCl. Due to COVID-19 shelter in place, the second experimental session was delayed and the study team scheduled weekly check-in calls. On [redacted] the participant was involved in a [redacted]. No injuries were sustained, but the participant reported feeling triggered and overwhelmed. On [redacted], they reported moderate intrusive thoughts which was documented as secondary to the [redacted] that persisted until they exited the study. The participant was lost to follow-up and terminated the study due to the COVID-19 pandemic.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included ADHD, insomnia, generalized anxiety disorder, adjustment disorder with mixed anxiety and depressed mood, hypervigilance, flashback, irritability, and negative thoughts. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted], they reported moderate intrusive thoughts that lasted seven days and fully resolved on [redacted]. They were prescribed alprazolam for their intrusive thoughts which they took for one day on [redacted].

Nervousness
There were three participants who reported TEAEs of nervousness, of which all were in the MDMA-AT group. Of these, two participants reported TEAEs of nervousness that initiated within 48 hours post-experimental session.

Nervousness TEAEs that initiated within 48 hours following an experimental session:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included intentional self-injury, panic disorder, major depression, palpitations, social fear, cannabis use, suicidal ideation, nightmares, intrusive thoughts, anxiety, irritability, feeling guilty, negative thoughts, cocaine use, selective eating disorder, and ADHD. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl), [redacted] (total dose 180 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On the day of their second Experimental Session, they reported nervousness that manifested as shaking and trembling, which was mild and resolved fully the same day. The shaking stopped when the participant was done emotionally processing. On the day of their third Experimental Session, they reported nervousness that again manifested as shaking and trembling, which was rated as mild and resolved fully the same day. The participant clarified that shaking is normal for them when they are nervous or emotionally processing.

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included depression, nightmares, anxiety, elevated blood pressure, somatic dysfunction, dizziness, major depression, intrusive thoughts, flashback, and suicidal ideation. Their Experimental Sessions took place on [redacted] (total dose 120 mg blinded MDMA HCl—they did not escalate), [redacted] (total dose 120 mg blinded MDMA HCl), and [redacted] (total dose 180 mg blinded MDMA HCl). On the day of their third Experimental Session, they reported nervousness that manifested as trembling inside the legs while processing sexual trauma history, which resolved fully the same day and was rated as moderate. There were no observable signs of the shaking and the MD onsite ruled out any neuromuscular events.

TEAEs of "nervousness" initiated more than 48-hours following an experimental session are described below:

- Participant [redacted] was a [redacted]-year-old [redacted] in the MDMA-AT overnight stay group. Their medical history included ADHD, generalized anxiety disorder, panic attack, migraine, marijuana use, and headaches. Their Experimental Sessions were on [redacted] (total dose 120 mg blinded MDMA HCl) and [redacted] (total dose 180 mg blinded MDMA HCl). On [redacted] (16 days after their second Experimental Session), they reported nervousness that they described as trembling inside which was rated as mild. It persisted at study termination and was diminishing.

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FDA Communication: *"5. We note that fewer AEs are reported in patients who did not stay overnight. Please describe how monitoring, vital signs, and AE reporting are conducted for the patients participating in the no overnight stay substudies."*

Sponsor Response 5:

Participants who did not complete an overnight stay underwent the same procedures for monitoring of vital signs and AE reporting following completion of the Experimental Session as those who did complete an overnight stay. Experimental Sessions concluded once all medical and psychiatric parameters were acceptable, elevations in vitals resolved to pre-IMP levels, the participant was alert, ambulatory, and emotionally stable, and the night attendant (for those with overnight stays) or support person (for those being dismissed with no overnight stay) had arrived. For all participants in the no-overnight stay sub-study, the therapist team made an assessment at the end of each experimental session to confirm that the participant could continue with the no-overnight stay as scheduled. Additional vital sign monitoring and AE reporting did not occur for either the overnight stay or no overnight stay group following conclusion of the Experimental Sessions.

Participants with an overnight stay remained overnight at the site following the Experimental Session until the Integrative Session the next morning. A night attendant stayed overnight at the study site and completed periodic check-ins with participants during the overnight stay. The primary function of the night attendants was to ensure the participant was comfortable and had a meal available, to provide minimal support, and to alert qualified site staff in case of need expressed by the participant or determined by observation per the overnight stay sub-study protocol. Night attendants did not provide any further safety monitoring. Participants who did not complete an overnight stay had a self-identified support person present overnight at the off-site location to fulfill a similar role to the night attendant for participants. All participants, regardless of overnight stay status, had their therapy team or site physician remain available to them via telephone for 24-hours following completion of each Experimental Session for integration, as needed.

Summary: We request the Division's review and consideration of the additional adverse event details provided in this response and agreement on removal of the clinical hold. Based on the data presented herein, the sponsor believes that the exclusion of participant overnight stays following the group treatment session in study MPG1 does not present an unreasonable or significant risk to participants. Accordingly, overnight stays should not be required in this study, and we request the Division agree to remove the clinical hold.

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: May 21, 2022 02:53 GMT+2

Amy Emerson
Chief Executive Officer
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Appendix

Appendix Table 1: 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)

*Includes all AEs with onset from first dosing to study termination