FDA Briefing Document

NDA/BLA# 215455

Drug name: midomafetamine

Applicant: Lykos Therapeutics

Psychopharmacologic Drugs Advisory Committee Meeting

June 4, 2024

Division of Psychiatry/Office of Neuroscience

DISCLAIMER STATEMENT

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Glossary

AC	Advisory Committee
ASI-MV	Addiction Severity Index-Multimedia Version
AE	adverse event
AESI	adverse event of special interest
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CDC	Centers for Disease Control
CI	confidence interval
CNS	central nervous system
DSM-5	Diagnostic and Statistical Manual of Mental Disorders version 5
DIM	drug-involved mortality
ECG	electrocardiogram
ETASU	elements to assure safe use
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
HAP	human abuse potential
HR	heart rate
ICSS	intracranial self-stimulation
LS	least squares
LTFU	long-term follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	midomafetamine
5-MEO-DMT	5-methoxy-N,N-dimethyltryptamine
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MTF	Monitoring the Future
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	new drug application
NMURx	nonmedical use of prescription drugs
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health

PC	Poison Center
PCL-5	PTSD Checklist for DSM-5
PK	pharmacokinetic
PTSD	posttraumatic stress disorder
PVC	premature ventricular contraction
RADARS	Researched Abuse, Division, and Addiction-Related Surveillance
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SDS	Sheehan Disability Scale
SSRI	selective serotonin reuptake inhibitor
SPA	special protocol assessment
SUDORS	State Unintentional Drug Overdose Reporting System
TCP	Treatment Center Program
TEAE	treatment-emergent adverse event
ToxIC	Toxicology Investigators Consortium

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Applicant has proposed the use of midomafetamine (also known as 3,4-methylenedioxymethamphetamine or MDMA) as a treatment for posttraumatic stress disorder (PTSD). The FDA is convening this Advisory Committee meeting to discuss the potential benefits and risks, as well as potential plans for risk mitigation, for the use of midomafetamine in the Applicant's proposed therapeutic context.

1.2 Context for Issues to Be Discussed at the AC

PTSD is a disabling psychiatric condition characterized by intrusive memories, hyperarousal, and avoidant behavior following exposure to actual or threatened death, serious injury, or sexual violence. Patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning that result in high healthcare utilization and diminished quality of life. The Veterans' Administration National Center for PTSD estimates that about 5% of the U.S. population has PTSD in any given year and that about 13 million Americans had PTSD in the year 2020. Women are more likely to develop PTSD than men, partly due to the types of traumatic events, such as sexual assault, that women are more likely to experience than men. Veterans are more likely to develop PTSD than civilians, and veterans who deployed to a war zone are more likely to develop PTSD than veterans who did not deploy.

The selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline are approved for the treatment of PTSD. Full onset of treatment effect is typically after 12 weeks of dosing. However, response rates for individuals with PTSD treated with SSRIs rarely exceed 60%, and less than 20 to 30% of patients achieve full remission (Berger et al. 2009). Thus, there remains an unmet need for additional options for safe and effective therapies to treat PTSD.

The Applicant is proposing a treatment regimen incorporating the use of midomafetamine with psychological intervention over a time-limited treatment course and has provided data intended to support short-term efficacy, durability of treatment effect, and safety of this treatment regimen.

1.3 Brief Description of Issues for Discussion at the AC

This application presents a first-in-class treatment for PTSD and a novel treatment paradigm. The Applicant's proposed treatment regimen consists of three medication sessions of midomafetamine administration in conjunction with psychological intervention for a single 4-month course of treatment.

Based on the clinical trial data submitted with this application, participants appear to experience rapid, clinically meaningful, durable improvement in their PTSD symptoms. However, several factors make these data challenging to interpret and complicate the benefit-risk assessment for this application. Chief among these factors is the nature of the treatment itself. First, midomafetamine produces profound alterations in mood, sensation, suggestibility, and cognition. As a result, studies are nearly impossible to blind. Although participants were randomized to either drug or placebo, the vast majority (approximately 90% of those assigned to drug and 75% of those assigned to placebo per a poststudy survey) were able to accurately guess their treatment assignment—the study was designed and

conducted as a double-blind trial, but participants experienced *functional* unblinding due to the effects of the drug itself. Functional unblinding can introduce bias in clinical studies. Along with bias from functional unblinding, there may also be expectation bias in which those who believed that they received active treatment expected that they would experience a clinical benefit, those who received placebo fared worse due to disappointment when they did not experience anticipated effects from the treatment, or some combination of both. In addition, it is likely that the in-session monitors could deduce a participant's treatment assignment based on that participant's behavior during the session. Thus, both the participant and the study staff were likely aware to which treatment arm a given participant was assigned. It is reasonable to assume that functional unblinding and expectation bias has impacted treatment effects observed in the clinical trials with MDMA to some extent.

Because the impact of unblinding cannot be quantified, we may consider other data sources to assess whether the observed results are driven by the midomafetamine. Assessments of durability of effect may assist in evaluating the treatment effects observed in the short-term treatment studies. To this end, the Applicant conducted a follow-up assessment after the end of the double-blind period at least 6 months (ranging from 6 months to more than 2 years) after the initial short-term treatment period. At this assessment, the mean change on the primary efficacy measure in the midomafetamine treatment arm remained and was greater than placebo, with some modest additional improvement. However, approximately 25% of participants dropped out between the parent study and the follow-up visit, there was a variable duration of follow-up, and some participants had intercurrent use of other therapeutic interventions, all of which limit the interpretability of these results. It is also unclear how long the impacts from functional unblinding and expectation bias in the controlled studies may last.

The Applicant is proposing that midomafetamine serves to facilitate a psychotherapeutic intervention by enhancing emotional and cognitive processing of trauma. However, the contribution of psychotherapy to the overall treatment effect observed in these clinical studies has not been characterized—all treatment arms in all studies submitted included psychotherapy. The manualized therapy (i.e., interventions performed according to specific guidelines) employed in this development program included therapeutic components that have previously been studied in people with PTSD. However, there have been no rigorous studies directly comparing this particular manualized therapy to other psychotherapeutic approaches or to a strictly pharmacological approach that administers MDMA without psychotherapy. Nonetheless, with psychotherapy present in all treatment arms, midomafetamine was superior to placebo following the acute treatment for PTSD and remained superior to placebo treatment at a long-term follow-up assessment.

In addition to factors that complicate assessment of efficacy, the assessment of safety presents numerous challenges. For example, the cardiac safety profile of midomafetamine is not well characterized and the QT-assessment is incomplete. Significant increases in both blood pressure and pulse were observed and were considered adverse events of special interest (AESI). This has the potential to trigger cardiovascular events, which have been described in literature reports of illicit MDMA use.

Additionally, there are limited clinical laboratory data available for review. Predose and postdose liver function studies were conducted in just one phase 1 study and two phase 2 studies, but liver function studies were not collected in the phase 3 studies. In the NDA submission, the Applicant designated hepatotoxicity to be an adverse event of special interest (AESI) based on cases of severe liver injury from literature reports of illicit MDMA use; however, this had not been previously identified as a safety signal

prior to or during the conduct of the clinical trials and hepatotoxicity was not designated as an AESI in the protocols. In the phase 1 and phase 2 midomafetamine clinical trials, there were no treatment-emergent adverse events (TEAEs) related to hepatocellular injury. However, the small sample sizes of the phase 1 and phase 2 studies make it difficult to use those studies to confirm the hepatocellular safety of the treatment regimen proposed for marketing. If this application were to be approved, the Agency would likely issue a postmarketing requirement to collect additional laboratory safety data, including liver function tests.

The subjective effects of midomafetamine present safety concerns for several reasons. Midomafetamine is known to cause a variety of effects including a sense of well-being, increased openness and empathy, enhanced sensory perception, and impaired ability to perceive and predict motion. (National Institute on Drug Abuse 2021). Although the Agency had advised the Applicant to collect adverse events that are associated with abuse, the studies did not capture effects deemed positive, favorable, or neutral, such as "euphoria" or "elated mood", that would be informative for an assessment of abuse potential or characterization of anticipated effects of the drug. The Applicant likely did not consider these as adverse events because adverse events are defined as events that are considered as "untoward". As a result, the application does not include verbatim terms from participants describing their experience and does not capture onset or duration of the acute effects of midomafetamine. The lack of information on abuse-related terms limits the assessment of abuse potential in the context of this program; however, there is extensive literature in both animals and humans and other available data related to midomafetamine's abuse potential to inform that assessment. The lack of data on the anticipated effects of midomafetamine makes it difficult to characterize the duration of the effects to inform recommendations for patient monitoring. It is known that subjective effects of MDMA can persist for several hours, rendering patients in an impaired and vulnerable state that necessitates safety monitoring.

Given the prolonged impairment and vulnerability that participants experience following midomafetamine administration, the clinical trials involved monitoring by two healthcare providers for the duration of the acute midomafetamine experience. The therapy manual describes the in-session intervention as nondirective and empathetic, and the therapist's role as a balance of facilitator and noninvasive observer.

Although this application presents a number of complex review issues, it does include two positive studies in which participants in the midomafetamine arm experienced statistically significant and clinically meaningful improvement in their PTSD symptoms, and that improvement appears to be durable for at least several months after the end of the acute treatment period despite no additional doses of midomafetamine. The committee will be asked to consider these data in the context of the uncertainties outlined above and described in detail below, the strategies proposed to mitigate risk, and the overall balance of benefits and risks of midomafetamine in the treatment of PTSD.

1.4 Draft Points for Consideration

Discuss the evidence of effectiveness for midomafetamine for the treatment of post-traumatic stress disorder. Consider the following:

The potential impact of functional unblinding on interpretability of efficacy results

The durability of effect

The role of psychological intervention in the treatment paradigm

Discuss whether the available data are adequate to characterize the safety of midomafetamine for the treatment of PTSD. In particular, consider the limited data collected on events deemed positive, favorable, or neutral that would inform abuse potential for this program and the lack of data from some clinical laboratory tests. Comment on whether you have concerns about other safety issues and what additional data would be useful to characterize the safety of midomafetamine.

Discuss the potential for patient impairment to occur with midomafetamine and the potential for serious harm that may result due to the impairment.

Discuss whether the proposed risk mitigation is sufficient to mitigate serious harm resulting from patient impairment. Include any additional safety monitoring conditions needed for the safe administration and monitoring of midomafetamine if approved for PTSD.

Do the available data show that the drug is effective in patients with posttraumatic stress disorder?

Do the benefits of midomafetamine with FDA's proposed risk evaluation and mitigation strategy (REMS) outweigh its risks for the treatment of patients with PTSD?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

The Applicant is developing midomafetamine for the treatment of PTSD in adults. PTSD is a psychiatric disorder that may occur following exposure to actual or threatened death, serious injury, or sexual violence. It is characterized by:

Intrusion symptoms (i.e., recurrent dreams or intrusive memories about the event, dissociative reactions in which the individual feels or acts as if the traumatic event were recurring, intense physiological reactions or psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event);

Persistent avoidance of memories, thoughts, feelings, or external reminders associated with the traumatic event;

Negative alterations in mood and cognition associated with the traumatic event (i.e., inability to experience positive emotions, inability to remember an important aspect of the traumatic event, distorted cognitions or guilt about the cause or consequences of the traumatic event); and

Marked alterations in arousal and reactivity (i.e., hypervigilance, exaggerated startle response, angry outbursts with little or no provocation, poor concentration, insomnia).

Patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning that result in high healthcare utilization and diminished quality of life. Per a 2007 Harvard Medical School National Comorbidity Survey (National Institute of Mental Health ; Martin et al. 2021), an estimated 3.6% of U.S. adults had PTSD in the past year, with higher past-year prevalence in women (5.2%) than men (1.8%), and a lifetime prevalence of 6.8%; the numbers are likely to have increased since then.

Current treatment options for PTSD include psychotherapy and pharmacotherapy. Two medications, the SSRIs paroxetine and sertraline, are approved for the treatment of PTSD. However, with SSRIs, full onset of treatment effect is typically after 12 weeks of daily dosing and response rates rarely exceed 60%. In addition, adverse effects such as nausea, headache, dry mouth, insomnia, and sexual dysfunctions may limit tolerability for some patients. Off-label treatments for PTSD include atypical antipsychotics, clonidine, prazosin, bupropion, buspirone, MAO inhibitors, mirtazapine, gabapentin, lamotrigine, trazodone, and propranolol. Efficacy data on off-label options is typically limited to case reports, making it difficult to assess the balance between benefits for this patient population and known risks of these drugs. The large number of off-label treatments that have been tried may reflect limited efficacy of the approved treatments for many patients. There is an unmet need for additional safe and effective treatment options for PTSD. Midomafetamine could potentially provide a new treatment alternative for patients with PTSD with the benefits of rapid onset of treatment effect, time-limited drug exposure, and improved tolerability compared to currently approved medications.

2.2 Pertinent Drug Development and Regulatory History

Midomafetamine acts as a serotonin, norepinephrine, and dopamine reuptake inhibitor and releasing agent. Midomafetamine is a ring-substituted phenylethylamine analog with a similar chemical structure to amphetamines. Although midomafetamine produces similar sympathomimetic effects to amphetamine and methamphetamine, it has more pronounced serotonergic effects compared to these other amphetamines. Midomafetamine has been historically included in the class of psychedelics, although it is less likely to produce the alterations in visual and auditory perception that are characteristic of “classic” psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and dimethyltryptamine (DMT). Midomafetamine may promote affiliative social behavior and a sense of connectedness with others and can reportedly lead to states of introspection and personal reflection. Midomafetamine is hypothesized to enhance the therapeutic process by increasing openness to experience, including processing memories of the traumatic experience that led to the onset of PTSD.

Highlights of Regulatory History

The Applicant opened IND 063384 in 2001 to develop midomafetamine for the treatment of PTSD. The Applicant conducted multiple phase 1 pharmacokinetic (PK) and safety studies and multiple phase 2 proof-of-concept studies before progressing towards phase 3 in 2016. The midomafetamine dosing strategy and FDA’s recommendations for the qualifications of staff that were monitoring research participants participating in clinical trials of psychedelics evolved during the course of the development program.

At an End-of-Phase 2 meeting in 2016, the Agency expressed concern about the adequacy of blinding, given that participants would likely be able to determine whether they are receiving midomafetamine or placebo. The Agency asked the Applicant to provide a plan to mask the identity of placebo, suggesting the use of niacin or low dose midomafetamine as comparators that would have enough physiological effect to limit recognizability as placebo. The Applicant argued against the use of low doses of midomafetamine, citing some evidence that low-dose midomafetamine had exacerbated anxiety in a few past study participants. The Applicant also argued against the use of niacin or of other stimulants, stating that these drugs could worsen PTSD symptoms, and felt that inert placebo would be the

preferable strategy, while acknowledging its limitations. The Agency and the Applicant did not reach agreement on the adequacy of the blind during this meeting.

In January 2017, the Agency received a protocol for phase 3 trial, MAPP1 as a special protocol assessment (SPA). A SPA is a process in which the sponsor of an investigational new drug (IND) attempts to reach agreement with FDA on the design of a study to adequately address scientific and regulatory requirements such that the study could support marketing approval. A SPA No Agreement letter was issued on March 9, 2017, as the Division did not agree with key elements of the protocol. However, the letter noted the following elements of the protocol would be acceptable.

A plan to minimize bias by using a blinded centralized independent rater pool to administer the primary outcome measure via live video interviews. The independent raters would be blinded to study design, visit number, treatment assignment, and any recorded adverse events (AEs), and would only see study participants by video at baseline and outcome assessments. The Agency stated that the proposed procedures for bias minimization were reasonable.

Midomafetamine-assisted psychotherapy would be the treatment arm for the trial and "identical psychotherapy with inactive placebo" would be the control. However, the Agency cautioned that "although we continue to have concerns regarding the adequacy of the blind and any inadvertent bias this may introduce to the study, we agree with your proposed plan."

The Agency agreed with several definitions for characterizing participants after midomafetamine-assisted psychotherapy in the phase 3 trial:

- Treatment response: the participant received at least one medication session and has a 10-point or greater reduction in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score.
- Loss of diagnosis: the participant received at least one medication session, has a 10-point or greater reduction in CAPS-5 total severity score, and no longer meets PTSD diagnostic criteria on the CAPS-5.
- Remission: the participant received at least one medication session, no longer meets PTSD diagnostic criteria on DSM-5, and has a CAPS-5 total severity score less than or equal to 11.
- There was agreement on standard safety endpoints with a few AEs of special interest (AESIs) designated related to cardiac function and abuse liability.

The Agency also advised the Applicant that: "For all Phase 1, 2 and 3 studies, [adverse events] associated with potential abuse or overdose must be documented." The Agency also referred to its *Guidance for Industry: Assessment of Abuse Potential of Drugs* (January 2017) for additional details regarding the documentation of adverse events.

A Type A meeting was held on May 11, 2017, to discuss the SPA No Agreement letter. During the meeting, the following agreements were reached between the Applicant and the Agency:

Two phase 3 trials with identical designs would be conducted to support the NDA and that a separate SPA for the second phase 3 trial, MAPP2, would not be necessary. The two trials would be run independently and sequentially, predominantly at the same sites.

A thorough QT study would be conducted prior to submission of the NDA, but not prior to the start of the phase 3 trial.

It would not be necessary to conduct new animal and human studies of the abuse potential of midomafetamine.

An SPA request was resubmitted in June 2017, and on July 28, 2017, the Agency issued a Special Protocol – Agreement Letter, stating that the design and planned analysis of the study adequately address the objectives necessary to support a regulatory submission. A clinical SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints, and planned analyses) for a study intended to support a future marketing application. However, a SPA agreement does not indicate FDA concurrence on every protocol detail. The existence of a SPA agreement does not guarantee that FDA will accept an NDA for filing or that the trial results will be adequate to support approval. Those issues are addressed during the review of a submitted NDA and are still based on the adequacy of the overall submission. The overall data package would still need to meet the regulatory standards of substantial evidence of effectiveness and demonstration of adequate safety for the proposed indication.

Breakthrough Therapy Designation for midomafetamine for the treatment of PTSD was granted on August 15, 2017.

Initially the MAPP1 protocol included an overnight stay for patients. Amendment 1, received on March 9, 2018, introduced a sub-study to assess the feasibility of medication sessions without an overnight stay. The protocol synopsis for the sub-study states: “In the sub-study, if a participant is deemed medically and psychologically stable by the therapy team at the end of the [Medication] Session, the participant will be escorted home via car, rideshare, or public transportation and will not remain overnight at the study site.” A support person selected by the participant was required to stay with the participant overnight.

MAPP1 Protocol Amendment 2, received on September 16, 2019, added nonpostural syncope as an AESI as this could potentially indicate QT interval prolongation. Additionally, the Applicant clarified that all events related to drug abuse, intentional misuse, dependence, overdose, or diversion would be captured as AEs, but only those AEs related to midomafetamine or ecstasy would be classified as AESIs.

MAPP1 Protocol Amendment 3, received on November 15, 2019, clarified the AESI of suicide risk to include AEs recorded under the terms suicide, suicide attempt, self-injurious behavior associated with suicidal ideation, and suicidal ideation judged to be serious or severe in the opinion of the investigator. Additionally, occurrences of scores of 4 or 5 on the C-SSRS were counted as AESIs.

After the Agency sent comments suggesting a Participant Blinding Survey on October 19, 2020 in response to a MAPP2 Amendment submission, the Applicant agreed to submit the results in the NDA submission.

During a Type B Breakthrough Therapy Designation advice meeting on September 14, 2022, the Agency discussed with the Applicant ongoing concerns about the adequacy of the safety database to support an NDA and the need for further data on durability of effect for midomafetamine. The Agency noted ongoing concerns about the adequacy of their proposed study MPLONG for supporting the durability of their existing treatment paradigm but agreed its results could be submitted for review.

A pre-NDA meeting was held on May 3, 2023. The Agency noted that the specific risks to be addressed through the REMS would be a matter of review.

The Applicant submitted an NDA on December 11, 2023. The submission includes a document titled "Hepatotoxicity Safety Signal Evaluation Report" as an appendix to the Integrated Summary of Safety. In the report, the Applicant's stated rationale for a signal evaluation is "Published literature reports of hepatobiliary disorders associated with illicit MDMA use. The majority of sponsor trials did not capture clinical laboratory data pertinent to the evaluation of treatment-emergent liver abnormalities." This issue is discussed in Section 3.3 .

3 Overview of Efficacy and Safety

3.1 Efficacy Issues

Key Efficacy Issue 1: Treatment effect and potential bias

- Has the Applicant demonstrated efficacy of midomafetamine?
- How does the demonstration of functional unblinding affect the interpretability of the efficacy data?

Key Efficacy Issue 2: Durability of treatment effect

- Has the Applicant demonstrated durability of treatment effect of midomafetamine?
- How does unblinding impact the interpretability of data from Study MPLONG?
- Do the open-label efficacy data from Study MPLONG provide supporting evidence for durability of treatment effect of midomafetamine?

Key Efficacy Issue 3: Contribution of psychotherapy

3.1.1 Sources of Data for Efficacy

The Applicant has submitted data from four 18-week studies shown in and an observational follow-up study, MPLONG. MPLONG enrolled participants from among those who participated in one of the 18-week studies.

Table 1. Eighteen-Week Studies

Study Name	Phase	Status	Control and Blinding	Inclusion Criteria	Sample Size	Primary Endpoints	Key Secondary Endpoints
MP16	2	Completed 8/10/2019	Open-label	Severe PTSD	33 enrolled, 32 completed	CAPS-5	none
MAPP1	3	Completed 8/21/2020	Placebo-controlled, double-blind	Severe PTSD	91 randomized	CAPS-5	SDS
MAPP2	3	Completed 11/2/2022	Placebo-controlled, double-blind	Moderate or severe PTSD	104 randomized	CAPS-5	SDS
MAPPUSX	Extension	Completed 11/6/2023	Open-label	Placebo or no study drug in MAPP1 or MAPP2	85 enrolled, 78 completed	PCL-5	none

Source: Table generated by the Clinical Reviewer.
Abbreviations: CAPS, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; PTSD, posttraumatic stress disorder

Placebo-Controlled Studies

Study MAPP1 was a randomized double-blind, placebo-controlled 18-week phase 3 study that assessed the efficacy of midomafetamine for the treatment of PTSD. The study enrolled participants with severe PTSD. The study was developed under an agreed SPA.

Study MAPP2 had the same design as MAPP1 but a different study population, enrolling participants with moderate or severe PTSD.

Open-Label Studies

Study MAPPUSX was an 18-week open-label, safety extension study designed to evaluate the safety and efficacy of midomafetamine in participants with moderate or severe PTSD who were assigned to the placebo arm of either MAPP1 or MAPP2.

Study MP16 was an open-label, 18-week phase 2 study designed to evaluate the safety and efficacy of midomafetamine in participants with severe PTSD.

Neither MAPPUSX nor MP16 was intended to provide substantial evidence of effectiveness, so we will not discuss them in detail.

Observational Study

MPLONG was an observational follow-up study consisting of a single visit at least 6 months after the end of Study MAPP1, MAPP2, MAPPUSX, or MP16. The primary objective was "to evaluate the long-term effectiveness of MDMA-assisted psychotherapy for the treatment of PTSD."

Following completion of MAPP1, MAPP2, MP16, or MAPPUSX, patients could enroll in MPLONG. MPLONG was initiated after completion of MAPP1, leading to differences in the length of time between completing the parent study and enrolling in MPLONG (i.e., the follow-up visit timepoint was usually greater than 12 months for participants from MAPP1 and 6 to 12 months for MAPP2). Participants from

MAPP1 were unblinded to their prior treatment before enrollment in MPLONG, but participants from MAPP2 remained blinded to their prior treatment during participation in MPLONG.

Only patients coming directly from MAPP1 or MAPP2 were included in the analyses of MPLONG presented in this briefing document.

MPLONG was completed on May 21, 2023. The Applicant's NDA submission includes an Interim Clinical Study Report (CSR) for MPLONG, with a data cut-off date of February 6, 2023, for the interim analysis. The Applicant's 120-Day Safety Update for the NDA includes updated safety data for MPLONG. The updated safety data for MPLONG was collected after the interim CSR cutoff date for that study. MPLONG enrolled 164 participants, including 142 participants enrolled from the phase 3 studies, MAPP1 and MAPP2.

3.1.2 Study Descriptions

3.1.2.1 Eighteen-Week Studies (MAPP1, MAPP2)

3.1.2.1.1 Study Design

MAPP1 and MAAP2 employed identical study designs in terms of dosing/treatment regimen and time course; however, MAPP1 enrolled participants with severe PTSD and MAPP2 enrolled participants with moderate to severe PTSD. The main design elements of the studies are shown in .

The placebo-controlled 18-week studies followed the study schedule and treatment regimen presented below under Sequence of Events. For MAPP1 and MAPP2, participants were randomized 1:1 to treatment with either midomafetamine plus psychological intervention or placebo plus psychological intervention. Randomization was stratified by clinical site.

There were no studies that included midomafetamine only or placebo only treatment arms without the psychological intervention and no study included the psychological intervention only (without midomafetamine or placebo).

Approach to Psychotherapy

Under their treatment paradigm, the Applicant hypothesized that midomafetamine serves to facilitate the effects of psychotherapy, rather than serve as a direct and primary mode of treatment for PTSD. The goal of psychological intervention differed at different stages of the treatment intervention. There were three preparatory sessions with the therapist prior to administration of study drug or placebo, followed by three medication sessions during which participants received either midomafetamine or placebo together with a psychological intervention (see details below). Each medication session was followed by three integrative sessions (nine integrative sessions total).

According to the *MAPS Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*, the purposes of the preparatory sessions were to gather participant history, to begin establishing a therapeutic alliance, to help the participant prepare to remain present with whatever inner experience arises during the medication session, to model attitudes such as respect for the participant's boundaries, and to help participants prepare for sensations such as anxiety and physical tension that may arise as traumatic memories emerge.

The therapeutic stance of the therapist during medication sessions was to be supportive and to follow the participant's lead rather than to direct the experience. The therapist might choose silence and empathetic listening or more active support, including helping the participant to verbally process

memories of the traumatic event, depending on the therapist's perception of the participant's needs during the session.

The purpose of the integrative sessions was to help the participants describe their experiences of the medication sessions, particularly the experience of remembering the trauma. These were the main sessions where more primary psychotherapeutic interaction appeared to occur, rather than just general support, reflection, and psychoeducation. However, the content or approach of these integrative sessions was not standardized in the treatment manuals and left mainly up to the individual therapist.

3.1.2.1.2 Study Population

Key inclusion criteria for the studies were:

Met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria for post-traumatic stress disorder for at least 6 months.

Key exclusion criteria for the studies were:

A history of or a current primary psychotic disorder, bipolar I disorder, or dissociative identity disorder

Current personality disorder, major depressive disorder with psychotic features, or eating disorder with active purging

Moderate (met 5 of 11 DSM-5 criteria) within the past 3 months or severe (met 6 or more of 11 DSM-5 criteria) within past 12 months alcohol or cannabis use disorder (note: participants with mild alcohol or cannabis use disorder (meets 3 of 11 criteria per DSM-5) or moderate alcohol or cannabis use disorder (met 5 of 11 DSM-5 criteria) in the 3 months prior to enrollment were allowed in the study)

Active illicit (other than cannabis) or prescription drug substance use disorder at any severity within the past 12 months

Any participant presenting current serious suicide risk (history of suicide attempts was not an exclusion) or a serious risk to others

Ongoing concomitant therapy with a psychiatric medication

History of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate including:

- Current uncontrolled essential hypertension
- A history of arrhythmia (other than occasional premature ventricular contractions [PVCs]) in the absence of ischemic heart disease, within 12 months of screening (patients with a history of atrial fibrillation, atrial tachycardia, atrial flutter, or paroxysmal supraventricular tachycardia or any other arrhythmia associated with a bypass tract were enrolled only if they had been successfully treated with ablation and had not had recurrent arrhythmia for at least 1 year off all antiarrhythmic drugs confirmed by a cardiologist.)
- Any history of ventricular arrhythmia
- Wolff-Parkinson-White syndrome or any other accessory pathway that had not been successfully eliminated by ablation

QTc interval >450 ms in males and >460 ms in females (corrected by Bazett's formula; for transgender or nonbinary participants, QTc interval was evaluated based on sex assigned at birth, unless the participant had been on hormonal treatment for 5 or more years), history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome), or

required use of concomitant medications that prolong the QT/QTc interval during medication sessions

Symptomatic liver disease or significant liver enzyme elevations

History of hyponatremia or hyperthermia

Engaged in ketamine-assisted therapy or used ketamine within 12 weeks of enrollment

Prohibited concomitant medications:

- Participants were required to refrain from use of any psychoactive medication not approved by the research team from baseline through study termination. Exceptions were gabapentin and the opiates hydrocodone, morphine, and codeine for pain control. Other opiates were required to be cross-tapered to an allowable opiate prior to the first medication session.
- Use of marijuana, St. John's Wort, and other herbs and medications with notable serotonergic effects were prohibited from baseline to study termination.
- Diphenhydramine was excluded from the study unless prior approval was granted by the site physician.
- The protocol required discontinuation from study treatment and continuing in follow-up if an SSRI, SNRI, MAOI, or other antidepressant was used between the first medication session and study termination.
- Opiates other than hydrocodone, morphine, and codeine were prohibited from enrollment confirmation to study termination.

Additional key exclusion criteria for MAPP2 were:

Had used ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first medication session; or had previously participated in a MAPS-sponsored MDMA clinical trial.

Were currently engaged in compensation litigation whereby financial gain was to be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.

The studies differed in the severity of PTSD symptoms required for eligibility. MAPP1 enrolled participants with severe PTSD symptoms (PCL-5 score ≥46 at screening; CAPS-5 score ≥35 at baseline). MAPP2 enrolled participants with moderate to severe PTSD symptoms (PCL-5 score ≥40 at screening; CAPS-5 score ≥28 at baseline).

3.1.2.1.3 Efficacy Assessments

For studies MAPP1, MAPP2, the primary efficacy endpoint was the clinician-reported outcome PTSD Scale for DSM-5 (CAPS-5). The Applicant used a blinded, centralized independent rater pool for the primary and key secondary efficacy endpoint assessments in MAPP1 and MAPP2. These independent raters completed a training program prior to administering any assessments. Training included videos on the specific clinical outcomes assessments to be administered by the independent raters, scoring of a demonstration video and completion of at least one mock efficacy assessment administration to assess their abilities. Additionally, independent reviewers were required to participate in ongoing trainings and review during the duration of the trial. The use of the independent rater was conducted via telemedicine and recordings of the assessments were used to establish inter-rater reliability.

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The CAPS-5 is a 20-item clinician-reported outcome measure in which a blinded, centralized independent clinician rater conducted a semistructured interview to assess key symptoms of PTSD over the last month. CAPS-5 served as the primary endpoint for MAPP1 and MAPP2 studies (and the open-label MP16 study). The CAPS-5 was designed to align with the DSM-5 clinical criteria for PTSD. Each item has a response option from 0 to 4, with a score of 4 indicating the highest severity. A total severity score is then created by summing the individual scores. The total severity score range is 0 to 80, with a higher score indicating more severe PTSD symptoms.

Sheehan Disability Scale (SDS)

The SDS is a three-item clinician-reported outcome that measures PTSD symptoms and the disability and impairment caused by those symptoms. SDS served as a key secondary endpoint for MAPP1 and MAPP2 studies. SDS examines three areas: family life, social life, and work/school. The SDS was assessed by blinded, centralized independent clinician rater who conducted a semistructured interview. The scale generates four scores: a family life disability score, a social life disability score, a work disability score, and a total score. The response options range from 0 to 10 with 0 indicating “not at all” and 10 indicating “extremely.” A total score is created by summing the three items, giving a total score range of 0 to 30, with a higher score indicating higher levels of disability/impairment. For the SDS, the Agency asked the Applicant to modify the SDS to reflect that if a person could not work due to reasons related to their PTSD, then the item should be scored as a 10 or the highest value instead as a missing value. For people who did not work for a reason other than PTSD, the missing value was imputed by averaging the other two items to create the total score.

PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 was used as a screening assessment for enrollment and as an efficacy outcome in MAPPUSX. The PCL-5 is a 20-item patient-reported outcome measure examining stress from PTSD symptoms. PCL-5 served as the primary endpoint for the open-label MAPPUSX study. Patients are asked to reflect over the past month on their experience with stress from individual PTSD symptoms. Response options range from 0 to 4 with 0 indicating “not at all” and 4 indicating “extremely.” A total score is created by summing each question for a range of 0 to 80; a higher score indicates higher levels of stress from PTSD symptoms.

3.1.2.1.4 Dosing Regimen

Based on literature reports, following an oral single dose of 100 mg dose of midomafetamine in healthy adult participants, mean peak plasma concentration (C_{max}) was 238 ng/mL and occurred approximately 2 hours (T_{max}) postdose in the fasting state. The decline after T_{max} in plasma midomafetamine concentrations was mono-exponential, with a mean terminal half-life ($t_{1/2}$) of 8.7 hours. Midomafetamine is extensively metabolized in humans primarily by CYP2D6 and CYP2B6. Midomafetamine is a strong CYP2D6 inhibitor, and it exhibits nonlinear PK due to its CYP2D6 auto-inhibition. Coadministration with food will not significantly impact the exposure but will delay the T_{max} for 2 hours.

The medication regimen used in the four 18-week studies consisted of three sessions of midomafetamine administration and is summarized in . For each session, there was an initial dose of

midomafetamine administered. A second dose was administered 1.5 to 2 hours after the initial administration, if the participant was tolerating the dose.

Based on the physiologically based pharmacokinetic (PBPK) simulations, the C_{max} and AUC are similar for single-dose and split-dose regimens. Therefore, incorporation of split dosing can extend the presence of the peak effects by the amount of time before the second dose without increasing the exposure of MDMA.

Table 2. Midomafetamine Dosing Regimen for Medication Sessions in Studies MAPP1, MAPP2

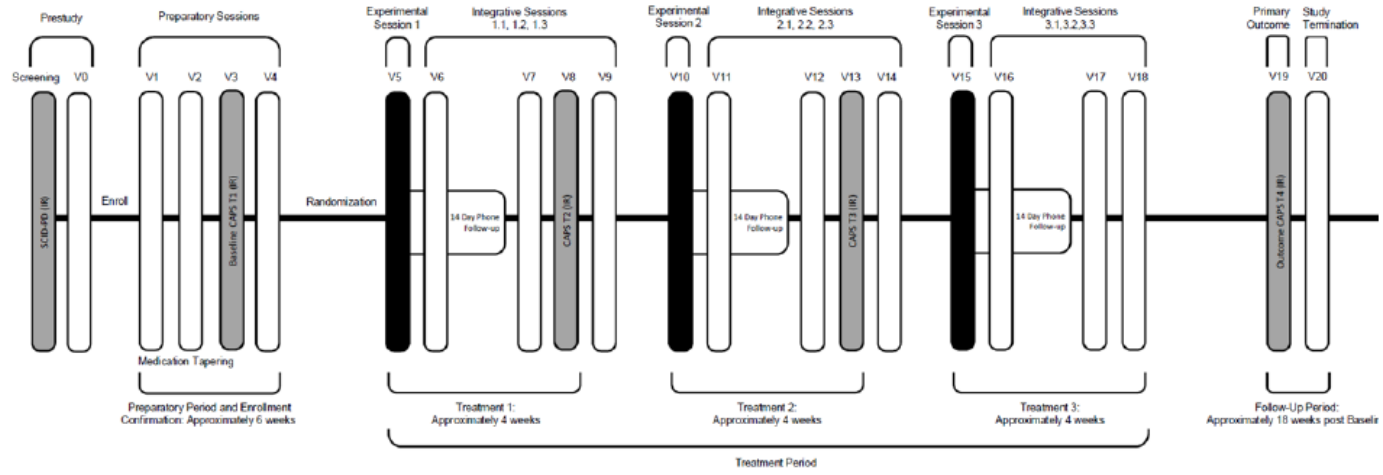
Medication Session	Initial Administration (mg)	Second Administration, 1.5 to 2 Hours Later (mg)	Total Dose (mg)
1	68 mg	34 mg	102 mg
At least 21 days between medication sessions			
2	100 mg	50 mg	150 mg
At least 21 days between medication sessions			
3	100 mg	50 mg	150 mg
Total cumulative dose			402 mg

Source: Table generated by the Clinical Reviewer.

3.1.2.1.5 Schedule of Events

The total duration of the treatment period was from 9 to 15 weeks. See for an overview of the study structure for MAPP1 and MAPP2.

Figure 1. MAPP1, MAPP2 Study Structures



Source: Applicant's Clinical Study Report: MAPP1, Figure 1, page 21.
Abbreviation: CAPS, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5

Study visits:

Screening and Enrollment (Visit 0): Consisted of the following assessments over 7 to 27 days: Screening for eligibility, including medical history, discussion of tapering medications that might interact with midomafetamine, symptom self-reports, independent rater assessments, laboratory assessments, and informed consent.

Preparatory Period (Visits 1, 2, and 4) and Baseline Assessment (Visit 3): Prior to the first medication session, participants had three preparatory psychotherapy sessions to discuss the process of treatment with midomafetamine. Prohibited medications were also tapered as needed due to potential interactions, such as those that could increase the risk of serotonin syndrome. The baseline assessment (CAPS-5 or PCL-5) was conducted by an independent rater at Visit 3. At Visit 4, final eligibility was confirmed following review of the baseline assessment conducted at Visit 3. The Preparatory Period lasted up to 11 weeks, depending on the time needed for medication tapering. Participants in the two placebo-controlled studies MAPP1 and MAPP2 were randomized to midomafetamine or placebo at Visit 4.

Treatment Period: Studies MAPP1, MAPP2 all evaluated the same treatment regimen. For each study, a participant was scheduled for three medication sessions (Visit 5, Visit 10, and Visit 15), each lasting approximately 8 hours and separated by at least 3 but no more than 5 weeks. Midomafetamine was provided at the research site in 34 mg or 50 mg capsules, depending on whether this was the first, second, or third medication session. A lower total midomafetamine dose was administered at the first session (102 mg, compared to 150 mg at subsequent sessions) to allow participants to acclimate to the effects of midomafetamine. Split dosing was used at each medication session, with participants taking two capsules of midomafetamine at the beginning of the medication session and one capsule 1.5 to 2 hours later.

- Each medication session was followed by three integrative sessions for a total of nine integrative sessions over the course of treatment.
- An efficacy assessment was conducted by an independent rater (CAPS-5 for MAPP1 and MAPP2) 18 to 30 days after each of the first two medication sessions.

Follow-up Period and Study Termination (Visits 19 and 20): The final efficacy assessment (CAPS-5) was conducted at Visit 19, approximately 4 weeks after the last integrative session. Study termination was conducted at Visit 20, 1 to 9 days after the final efficacy assessment.

3.1.2.1.6 Statistical Analysis Methods for MAPP1 and MAPP2

For both MAPP1 and MAPP2, an independent data monitoring committee with expertise in PTSD clinical trials acted in an advisory capacity to review safety and study data provided by an independent statistical programmer.

Randomization was stratified by clinical site. The modified intent-to-treat population (mITT) was used for the analysis of efficacy and included all randomized participants who received the investigational product in at least one blinded medication session and who had at least one follow-up CAPS-5 assessment post-treatment. The Applicant prespecified the use of a *de jure* estimand for the primary analysis of the primary endpoint, which targets the treatment effect of the initially randomized treatment by excluding data after early termination. No missing data for the primary endpoint analysis was imputed.

To control the overall type I error rate, the Applicant used a hierarchical testing strategy. The primary endpoint, the CAPS-5 total severity score at Visit 19, was tested first. If the analysis of the primary endpoint was significant, the Applicant tested the key secondary endpoint, the SDS total score.

Sample Size Re-estimation

For both studies, an independent DMC statistician conducted an unblinded sample size re-estimation when at least 60% of the participants in the mITT set completed the primary endpoint. If the conditional power was between 50% and 90%, the sample size could be increased to the amount that would provide 90% power. The Sponsor allocated 2% of the alpha (0.0001) to the unblinded sample size re-estimation to account for any possible downward bias in the variance estimate. For both studies, based on the results of the unblinded sample size re-estimation, the independent data monitoring committee recommended not increasing the sample size.

Analysis of the Primary Endpoint: CAPS-5 Total Severity Score

CAPS-5 total score was assessed at Visits 8, 13, and 19, which were approximately 6 weeks, 10 weeks, and 18 weeks after randomization, respectively. The primary endpoint, the change from baseline in CAPS-5 total severity score to 18 weeks after randomization (Visit 19), was analyzed using a mixed model for repeated measures (MMRM). The treatment effect at Visit 19 was conducted at a two-sided, 0.0499 level of alpha because the remaining alpha of 0.0001 was allocated to the interim sample size re-estimation. The change from Baseline to Visits 8, 13, and 19 were included in the model. To estimate the treatment effect at each visit, an interaction between visit and treatment was included in the model. The baseline CAPS-5 total severity score and an indicator for dissociative subtype at baseline were included as covariates in the model and investigative site was included as a fixed effect. The MMRM was fit using restricted maximum likelihood and an unstructured covariance matrix. The Applicant prespecified that the effective degrees of freedom would be calculated using the Satterthwaite approximation, but they actually used the between-within method (which made no practical difference in the results).

Supplementary and Sensitivity Analyses of the Primary Endpoint

As a supplementary analysis of the primary endpoint, the Applicant repeated the MMRM model but used a *de facto* estimand, which estimates the treatment effect using a treatment policy approach by including all available CAPS-5 outcome data from all participants in the mITT set regardless of adherence to the treatment.

The Applicant conducted a tipping point analysis to assess the sensitivity to the assumption for the primary analysis that data after treatment discontinuation was missing at random. If the “missing at random” assumption is reasonable, the response trajectories of dropouts would be similar on average to those of the completers within treatment groups. Tipping point analysis involves first using multiple imputation to impute missing Visit 13 and Visit 19 CAPS-5 total severity scores within treatment arms under the missing at random assumption. Imputed Visit 19 CAPS-5 scores for patients in the midomafetamine arm were then penalized by a shift parameter. The shift parameter was increased until the results of the primary analysis were no longer statistically significant. This analysis assessed how large a deviation from the missing at random assumption would have to be to impact the conclusion. One thousand datasets with imputed values were generated and the analysis of the primary endpoint was replicated.

Analysis of the Key Secondary Endpoint: SDS Total Score

The key secondary endpoint, the change from baseline in SDS total score to 18 weeks after randomization (Visit 19), was analyzed using the *de jure* estimand, a two-sided 0.0499 level of alpha and an analogous MMRM model as the one used for the primary endpoint.

3.1.2.2 Observational Study MPLONG

3.1.2.2.1 Study Design

MPLONG was an observational, noninterventional study that consisted of a single follow-up assessment. It was intended to evaluate the long-term safety and durability of the treatment effect for midomafetamine-assisted therapy. The study enrolled participants who had received at least one dose of midomafetamine in Study MAPP1, MAPP2, MP16, or MAPPUSX; however, the Agency's analyses of MPLONG data presented in this briefing document only include participants from MAPP1 and MAPP2. Participants from MAPP1 were unblinded to prior treatment and those from MAPP2 remaining blinded to prior treatment during follow-up on enrollment in MPLONG.

The study involved a single follow-up visit scheduled at least 6 months after the last dose of study drug in the parent study. The actual amount of time between the last dose of study drug and the MPLONG visit varied from 6 months to more than 2 years. The study protocol included a review of adverse events, a single administration of the C-SSRS, and a single administration of the primary efficacy assessment tool used in the parent study.

Per protocol, no additional doses of midomafetamine were administered to any participants participating in MPLONG; however, some participants received interim potentially therapeutic interventions during this time, including psychotherapy and use of other substances such as ketamine, 5-methoxy-N,N-dimethyltryptamine (5-MEO-DMT), MDMA obtained outside of the study, and other psychedelics.

3.1.2.2.2 Statistical Analysis Methods

The effectiveness set included all participants from MAPP1 and MAPP2 who directly enrolled in MPLONG and completed a follow-up PTSD endpoint assessment in MPLONG. Although placebo participants from MAPP1 and MAPP2 were eligible to enroll in MAPPUSX either directly from those studies or following an initial participation period in MPLONG, this set did not include any data from participants after participation in MAPPUSX. The effectiveness subset was used for the efficacy analyses. The Applicant did not prespecify a plan to control the type I error rate or an estimand strategy, so these results should be considered exploratory. The statistical analysis plan states that no missing data would be imputed in the efficacy analyses.

Analysis of the CAPS-5 Total Severity Score

The change from parent study (MAPP1 or MAPP2) baseline in CAPS-5 total severity score was analyzed using an MMRM. The change from Baseline to Visits 8, 13, and 19 from the parent studies and the change from Baseline to the long-term follow-up (LTFU) Visit 1 was included in the model.

The parent study baseline CAPS-5 total severity score, an indicator for dissociative subtype at baseline, an indicator for study (MAPP1 or MAPP2), visit, and an interaction between visit and treatment were included as covariates in the model. Investigative site was included as a fixed effect and an unstructured

covariance matrix was used. The model was fit using restricted maximum likelihood. They used the between-within method of estimating degrees of freedom.

The change from Visit 19 to the LTFU Visit 1 was estimated using least squares (LS) means for each treatment arm. The applicant presented pooled results for both MAPP1 and MAPP2, but because participants from MAPP1 were unblinded to prior treatment before enrolling in MPLONG and because the studies enrolled participants with different levels of symptom severity (severe for MAPP1 and moderate-to-severe for MAPP2), results are presented from separate models for each study.

MPLONG was initiated after MAPP1 completed, but while MAPP2 was ongoing. As a result, there were differences in the length of time between completing the parent study and enrolling in MPLONG (i.e., greater interstudy interval between MAPP1 and MPLONG than MAPP2 and MPLONG). The LTFU Visit 1 was conducted at least 6 months after parent study completion, and the timing ranged from 6 to 24 months after. To assess the impact of the timing of the LTFU Visit 1, the Applicant repeated the analysis of CAPS-5 but stratified analyses based on timing of the LTFU visit (6 to 12 months or >12 months after the parent study). Each participant fell into only one time window.

3.2 Efficacy Results

3.2.1 Efficacy Results for MAPP1, MAPP2

3.2.1.1 Populations and Baseline Characteristics for MAPP1, MAPP2

The number of participants who enrolled, who were included in different analysis populations, and who completed MAPP1, MAPP2, and enrolled in MPLONG is shown in .

Table 3. Analysis Populations

	MAPP1			MAPP2		
Analysis Population	**Midomafetamine**	**Placebo**	**Total**	**Midomafetamine**	**Placebo**	**Total**
Screened			345			324
Screen failed			214			203
All randomized	46	45	91	53	51	104
Safety	46	44	90	53	51	104
mITT	46	44	90	53	50	103
Per protocol	42	37	79	52	42	94

	MAPP1			MAPP2		
Analysis Population	**Midomafetamine**	**Placebo**	**Total**	**Midomafetamine**	**Placebo**	**Total**
# Completed Visit 19	**42**	**37**	**79**	**53**	**43**	**96**
# Enrolled in MPLONG (analysis subset)	30	30	60	45	37	82
MPLONG Effectiveness subset	**27**	**29**	**56**	**44**	**37**	**81**
# completed MPLONG	26	29	55	43	37	80
# ongoing	0	0	0	0	0	0
# terminated MPLONG early	4	1	5	2	0	2

Source: Table 6 and Table 8 in MAPP1 CSR; Table 5 and Table 7 MAPP2 CSR; Table 14.1-1.1, Table 14.1-1.2, Table 14.1-2.1, and Table 14.1-2.2 in MPLONG ISE from durability update submitted to eCTD Seq 0047.
Safety: All participants who received any IMP.
mITT: All randomized participants who received IMP in at least one blinded medication session (Visit 5) and had at least one follow-up CAPS-5 assessment posttreatment.
PP: All randomized participants who met the eligibility criteria, who received IMP in three medication sessions, and had three follow-up CAPS-5 assessments posttreatment.
MPLONG analysis subset: All MAPP1/MAPP2 participants who enrolled in MPLONG.
MPLONG effectiveness subset: All MAPP1/MAPP2 participants who enrolled in MPLONG and who completed a follow-up PTSD endpoint assessment in the LTFU study.
Ongoing as of the date of data extraction.
Abbreviations: CAPS, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; CSR, clinical study report; eCTD, electronic common technical document; IMP, investigational medicinal product; ISE, integrated summary of efficacy; LTFU, long-term follow-up; mITT, modified intent-to-treat; PP, per protocol; PTSD, posttraumatic stress disorder

The demographic and baseline characteristics of the safety set of MAPP1 and MAPP2 are shown in Table 4. The midomafetamine and placebo arms were generally balanced. Percentages are calculated using the number of participants in each treatment group as the denominator. Participants in MAPP2 were more racially and ethnically diverse relative to participants in MAPP1.

Table 4. Demographics and Baseline Characteristics of the Safety Set for MAPP1 and MAPP2

	MAPP1			MAPP2		
Variable	**Midoma-fetamine N=46**	**Placebo N=44**	**Total N=90**	**Midoma-fetamine N=53**	**Placebo N=51**	**Total N=104**
Sex						
Female	27 (58.7)	32 (72.7)	59 (65.6)	32 (60.4)	42 (82.4)	74 (71.2)
Male	19 (41.3)	12 (27.3)	31 (34.4)	21 (39.6)	9 (17.6)	30 (28.8)
Age (years)						
Mean (SD)	43.6 (12.9)	38.2 (10.4)	40.9 (11.9)	38.2 (11.0)	40.0 (9.6)	39.1 (10.3)
Ethnicity						
Hispanic or Latino	5 (10.9)	3 (6.8)	8 (8.9)	17 (32.1)	11 (21.6)	28 (26.9)
Not Hispanic or Latino	41 (89.1)	40 (90.9)	81 (90.0)	36 (67.9)	39 (76.5)	75 (72.1)
Missing	0	1 (2.3)	1 (1.1)	0	1 (2.0)	1 (1.0)

Variable	MAPP1 Midomafetamine N=46	MAPP1 Placebo N=44	MAPP1 Total N=90	MAPP2 Midomafetamine N=53	MAPP2 Placebo N=51	MAPP2 Total N=104
Race						
American Indian or Alaska Native	3 (6.5)	0	3 (3.3)	0	2 (3.9)	2 (1.9)
Asian	2 (4.3)	5 (11.4)	7 (7.8)	5 (9.4)	6 (11.8)	11 (10.6)
Black or African American	0	2 (4.5)	2 (2.2)	5 (9.4)	3 (5.9)	8 (7.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0	1 (2.0)	1 (1.0)
White	39 (84.8)	30 (68.2)	69 (76.7)	37 (69.8)	32 (62.7)	69 (66.3)
Multiple	2 (4.3)	6 (13.6)	8 (8.9)	6 (11.3)	7 (13.7)	13 (12.5)
Missing	0	1 (2.3)	1 (1.1)	0	0	0
Baseline CAPS-5 Total Severity Score						
Mean (SD)	44.0 (6.0)	44.2 (6.2)	44.1 (6.0)	39.4 (6.6)	38.7 (6.7)	39.0 (6.6)

Source: Adapted by Statistical Reviewer from Table 14.1.3.1 in MAPP1 study report and Table 14.1.3.1 in MAPP2 study report.
Abbreviation: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5

3.2.1.2 Efficacy Results for MAPP1 and MAPP2

3.2.1.2.1 Primary Efficacy Endpoint

For both MAPP1 and MAPP2, the primary efficacy endpoint was the change in the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) total score from Baseline to Visit 19 (Week 18). For both studies, results showed a statistically significant difference between the midomafetamine arm and placebo arm in reduction in CAPS-5 scores. The results for both studies are presented in .

Table 5. Primary Endpoint: Change From Baseline in CAPS-5 Total Severity Score at Visit 19 (Week 18)—*De Jure* Estimand (mITT Population)

Variable	MAPP1 Midomafetamine (N=46)	MAPP1 Placebo (N=44)	MAPP2 Midomafetamine (N=53)	MAPP2 Placebo (N=50)
Mean baseline score (SD)	44.0 (6.01)	44.2 (6.15)	39.4 (6.64)	38.8 (6.63)
Visit 19				
N	42	37	52	42
Raw mean (SD)	19.5 (13.50)	29.8 (12.37)	15.8 (12.40)	23.3 (12.79)
LS Mean change from baseline (95% CI)[a]	-24.50 (-28.28, -20.71)	-12.64 (-16.61, -8.66)	-23.69 (-26.94, -20.44)	-14.78 (-18.28, -11.28)
Placebo-subtracted difference (95% CI)[a]		-11.86 (-17.41, -6.32)		-8.91 (-13.70, -4.12)
p-value[a]		<0.0001		0.0004

Source: MAPP1 CSR Table 17; MAPP2 CSR Table 16.
The *de jure* estimand does not include data after participants discontinued treatment.
[a] LS Mean, LS mean difference, 95% CI and p-value of treatment effect at Visit 19 were obtained from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baseline CAPS-5 as a covariate.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the DSM-5; CI, confidence interval; CSR, clinical study report; DSM-5, Diagnostic and Statistical Manual of Mental Disorders version 5; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed models repeated measures; N, total number of participants in each group; PTSD, posttraumatic stress disorder

In MAPP1, there was an estimated -11.86 (95% confidence interval [CI]: -17.41, -6.32; p<0.0001) point larger reduction in LS mean change from baseline in CAPS-5 scores for participants randomized to

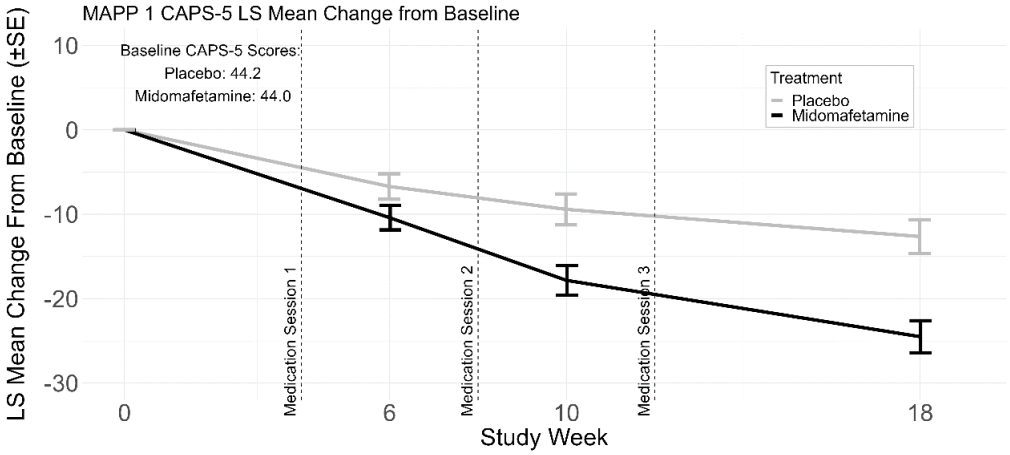
midomafetamine compared to those randomized to placebo. In MAPP2, there was an estimated -8.91 (95% CI: -13.70, -4.12; p=0.0004) greater reduction in LS mean change from baseline for participants in the midomafetamine arm compared to those in the placebo arm.

displays the estimated mean changes from baseline in CAPS-5 total score throughout the three assessment visits (approximately 6 weeks, 10 weeks, and 18 weeks from baseline). In each study, the LS mean change from baseline increased over time regardless of treatment group. For MAPP1, the difference between the two treatment groups appeared to be increasing over the three visits, but for MAPP2 the difference appeared to be similar for the last two visits (Week 10 and Week 18).

The results of a supportive analysis using a *de facto* analysis were similar to the *de jure* analysis for both studies. A tipping point analysis also suggested the results of the analysis of the primary endpoint were robust to the missing at random assumption.

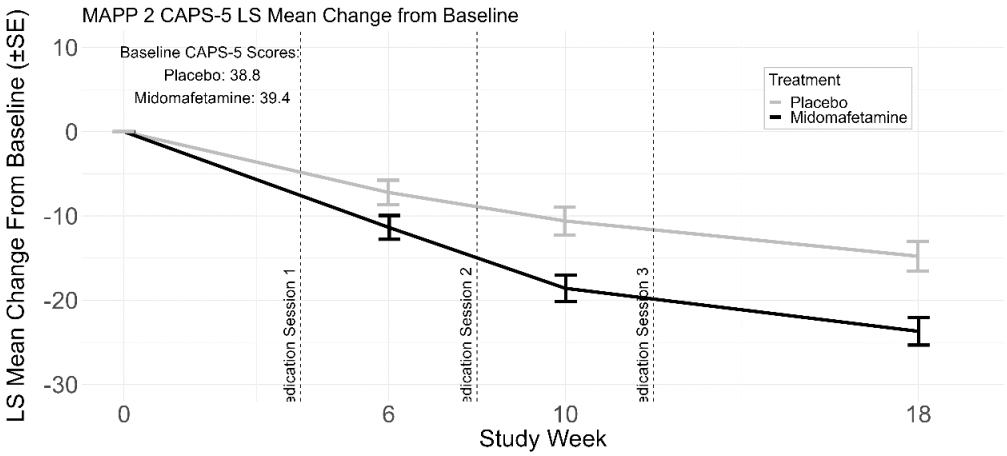
Figure 2. LS Mean Change From Baseline in CAPS-5 Total Score Over Time

a) Study MAPP1



Placebo	44	43	39	37
Midomafetamine	46	46	42	42

b) Study MAPP2



Placebo	50	50	44	42
Midomafetamine	53	53	53	52

Source: FDA Statistical Analyst.
Timing of the CAPS-5 assessments are based on the target timings according to Table 2 in the MAPP1 and MAPP2 protocols. Timing of medication sessions varied and is included in the plot for illustrative purposes.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; LS, least squares

3.2.1.2.2 Secondary Efficacy Endpoint

For both MAPP1 and MAPP2, the prespecified secondary efficacy endpoint was the change in the Sheehan Disability Scale (SDS) score from Baseline to Visit 19 (Week 18). The type I error rate in both studies was controlled using a hierarchical testing strategy where the difference in SDS scores would only be formally tested if the difference in CAPS-5 scores was statistically significant (which is the case here). Results of both studies showed a statistically significant difference between the midomafetamine arm and the placebo arm in reduction in SDS scores. The results for both studies are shown in .

In MAPP1, participants in the midomafetamine arm had an estimated -1.36 point (95% CI: -2.46, -0.25; p=0.0167) larger in LS mean change in SDS scores from baseline compared to those in the placebo arm. In MAPP2, participants in the midomafetamine arm had a -1.2 point (95% CI: -2.26, -0.14; p=0.0271) larger in LS mean change in SDS scores from baseline compared to the placebo arm.

Table 6. Key Secondary Endpoint: Change from Baseline in SDS Total Scores at Visit 19 (Week 18)—*De Jure* Estimand (mITT Population)

	MAPP1		MAPP2	
Variable	**Midomafetamine (N=46)**	**Placebo (N=44)**	**Midomafetamine (N=53)**	**Placebo (N=50)**
Mean baseline score (SD)	6.8 (2.07)	7.4 (1.63)	6.0 (1.80)	6.1 (1.79)
Visit 19				
N	42	37	52	42
Raw mean (SD)	3.8 (2.98)	5.3 (2.31)	2.7 (2.67)	4.0 (2.82)
LS mean change from baseline (95% CI)[a]	-3.15 (-3.90, -2.40)	-1.79 (-2.58, -1.00)	-3.31 (-4.03, -2.60)	-2.11 (-2.89, -1.33)
Placebo-subtracted difference (95% CI)[a]	-1.36 (-2.46, -0.25)		-1.20 (-2.26, -0.14)	
p-value[a]	0.0167		0.0271	

Source: MAPP1 CSR Table 21; MAPP2 CSR Table 20.
The *de jure* estimand does not include data after participants discontinued treatment.
[a] LS Mean, LS mean difference, 95% CI and p-value of treatment effect at Visit 19 were obtained from a mixed model for repeated measures, with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effects, subject as a random effect, and baseline SDS total score as a covariate. An unstructured covariance matrix was used.
Abbreviations: CI, confidence interval; CSR, clinical study report; LS, least squares; mITT, modified intent-to-treat; N, number of participants; SDS, Sheehan Disability Scale; V, visit

3.2.2 Exploratory Efficacy Assessments for MPLONG

3.2.2.1 Populations and Baseline Characteristics for MPLONG

Eligible participants who have completed at least one medication session in the main study protocols of MAPP1, MAPP2, MP16, or MAPPUSX, were asked to enroll in MPLONG, which consisted of a single follow-up assessment at an interval 6 months or longer after completion of the parent study. However, MPLONG was not properly planned, designed, and implemented to evaluate durability of treatment effect. Some participants also sought out potentially therapeutic interventions in the interim between the parent study and the assessment in MPLONG. The results are, at best, quite limited given several confounding factors, including functional unblinding, a dropout rate of approximately 25%, and the very

long and variable follow-up time with only a single visit in the observational study. Refer to discussions in Section 3.2.3.

A total of 142 participants enrolled in MPLONG following completion of MAPP1 or MAPP2, including 30 participants (65.2% of participants treated in the parent study) from the midomafetamine arm of MAPP1, 30 participants (68.2%) from the placebo arm of MAPP1, 45 participants (84.9%) from the midomafetamine arm of MAPP2, and 37 participants (72.5%) from the placebo arm of MAPP2. Most of those enrolled in MPLONG (137 out of 142) were included in the MPLONG effectiveness subset (56 from MAPP1 and 81 from MAPP2). Comparing the sample sizes in MPLONG with those in parent studies, 62% (56/91) of randomized participants in MAPP1 and 78% (81/104) of randomized participants in MAPP2 were included in the MPLONG effectiveness subset.

The demographic and baseline characteristics of the mITT population from MAPP1 and MAPP2 stratified by whether or not participants enrolled in MPLONG are shown in .

Table 7. Demographics and Baseline Characteristics of the Modified Intent-to-Treat Population From MAPP1 and MAPP2 Comparing Patients Who Did and Did Not Enroll in MPLONG

	Enrolled[a]			Not Enrolled[b]		
Variable	**Midoma-fetamine N=75**	**Placebo N=67**	**Total N=142**	**Midoma-fetamine N=24**	**Placebo N=27**	**Total N=51**
Age (years)						
Mean (SD)	41.4 (13.1)	39.4 (10.4)	40.4 (11.9)	38.6 (8.5)	38.6 (9.0)	38.6 (8.7)
Sex: N (%)						
Female	43 (57.3)	50 (74.6)	93 (65.5)	16 (66.7)	23 (85.2)	39 (76.5)
Male	32 (42.7)	17 (25.4)	49 (34.5)	8 (33.3)	4 (14.8)	12 (23.5)
Ethnicity: N (%)						
Hispanic or Latino	18 (24.0)	9 (13.4)	27 (19.0)	4 (16.7)	5 (18.5)	9 (17.6)
Not Hispanic or Latino	57 (76.0)	57 (85.1)	114 (80.3)	20 (83.3)	21 (77.8)	41 (80.4)
Missing	0	1 (1.5)	1 (0.7)	0	1 (3.7)	1 (2.0)
Race: N (%)						
American Indian or Alaska Native	3 (4.0)	2 (3.0)	5 (3.5)	0	0	0
Asian	6 (8.0)	6 (9.0)	12 (8.5)	1 (4.2)	5 (18.5)	6 (11.8)
Black or African American	5 (6.7)	5 (7.5)	10 (7.0)	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (1.5)	1 (0.7)	0	0	0
White	54 (72.0)	42 (62.7)	96 (67.6)	22 (91.7)	19 (70.4)	41 (80.4)
Multiple	7 (9.3)	10 (14.9)	17 (12.0)	1 (4.2)	3 (11.1)	4 (7.8)
Missing	0	1 (1.5)	1 (<1)	0	0	0
Baseline CAPS-5 total severity score						
Mean (SD)	40.3 (6.0)	40.9 (6.7)	40.6 (6.3)	45.3 (7.5)	42.6 (7.4)	43.8 (7.5)

Variable	Enrolled[a] Midomafetamine N=75	Placebo N=67	Total N=142	Not Enrolled[b] Midomafetamine N=24	Placebo N=27	Total N=51
Study termination CAPS-5 total score[c]						
Mean (SD)	15.9 (12.6)	24.9 (12.3)	20.2 (13.2)	25.4 (14.1)	35.8 (12.5)	30.9 (14.1)

Source: Adapted by Statistical Reviewer from Table 14.1-4.1 in MPLONG ISE from durability update submitted to eCTD Seq 0047
Percentages are calculated using the number of participants in each treatment group as the denominator.
Participant demographic and baseline characteristics were collected from the parent study.
[a] Participants from MAPP1 or MAPP2 who enrolled in MPLONG.
[b] Participants from MAPP1 or MAPP2 not enrolled in MPLONG.
[c] Last available assessment in the parent study.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; eCTD, electronic common technical document; ISE, integrated summary of efficacy

3.2.2.2 Interim Interventions between MAPP1, MAPP2 and MPLONG

Most participants engaged in some form of psychotherapy during the time from the last dose of study drug to the date of the MPLONG visit. Of the 151 participants who entered MPLONG from MAPP1, MAPP2, or MP16, 75 (82.4%) of participants treated with midomafetamine in the parent study and 43 (71.7%) of participants treated with placebo in the parent study received psychotherapy during the time between the end of the parent study and the MPLONG assessment. The types of psychotherapy in which participants engaged varied and included psychodynamic psychotherapy, group psychotherapy, cognitive behavioral therapy, eye movement desensitization reprocessing, prolonged exposure therapy, cognitive processing therapy, and interpersonal therapy.

Some participants received nonstudy drugs as part of subsequent, nonstudy therapy sessions, including ketamine, dimethyltryptamine (DMT), and other, unspecified psychedelics. Among participants entering MPLONG from MAPP1 and MAPP2, 12 participants (6 from the midomafetamine arms and 6 from the placebo arms) reported ketamine-assisted psychotherapy during the interim between those studies. There was one participant from the placebo arm of MAPP2 who reported “psychedelic assisted therapy (5-MEO-DMT)” as the type of therapy in between MAPP2 and MPLONG. Of participants entering MPLONG from MP16, there were four participants who reported ketamine-assisted psychotherapy and one participant who reported “psychedelic psychotherapy in Amsterdam” between those studies.

In addition to seeking potentially therapeutic interventions between MAPP1/MAPP2 and MPLONG, 13 participants from the midomafetamine arms and 7 participants from the placebo arms reported use of illicit MDMA in the interstudy interval. It is also possible that some additional participants did not report nonstudy drug use despite having done so.

3.2.2.3 Exploratory Efficacy Assessments in Participants from MAPP1 and MAPP2

In Study MPLONG, the observational study of participants assessed at a long-term follow-up visit (LTFU Visit 1) 6 months or longer after the end of MAPP1 or MAPP2. shows data for participants who entered MPLONG from either MAPP1 or MAPP2. The results for MAPP1 and MAPP2 participants in MPLONG are not pooled because MAPP1 participants were unblinded and MAPP2 participants remained blinded during MPLONG, although functional unblinding was a great concern for both studies. The LS mean changes from parent study baseline in CAPS-5 score to the LTFU Visit 1 were generally comparable with those at Visit 19 (the primary endpoint in parent studies) for each treatment group.

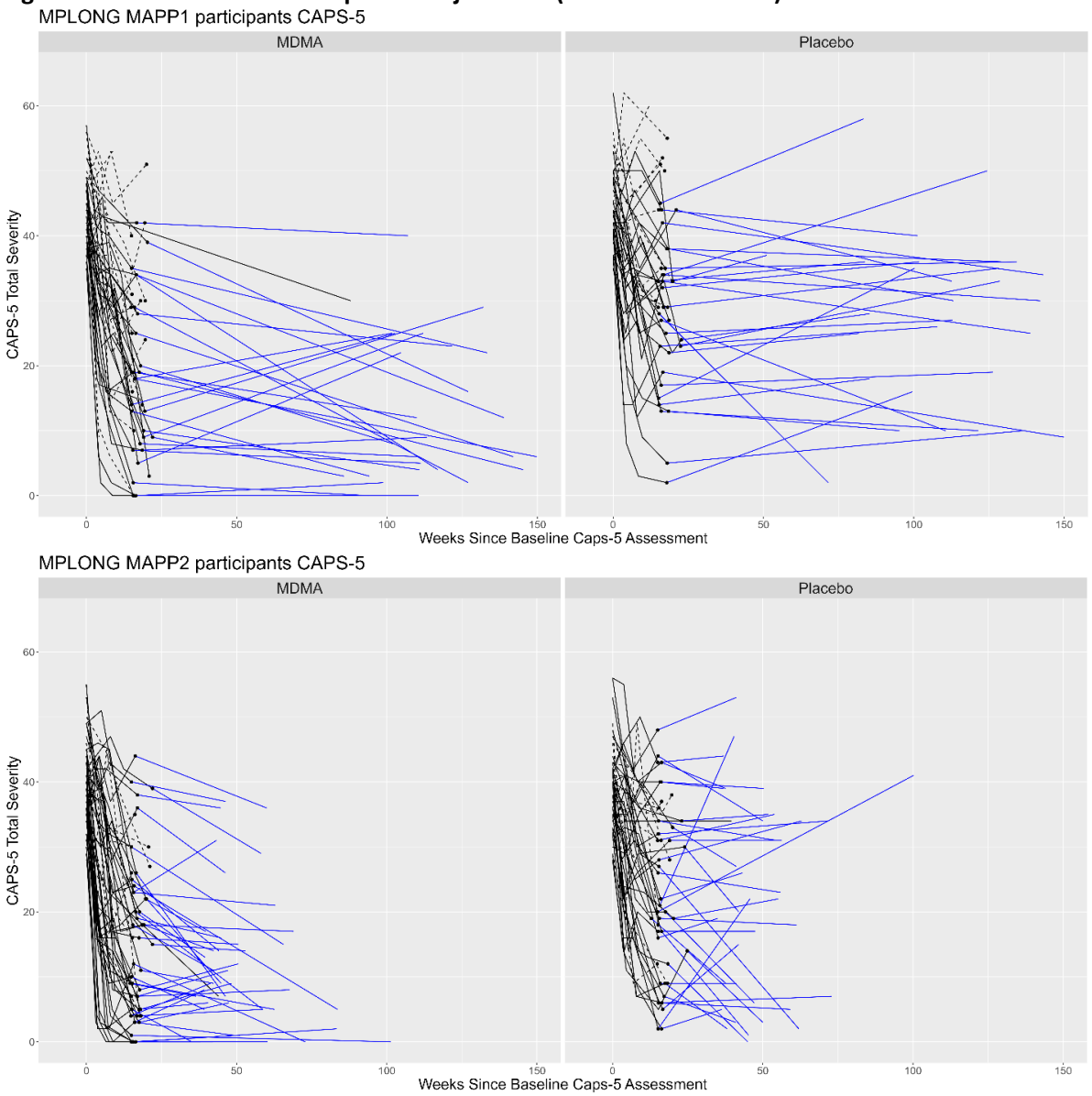
Table 8. MPLONG: Summary of Changes in CAPS-5 Total Severity Scores (Effectiveness Subset)

	MAPP1		MAPP2	
Visit	Midomafetamine (N=27)	Placebo (N=29)	Midomafetamine (N=44)	Placebo (N=37)
Mean baseline score in parent study (SD)	42.6 (5.39)	43.5 (5.85)	39.1 (6.31)	38.9 (6.79)
Visit 19 in parent study, n	26	29	43	36
Raw mean (SD)	17.6 (12.32)	27.0 (11.52)	14.9 (12.40)	22.9 (13.01)
LS mean change from baseline (SE)	-24.80 (-29.73, -19.87)	-15.96 (-20.68, -11.24)	-24.41 (-28.11, -20.72)	-15.36 (-19.41, -11.32)
LTFU Visit 1, n	27	29	44	37
Raw mean (SD)	12.7 (11.18)	27.4 (12.99)	11.3 (10.17)	22.5 (15.23)
LS mean change from baseline (SE)	-30.31 (-35.02, -25.61)	-15.61 (-20.15, -11.08)	-28.01 (-31.86, -24.16)	-16.05 (-20.25, -11.85)
Difference between LTFU visit 1 and visit 19 in LS mean change from baseline (95% CI)	-5.51 (-9.95, -1.07)	+0.34 (-3.90, 4.59)	-3.60 (-6.10, -1.09)	-0.69 (-3.43, 2.05)

Source: MPLONG ISE tables and listings from the Durability Update Report (Table 14.2-5.1, Table 14.2-5.2, Table 14.2-5.3) submitted to eCTD Seq 0047 and MPLONG ISE tables for the MAPP1 subset (Table 14.2-5.4, Table 14.2-5.5, and Table 14.2-5.6) submitted to eCTD Seq 0054.
All available data from the effectiveness subset were used, regardless of whether the participant dropped from treatment in the parent study.
Effectiveness subset: All MAPP1/MAPP2 participants who enrolled in MPLONG and who completed a follow-up PTSD endpoint assessment in the long-term follow-up study.
Baseline is defined as Visit 3 values from the parent study.
LSMs and CIs were derived from MMRM with treatment group from parent study, parent study, baseline dissociative subtype, visit and parent investigative site as factors and baseline CAPS-5 as covariates. The visit treatment group from parent study interaction term was also included. Note that the change from baseline to visit 13, visit 15, and visit 19 from the parent studies along with the change from baseline to the LTFU visit 1 in MPLONG were included in the model. An unstructured covariance structure was used.
[a] Last available assessment in the parent study
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; CI, confidence interval; eCTD, electronic common technical document; ISE, integrated summary of efficacy; LSM, least squares mean; LTFU, long-term follow-up; MMRM, mixed model with repeated measures; n, number of participants who have values at baseline, study Termination, and that timepoint; N, total number of participants; V, visit

The timing of the LTFU Visit varied and was conducted more than 2 years after the parent study for some participants. MAPP1 was conducted prior to both MAPP2 and the start of MPLONG, so participants from MAPP1 tended to have a longer period of time between completing the parent study and their LTFU Visit 1 in MPLONG (). The median (minimum to maximum) time from the last treatment to the long-term follow-up visit was 23.4 months (7.9 months to 32.4 months) for participants from the efficacy set from MAPP1 and 8.5 months (6.0 to 22.8 months) for participants from the efficacy set from MAPP2.

Figure 3. Individuals Entire Response Trajectories (CAPS-5 Total Score) From Parent Studies



Source: Statistical Analyst.
CAPS-5 total scores for participants from the parent study (MAPP1 or MAPP2) who did not enroll in MPLONG are represented by a black dashed line. CAPS-5 total scores in the parent study for participants who enrolled in MPLONG are shown by a black solid line and the scores in MPLONG for the same participants are shown by a blue line. Black dots represent the scores collected at Visit 19.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; MDMA, midomafetamine

We conducted an exploratory analysis to examine if there were any differences in efficacy for participants who were in MPLONG for 6 to 12 months from their final assessment (Visit 19) in parent studies versus those who had it greater than 12 months out. The majority of participants who were assessed during 6 to 12 months were from MAPP2, and conversely the majority of participants who were assessed after 12 months were from MAPP1; so these efficacy results generally follow similar trends to the original MPLONG subset analyses for MAPP2 and MAPP1.

Some MPLONG participants reported using ketamine, 5-MEO-DMT, or illicit MDMA in the interim period after completing MAPP1 or MAPP2 but before enrolling in MPLONG. To address the concern that

participants chose to use midomafetamine, ketamine, or 5-MEO-DMT in the interim period because of worsening symptoms, the Agency conducted an exploratory analysis by treating any data collected after interim use as missing and performed a tipping point analysis of patients from the mITT population from MAPP1 and MAPP2. All missing data were imputed under the missing at random assumption, and a shift parameter was added to penalize imputed values for participants in the midomafetamine arm who reported interim midomafetamine, ketamine, or 5-MEO-DMT use. Participants with missing data who did not report interim use were not penalized to isolate the impact of increased scores for participants with interim use. A shift parameter was not applied to imputed values for participants with interim use in the placebo arm because that would make the results in the placebo arm look worse, which would make the treatment arm look better in comparison.

Based on the results of this tipping point analysis, the interim use of ketamine, 5-MEO-DMT, or illicit MDMA use in the interim period may have had some impact on the estimate at the LTFU visit (,). When the observed CAPS-5 scores at LTFU Visit 1 for participants with illicit use were replaced with imputed values (as if they were similar to non-users in the same treatment group), the estimated LS mean change from baseline for the midomafetamine arm increased slightly, and it continued to increase as the imputations were penalized. It is unclear what this trend fully indicates, although it appears that MAPP2 participants who used ketamine, 5-MEO-DMT, or illicit MDMA experienced additional improvement in CAPS-5 scores than those who did not use any of these interim drugs at LTFU Visit 1. This trend was not observed in MAPP1 participants. It is unclear if this result is related to the treatment in the parent studies. Additionally, this result does not account for any potentially unreported interim use of MDMA, ketamine, or 5-MEO-DMT.

3.2.3 Efficacy Issues in Detail

Efficacy Issue #1: Short-term Treatment Effect and Potential Bias

In both MAPP1 and MAPP2, there was a statistically significant difference between the midomafetamine arm and placebo arm in reduction in the total score on the CAPS-5, an efficacy endpoint to which the Agency agreed for the evaluation of treatments for PTSD. For MAPP1, the LS mean change from baseline in CAPS-5 scores decreased in both the midomafetamine and placebo arms (midomafetamine, 24.50 [95% CI: -28.28, -20.71]; placebo, -12.64 [95% CI: -16.61, -8.66]). Similarly, for MAPP2, the LS mean change from baseline in CAPS-5 scores is decreased in both the midomafetamine and placebo arms (midomafetamine, -23.69 [95% CI: -26.94, -20.44]; placebo, -14.78 [95% CI: -18.28, -11.28]).

The Agency agreed to a 10-point or greater change on the CAPS-5 score as the threshold for a treatment response during the development program. A systematic review of the literature on treatment response in PTSD describes a range of potential thresholds of change in the total CAPS-5 score that could be considered to demonstrate a treatment response, which includes a 10-point change as the minimum amount of change (Varker et al. 2020). Based on the Agency's review of the CAPS-5 scale, including the total score range and the response options, multiple items and the associated response would have to shift or decrease since the prior administration of the CAPS-5 in order to achieve a 10-point change in the total score of the CAPS-5. Based on the Agency's review of the published literature and review of the scale, a 10-point change in the total CAPS-5 score could be viewed as clinical meaningful change.

The ability of participants to determine whether they were randomized to the midomafetamine or placebo arm of the trial could potentially bias participants' reports of symptom severity. Bias from

functional unblinding may contribute to expectation bias in which those who believed that they received active treatment expected that they would experience a clinical benefit, those who received placebo fared worse due to disappointment when they did not experience anticipated effects from the treatment, or some combination of both. Of note, more participants on active drug were able to accurately guess their treatment assignment with a higher degree of certainty ("I think" = 15.4%; "I am positive" = 78.8%) compared to those on placebo ("I think" = 31.8%; "I am positive" = 43.2%), suggesting the impact of functional unblinding and expectation bias may be imbalanced between groups.

Historically, it has been difficult to design clinical trials of psychedelics such that functional unblinding could definitively be avoided due to the marked experiential effects of drugs in that class. During early discussions with the Applicant on the study design, the use of a low-dose midomafetamine arm to serve as an active control was considered as an alternative or addition to a placebo arm. However, the Applicant noted occurrences of increased anxiety and difficulty tolerating the medication sessions in participants treated with low-dose midomafetamine (25 or 30 mg) in their phase 2 studies. In one phase 2 study, five participants in the 25 mg group had an increase in CAPS scores post-treatment. In another phase 2 study, seven participants in the 30 mg group had a smaller decrease in CAPS scores than did eight participants in a different phase 2 study who worked with the same therapy team but received inactive placebo. The Agency and the Applicant ultimately agreed on a study design that would randomize participants to midomafetamine or placebo, with the understanding that this study design may be susceptible to functional unblinding. To reduce bias in the efficacy assessments, the Applicant used a blinded, centralized independent rater pool for the primary and secondary efficacy endpoint assessments.

At the Agency's behest (per comments sent by the Agency on October 19, 2020, in response to a September 2020 MAPP2 protocol amendment submission), the Applicant incorporated an unblinding survey into the protocol for Study MAPP2 to assess the degree to which participants could correctly guess their treatment arm assignment. Data from the survey, shown in , indicated that study participants could guess their treatment arm assignment with a high degree of accuracy. These results demonstrate the occurrence of functional unblinding.

Table 9. MAPP2: Blinding Survey at Study Termination (Safety Set)

Variable	Midomafetamine (N=53) n (%)	Placebo (N=51) n (%)
Belief on study drug received, n	52	44
Active drug I am positive	41 (78.8)	2 (4.5)
Active drug I think	8 (15.4)	7 (15.9)
Cannot tell	2 (3.8)	2 (4.5)
Placebo I am positive	1 (1.9)	19 (43.2)
Placebo I think	0 (0.0)	14 (31.8)

Variable	Midomafetamine (N=53) n (%)	Placebo (N=51) n (%)
Reasons for selection[a]		
Experienced positive mental or emotional effect	45 (86.5)	8 (18.2)
Experienced negative mental or emotional effect	10 (19.2)	3 (6.8)
Experienced positive physical effect	29 (55.8)	3 (6.8)
Experienced negative physical effect	11 (21.2)	6 (13.6)
Experienced no effects	1 (1.9)	28 (63.6)
I do not know	1 (1.9)	3 (6.8)
Other	9 (17.3)	6 (13.6)

Source: Clinical Study Report MAPP2 pages 80-81.
Safety set: All participants who received any IMP.
[a] Participants could select more than one reason.
Abbreviations: N, total number of participants in each group; n, total number of participants in each category

Participants randomized to the placebo arm in Studies MAPP1 and MAPP2 experienced some improvement in PTSD symptoms, despite the high likelihood that those participants could guess that they were assigned to placebo; however, both treatment arms received psychotherapy sessions. Some participants randomized to placebo in Studies MAPP1 and MAPP2 who went on to enroll in Study MPLONG maintained their improvement in PTSD symptoms for at least 6 months after their final dose of placebo, although the magnitude of improvement was not as large as the midomafetamine group.

Given that the placebo arm showed some degree of improvement, disappointment at not receiving active drug does not appear to have caused worsening PTSD symptoms. However, 94% of participants who received midomafetamine either knew or thought that they received the drug. Therefore, expectation bias would potentially have had a greater impact on those who received midomafetamine than in those who received placebo. The contribution of expectation bias remains difficult to quantify in these studies and may remain a factor in the degree of observed drug-placebo difference.

The Agency considered whether data from MPLONG could provide information on durability of effect of midomafetamine for the treatment of PTSD. It is notable that the difference in treatment effect between the midomafetamine and placebo arms in the two studies persisted into MPLONG for at least 6 months and, in some cases, for more than a year after the last dose of study drug. However, it is unclear how long expectation bias might last in a chronic psychiatric illness, particularly for a condition such as PTSD which historically has been very difficult to treat effectively. This apparent durability, even if it incorporates some expectation bias, might suggest that the magnitude of difference between midomafetamine and placebo reflects a true treatment effect for midomafetamine. However, there are major limitations to the interpretability of this data due the proportion of dropouts between parent study and follow-up, the variable times of follow-up, and the interim use of potentially therapeutic interventions, and as described in greater detail in the section that follows.

In summary, the submission includes data from two positive controlled clinical trials, MAPP1 and MAPP2, that appear to demonstrate clinically meaningful treatment effects of midomafetamine for the treatment of PTSD. However, the interpretation of the data from these studies is challenging due to likely impacts of functional blinding and expectation bias. Additionally, data from MPLONG provided a single follow-up assessment 6 months or longer after completion of the parent studies that suggests that the treatment effect may be durable; however, that data is likely also impacted by functional

unblinding and expectation bias. Also, interpretation is further confounded due to the variable times of follow-up and use of interim potentially therapeutic interventions.

Efficacy Issue #2: Durability of Treatment Effect

While the data from MPLONG may suggest a durable treatment effect of midomafetamine, the study and its results are not without challenges of interpretation. For instance, MPLONG consisted of a single visit for assessment of durability of effect, and at varying timepoints. The limitation of the MPLONG assessment to a study visit at a single and variable point in time could raise the question of whether the single assessment adequately represents the participant's long-term control of PTSD symptoms, given the possibility of day-to-day variability in symptom severity. During a Type B Breakthrough Therapy Designation advice meeting on September 14, 2022, the Agency raised concerns with the ability of data from MPLONG to support the durability of the treatment paradigm but agreed its results could be submitted for review.

Although the MPLONG assessment visit was scheduled by protocol to occur at least 6 months after the end of the parent study, the timing of the visit varied considerably—from 6 months to greater than 2 years after the end of the parent study. This variability in the timing of the visit could further complicate the interpretability of summary statistics for the study population (which are already exploratory in nature).

To address concerns about comparing participants assessed at very different time points after the end of the parent study, the review team and the Applicant both divided the study population into subgroups based on the amount of time elapsed between the end of the parent study and the time of the MPLONG assessment. The analysis by the Applicant and the analysis by the review team both indicated that participants in the different time-based subgroups showed comparable control of PTSD symptoms, with no meaningful difference between participants evaluated 6 to 12 months after the end of the parent study and participants evaluated more than 1 year after the end of the parent study. Participants evaluated more than 1 year after the end of the parent study mainly came from MAPP1 (severe PTSD), and those evaluated between 6 to 12 months mainly came from MAPP2 (moderate-to-severe PTSD).

As another concern, participants who entered Study MPLONG from Study MAPP1 were unblinded prior to entry into MPLONG. The unblinding after MAPP1 could potentially bias participant reports of symptom severity in the evaluation of durability of treatment effect (i.e., participants who know that they received midomafetamine might be more likely to report a favorable response during MPLONG). However, the impact of this protocol-driven unblinding is unclear given the functional unblinding that likely occurred.

In addition to the unblinding of MAPP1 participants, differences in durability for participants from MAPP1 compared to MAPP2 could be caused by the timing of the two studies. MPLONG started in March of 2021, and there was a larger gap of time for MAPP1 participants compared to MAPP2 participants between completing the parent study and being eligible to enroll in MPLONG.

There is also the potential for selection bias in the estimated durability of effect in MPLONG due to patients' self-selection into the study. Participants from MAPP1 and MAPP2 had to consent to participant in MPLONG, and there could be differences between those who chose to enroll versus those who did not. Participants on placebo who enrolled in MPLONG may have been more stable compared to

those who chose not to enroll, and if so, this would lead to a more optimistic estimate of the durability of effect in the placebo arm. If participants on midomafetamine who enrolled in MPLONG were more stable, there may have been a more optimistic estimate in the midomafetamine arm.

To explore for possible selection bias, we compared the demographics and outcomes in the parent studies (MAPP1 and MAPP2) for patients who enrolled and those who did not enroll in MPLONG. As discussed in Section 3.2.1, 62% of randomized participants in MAPP1 and 78% of randomized participants in MAPP2 were included in the MPLONG effectiveness subset (). A higher proportion of participants enrolled in MPLONG from the placebo arm compared to the midomafetamine arm (85% and 73%, respectively) from MAPP2, but the proportions were similar for participants from MAPP1. Differences in the enrollment rate could be caused by unblinding of MAPP1 participants, functional unblinding of MAPP2 participants, or the timing of the studies.

There were several differences between patients who enrolled in MPLONG and those who did not. First, patients who enrolled generally had a lower CAPS-5 total score at parent study termination compared to those who did not enroll ().

Finally, a number of participants either sought additional treatment or took illicit MDMA in the time between MAPP1/2 and MPLONG. One could assume that, for the participants who sought additional treatment between the parent study and MPLONG, the treatment effect was not as durable. (Results of the aforementioned exploratory tipping point analysis of missing participants from MAPP1 and MAPP2 seem consistent with this assumption.)

Because MAPP1 and MAPP2 are functionally unblinded, demonstration of the durability of effect could be informative to support whether the observed treatment effect in the phase 3 studies is a true effect; however, there are potential biases, discussed above, that do raise concerns about the interpretability of the MPLONG results.

Efficacy Issue #3: Contribution of Psychotherapy to Efficacy

FDA does not regulate the practice of psychotherapy, and the Agency is limited in our ability to describe the elements of psychotherapy in product labeling. Labeling regulations[1] allow for specification that a drug should be used only in conjunction with another mode of therapy; specifically, if the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), the indications and usage section of the prescribing information must include a statement that the drug is indicated as an adjunct to that mode of therapy.

In the midomafetamine development program, the necessity of psychotherapy for achieving a therapeutic response was assumed. The two placebo-controlled trials, MAPP1 and MAPP2, each had two treatment arms: midomafetamine + psychotherapy and placebo + psychotherapy. There is no data on the efficacy of midomafetamine without psychotherapy—nor data on the effect of the psychotherapy alone using a comparison to a no treatment group. It is not clear whether the psychotherapy provided on the days of medication visits and the therapy sessions scheduled in between medication visits are necessary for the therapeutic effect of midomafetamine (i.e., whether the psychological intervention contributes to the treatment effect of midomafetamine). This lack of data

[1] 21 CFR 201.57(c)(2)(i)(A)

raises the question of how to describe the role of concomitant psychotherapy or other psychological intervention in the product label.

The MAPS therapy manual gives broad guidelines on the conduct of medication sessions, such as the physical environment and supportive therapist stance. The therapist is given considerable flexibility in the selection of specific therapeutic modalities. The difference in magnitude of treatment effect between midomafetamine and placebo arms was demonstrated in both MAPP1 and MAPP2 without a very tight specification of a psychotherapy protocol. This difference may suggest that midomafetamine contributes a treatment effect that can be differentiated from placebo, even if participants are not matched by the type of psychological intervention provided. However, it does not provide any information on whether the psychotherapy makes an independent contribution to the treatment effect of the combination of midomafetamine and psychological intervention.

3.3 Safety Issues

Key safety issue: Is the safety database adequate to characterize the safety of midomafetamine?

- Limited total exposure to midomafetamine in the development program
- Clinical laboratory data are limited
- Limited data to assess pro-arrhythmic potential of midomafetamine and other cardiovascular effects
- Midomafetamine effects perceived as positive were not recorded.

3.3.1 Sources of Data for Safety

A total of 426 participants were exposed to midomafetamine in the Applicant's trials. The Applicant obtained the right for their safety database to include data from 50 participants exposed to midomafetamine in National Institute on Drug Abuse (NIDA) studies. Accordingly, there is a safety database of 476 participants with exposure to midomafetamine.

All studies included in the development program were reviewed for occurrences of deaths, serious adverse events (SAEs), and adverse events of special interest (AESIs). For occurrences of treatment-emergent adverse events (AEs), we conducted the safety analysis on pooled data from the placebo-controlled phase 3 studies, MAPP1 and MAPP2. This combined data set included 99 participants treated with midomafetamine and 95 participants treated with placebo. This assessment of pool of data was feasible because the two studies had identical designs and used the same doses of study drug.

Of note, predose and postdose laboratory studies were not conducted in the phase 3 studies. Limited predose and postdose laboratory data were collected during phase 1 and phase 2 studies.

Additional sources of safety data include information on patterns of illicit MDMA nonmedical use and related adverse outcomes based on population surveys, poison center cases and fatality abstracts, substance use treatment admissions, emergency department encounters, toxicologist consultation registry data, published literature over the course of several decades including case reports, and death certificate literal text data.

3.3.2 Safety Summary

3.3.2.1 Deaths

There were two deaths in the development program in two phase 2 studies: one in Study MP-2, a phase 2 study of midomafetamine for treatment of PTSD, with death caused by relapse of breast cancer with

brain metastasis; and one in a phase 2 study, Study MDA-1, a phase 2 study of midomafetamine for treatment of anxiety related to a life-threatening illness, with death caused by relapse of chordoma. Both deaths occurred due to relapse of previously diagnosed cancer more than 6 months after the last dose of midomafetamine, and the reviewer assessed these events as not related to the study drug.

3.3.2.2 Serious Adverse Events (SAEs)

See for SAEs that occurred during the midomafetamine development program.

Table 10. Serious Adverse Events During Midomafetamine Development, Non-Placebo-Controlled Studies

System Organ Class	Preferred Term	Midomafetamine	Study
Eye disorders	Retinal detachment	1	MAPPUSX
Infections and infestations	Appendicitis	1	MP-8
	Diverticulitis	1	MAPPUSX
Injury, poisoning, and procedural complications	Tibia fracture	1	MP-12
	Procedural pain (hysterectomy)	1	MAPPUSX
Neoplasms	Breast cancer stage I	1	MP-12
Psychiatric disorders	Suicidal behavior	1	MP-2
Reproductive system and breast disorders	Ovarian cyst rupture	1	MP-12

Source: Table generated by Clinical Reviewer.

Table 11. Serious Adverse Events (SAEs) During Midomafetamine Development, Placebo-Controlled Studies

System Organ Class	Preferred Term	Midomafetamine	Placebo (N)	Study
Cardiac disorders	Ventricular extrasystoles	1	0	MP-8
Injury, poisoning, and procedural complications	Clavicle fracture	1	0	MP-1
Musculoskeletal and connective tissue disorders	Arthritis, hip	1	0	MT-1
Neoplasms	Invasive ductal breast carcinoma	1	0	MDA-1
	Intraductal proliferative breast lesion	1	0	MDA-1
	Chordoma	1	0	MDA-1
Nervous system disorders	Vasovagal syncope	1	0	MP-1
Psychiatric disorders	Suicidal ideation	1[a]	0	MP-8
	Suicidal ideation	0	1[b]	MAPP1
	Suicide attempt	0	2[c]	MAPP1
	Major depression	1[a]	0	MP-8

Source: Table generated by Clinical Reviewer.

[a] An SAE of suicidal ideation and an SAE of major depression occurred in the same participant.

[b] Participant dropped out of study.

[c] Two suicide attempts by the same participant in the placebo group on Day 12 and Day 83. Study drug was withdrawn. The participant initially remained in the study but elected to terminate on Day 132.

In MAPP1, one SAE of suicidal ideation occurred in one participant in the placebo group, and two SAEs of suicide attempt occurred in one participant in the placebo group (on Day 12 and Day 83). In MAPP2, there were no SAEs.

Of the SAEs reported in the development program, the investigator assessed one SAE as probably related to the study drug. In Study MP-8, a phase 2 study, one participant had an SAE of ventricular extrasystoles after receiving the first part of a low-dose split dose (125 mg + 62.5 mg) at the third medication session. The second part of the split dose was held. The participant was hospitalized for cardiac monitoring. Electrocardiogram (ECG) in the emergency department showed normal sinus rhythm with multiple PVCs and runs of trigeminy. He received one dose of metoprolol 25 mg. PVCs decreased during the night. Serial troponin levels were negative. ECG, echocardiogram, and cardiac stress test were all normal the next day, and the participant was discharged. The participant had no previous history of cardiovascular disease. However, the baseline ECG at the time of entry into Study MP-8 showed one PVC. The baseline ECG was considered abnormal but not clinically significant. The investigator assessed the event as an exacerbation of pre-existing ventricular ectopy and as probably related to midomafetamine, with increased ventricular ectopy attributed to amphetamine-like effects of midomafetamine.

3.3.2.3 Treatment-Emergent Adverse Events (AEs) Leading to Treatment Discontinuation

presents the TEAEs leading to treatment discontinuation in the placebo-controlled phase 3 studies MAPP1 and MAPP2. In the rest of the midomafetamine development program outside of these two studies, the following TEAEs resulting in treatment discontinuation each occurred in one participant: ventricular extrasystoles, concussion, obsessive thoughts, musculoskeletal chest pain, back pain, agoraphobia, benzodiazepine withdrawal, relapse of major depressive disorder, diarrhea, and vomiting. The TEAE of anxiety resulted in discontinuation for two participants.

Table 12. Treatment-Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation, MAPP1 and MAPP2

System Organ Class	Preferred Term	Midomafetamine	Placebo (N)	Study
Gastrointestinal disorders	Abdominal pain	0	1	MAPP2
Psychiatric disorders	Depression	1	0	MAPP1
	Insomnia	0	1	MAPP1
	Panic attack	0	1[a]	MAPP1
	Suicidal ideation	0	2	MAPP1, MAPP2
	Suicide attempt	0	2[a,b]	MAPP1

Source: Table generated by Clinical Reviewer.

[a] These three AEs occurred in the same participant.

[b] Two suicide attempts by the same participant in the placebo group on Day 12 and Day 83. Study drug was withdrawn. The participant initially remained in the study but elected to terminate on Day 132. Both suicide attempts were considered SAEs.

3.3.2.4 Frequent AEs in the Phase 3 Studies

The most frequent AEs in the combined set of participants in MAPP1 and MAPP2 were headache, bruxism and jaw tightness, decreased appetite, insomnia, nausea, hyperhidrosis, fatigue, dizziness, muscle tightness, and feeling cold. AEs occurring in the combined MAPP1 and MAPP2 set in ≥2% of participants and at frequencies greater than placebo are presented in organized by system organ class.

Table 13. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 2% of Midomafetamine-Treated Participants and Greater Than Placebo, Safety Population, Pooled Trials MAPP1 and MAPP2

System Organ Class Preferred Term	Midomafetamine N=99 n (%)	Placebo N=95 n (%)
Cardiac disorders (SOC)		
Palpitations	9 (9.1)	7 (7.4)
Tachycardia	2 (2.0)	0
Ear and labyrinth disorders (SOC)		
Ear pain	3 (3.0)	2 (2.1)
Tinnitus	3 (3.0)	1 (1.1)
Eye disorders (SOC)		
Mydriasis	13 (13.1)	0
Vision blurred	12 (12.1)	1 (1.1)
Visual impairment	4 (4.0)	0
Photophobia	3 (3.0)	0
Eye movement disorder	2 (2.0)	0
Gastrointestinal disorders (SOC)		
Nausea	38 (38.4)	16 (16.8)
Dry mouth	14 (14.1)	6 (6.3)
Abdominal pain upper	10 (10.1)	5 (5.3)
Abdominal discomfort	9 (9.1)	6 (6.3)
Vomiting	8 (8.1)	2 (2.1)
Gastroesophageal reflux disease	3 (3.0)	1 (1.1)
General disorders and administration site conditions (SOC)		
Fatigue	28 (28.3)	23 (24.2)
Feeling cold	20 (20.2)	6 (6.3)
Feeling hot	18 (18.2)	10 (10.5)
Feeling jittery	13 (13.1)	0
Chest discomfort	11 (11.1)	4 (4.2)
Chills	11 (11.1)	1 (1.1)
Feeling abnormal	7 (7.1)	3 (3.2)
Feeling of body temperature change	7 (7.1)	1 (1.1)
Asthenia	6 (6.1)	3 (3.2)
Thirst	6 (6.1)	3 (3.2)
Pain	5 (5.1)	3 (3.2)
Non-cardiac chest pain	5 (5.1)	2 (2.1)
Gait disturbance	5 (5.1)	1 (1.1)
Influenza-like illness	4 (4.0)	3 (3.2)
Discomfort	4 (4.0)	2 (2.1)
Temperature intolerance	4 (4.0)	2 (2.1)
Pyrexia	3 (3.0)	2 (2.1)
Swelling	2 (2.0)	0
Infections and infestations (SOC)		
Upper respiratory tract infection	8 (8.1)	7 (7.4)
Oral herpes	3 (3.0)	0
Investigations (SOC)		
Blood pressure increased	7 (7.1)	0
Heart rate increased	3 (3.0)	0
Metabolism and nutrition disorders (SOC)		
Decreased appetite	43 (43.4)	10 (10.5)

System Organ Class Preferred Term	Midomafetamine N=99 n (%)	Placebo N=95 n (%)
Musculoskeletal and connective tissue disorders (SOC)		
Bruxism and jaw tightness[1]	57 (57.6)	14 (14.7)
Muscle tightness[2]	21 (21.2)	9 (9.5)
Pain in jaw	9 (9.1)	7 (7.4)
Myalgia	9 (9.1)	4 (4.2)
Back pain	8 (8.1)	7 (7.4)
Muscle spasms	6 (6.1)	2 (2.1)
Musculoskeletal pain	4 (4.0)	1 (1.1)
Musculoskeletal stiffness	3 (3.0)	2 (2.1)
Fibromyalgia	3 (3.0)	0
Muscle twitching	3 (3.0)	0
Muscular weakness	2 (2.0)	0
Trismus	2 (2.0)	0
Nervous system disorders (SOC)		
Headache	71 (71.7)	55 (57.9)
Dizziness	24 (24.2)	13 (13.7)
Paresthesia	15 (15.2)	4 (4.2)
Nystagmus	13 (13.1)	1 (1.1)
Tremor	11 (11.1)	3 (3.2)
Hypoesthesia	8 (8.1)	3 (3.2)
Disturbance in attention	7 (7.1)	6 (6.3)
Dizziness postural	7 (7.1)	2 (2.1)
Somnolence	3 (3.0)	1 (1.1)
Dyskinesia	2 (2.0)	1 (1.1)
Poor quality sleep	2 (2.0)	1 (1.1)
Hyperesthesia	2 (2.0)	0
Tension headache	2 (2.0)	0
Psychiatric disorders (SOC)		
Insomnia	39 (39.4)	28 (29.5)
Restlessness	15 (15.2)	2 (2.1)
Nightmare	11 (11.1)	10 (10.5)
Depression	6 (6.1)	5 (5.3)
Intrusive thoughts	6 (6.1)	0
Flashback	5 (5.1)	2 (2.1)
Nervousness	5 (5.1)	0
Panic attack	4 (4.0)	3 (3.2)
Stress	4 (4.0)	2 (2.1)
Dissociation	3 (3.0)	2 (2.1)
Fear	3 (3.0)	2 (2.1)
Grief reaction	3 (3.0)	2 (2.1)
Sleep disorder	3 (3.0)	0
Obsessive rumination	2 (2.0)	1 (1.1)
Poor quality sleep	2 (2.0)	1 (1.1)
Tachyphrenia	2 (2.0)	1 (1.1)
Time perception altered	2 (2.0)	1 (1.1)
Affect lability	2 (2.0)	0
Binge drinking	2 (2.0)	0

System Organ Class Preferred Term	Midomafetamine N=99 n (%)	Placebo N=95 n (%)
Renal and urinary disorders (SOC)		
Pollakiuria	6 (6.1)	1 (1.1)
Dysuria	4 (4.0)	0
Micturition urgency	3 (3.0)	0
Reproductive system and breast disorders (SOC)		
Dysmenorrhea	2 (2.0)	1 (1.1)
Skin and subcutaneous tissue disorders (SOC)		
Hyperhidrosis	28 (28.3)	4 (4.2)
Cold sweat	3 (3.0)	2 (2.1)
Erythema	2 (2.0)	0
Social circumstances (SOC)		
Substance use	3 (3.0)	0
Vascular disorders (SOC)		
Peripheral coldness	3 (3.0)	2 (2.1)
Hot flush	3 (3.0)	1 (1.1)

Source: adae.xpt; software: R.

[1] Bruxism and jaw tightness includes events related to jaw tension, tightness, clenching, grinding, or stiffness (MedDRA PT bruxism and LLTs jaw stiffness and tightness in jaw).

[2] Muscle tightness includes only non-jaw-related events.

Treatment-emergent adverse events defined as AEs that occur during the treatment period from the first medication session to study termination.

Duration is 9 to 15 weeks and consists of three medication sessions, 3 to 5 weeks apart.

Abbreviations: AE, adverse event; LLT, lowest-level term; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

Adverse Events of Special Interest (AESIs)

The Applicant selected AESIs based on the mechanism of action of midomafetamine, potential safety issues identified in clinical trials, and potential safety issues reported in the published literature on illicit midomafetamine use.

1. Increases in heart rate and blood pressure

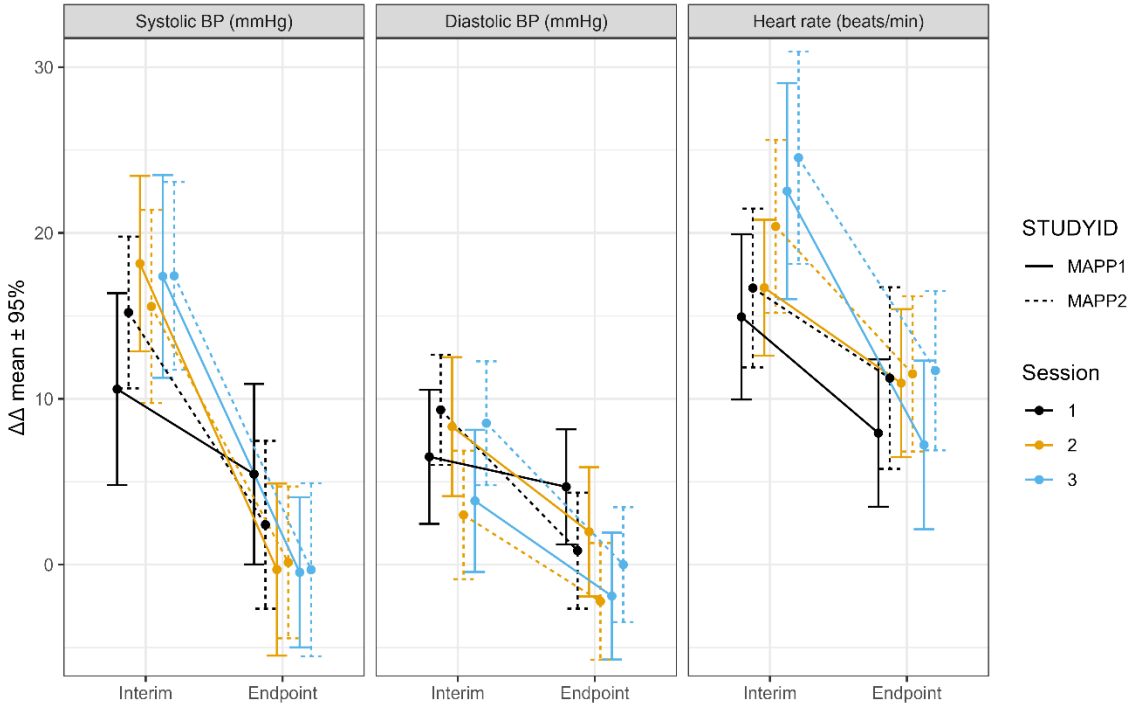
   On treatment days, baseline blood pressure and heart rate were recorded at 0955. Study drug was administered at 1000. Blood pressure and heart rate were measured again at 1130. At that time, if the initial dose was tolerated, a supplemental dose of study drug was administered. Blood pressure and heart rate were then collected at 1730 during the close of the session.

   a. Of participants in the pooled MAPP1 and MAPP2 safety population, 46% of participants treated with midomafetamine versus 17% of participants treated with placebo had an increase in systolic blood pressure ≥20 mm Hg during the third of three medication sessions, and 45% of participants treated with midomafetamine versus 32% of participants treated with placebo had an increase in diastolic blood pressure ≥10 mm Hg during the third of three medication sessions.

   b. At the end of each of the three medication sessions:

      Significant elevations in mean blood pressure and heart rate were observed (). The mean change across both studies in SBP was 17 mm Hg and DBP 7 mm Hg and the mean heart rate after session 3 increased by 23 bpm. Mean systolic and diastolic blood pressures tended to return to predose levels; however, pulse rates remained elevated by approximately 10 bpm.

Figure 4. Change From Placebo and Predose Baseline in Systolic BP, Diastolic BP, and Heart Rate by Medication Session in MAPP 1 and MAPP 2



Source: Cardiac Safety Interdisciplinary Review Team; Division of Cardiology and Nephrology.
Abbreviation: BP, blood pressure

- Outlier analysis () demonstrated a greater proportion of MDMA-treated patients who manifested blood pressure at or above 140/90 mm Hg (68% versus 22%, risk difference 45.6 (95% CI 33.1 to 58), and severe hypertension with SBP >180 mm Hg 6.1 versus 0.0%, risk difference 6.1 (1.4 to 10.8). The latter may be most relevant with regard to potential triggering of cardiovascular events as drug exposure will be intermittent.

Table 14. Outlier Analysis for Vital Signs for MAPP 1 and 2

Parameter Level	MDMA N=99 n/Nw (%)	Placebo N=95 n/Nw (%)	Risk Difference 95% CI
Systolic blood pressure, high, (mm Hg)			
≥140 mm Hg	67/99 (67.7)	21/95 (22.1)	45.6 (33.1, 58.0)
≥160 mm Hg	33/99 (33.3)	4/95 (4.2)	29.1 (19.0, 39.2)
≥180 mm Hg	6/99 (6.1)	0/95 (0.0)	6.1 (1.4, 10.8)
≥20 over baseline	58/99 (58.6)	15/95 (15.8)	42.8 (30.6, 55.0)
≥30 over baseline	26/99 (26.3)	8/95 (8.4)	17.8 (7.5, 28.2)
≥40 over baseline	13/99 (13.1)	1/95 (1.1)	12.1 (5.1, 19.0)

Parameter Level	MDMA N=99 n/Nw (%)	Placebo N=95 n/Nw (%)	Risk Difference 95% CI
Diastolic blood pressure, high, (mm Hg)			
≥90 mm Hg	68/99 (68.7)	33/95 (34.7)	34.0 (20.7, 47.2)
≥100 mm Hg	29/99 (29.3)	8/95 (8.4)	20.9 (10.3, 31.4)
≥110 mm Hg	4/99 (4.0)	1/95 (1.1)	3.0 (-1.4, 7.4)
≥10 over baseline	59/99 (59.6)	25/95 (26.3)	33.3 (20.2, 46.4)
≥20 over baseline	17/99 (17.2)	8/95 (8.4)	8.8 (-0.5, 18.0)
≥25 over baseline	6/99 (6.1)	4/95 (4.2)	1.9 (-4.3, 8.0)
Heart rate, high, (beats/min)			
≥110 and ≥10 over baseline	23/99 (23.2)	0/95 (0.0)	23.2 (14.9, 31.6)
≥110 and ≥15 over baseline	22/99 (22.2)	0/95 (0.0)	22.2 (14.0, 30.4)

Source: Cardiac Safety Interdisciplinary Review Team; Division of Cardiology and Nephrology.
Abbreviations: CI, confidence interval; MDMA, 3,4-methylenedioxymethamphetamine

2. Proarrhythmic potential

   In MAPP1 and MAPP2, AEs involving cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias were considered AESIs. These AEs included torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardias, ventricular fibrillation and flutter, syncope, and seizures.

   a. Across the development program, only one AE of cardiac arrhythmia occurred: the SAE of ventricular extrasystoles described previously. However, there were no scheduled postdose ECGs in the phase 2 and 3 studies.
   b. The Applicant has submitted nonclinical CV studies, AEs reports in phase 2 and phase 3 studies, and literature search suggesting low proarrhythmic potential for midomafetamine. However, the Applicant's literature search was not exhaustive, and additional cases of MDMA-associated arrhythmia were identified.

3. Midomafetamine abuse and misuse

   Midomafetamine effects considered to be neutral, positive, or favorable were not systematically recorded. This safety issue is discussed in more detail under Safety Issue #3 and reviewed in the abuse potential section.

4. Suicidal ideation

   Documentation of AEs related to suicidal ideation included narrative text describing the incidents; recording of preferred terms; severity rankings of incidents as mild (no limitation in normal daily activity), moderate (some limitation in normal daily activity), or severe (unable to perform normal daily activity); and use of the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a clinician-administered questionnaire used to assess suicidal ideation based on the participant's answers to five questions eliciting the participant's thought content and behavior on themes related to suicide:

   [1] The wish to be dead;
   [2] Nonspecific active suicidal thoughts;
   [3] Active suicidal ideation without intent to act;

[4] Active suicidal ideation with some intent to act, without a specific plan;
[5] Active suicidal ideation with specific intent and plan.

The participant's score on the C-SSRS corresponds to the highest-numbered question to which the participant gives an answer of "Yes." Thus, score on the C-SSRS ranges from 0 (no "Yes" answers to any of the questions) to 5 (an answer of "Yes" to question 5). A score of 4 or 5 indicates a clinical assessment of high risk for suicide.

AESIs indicative of suicide risk included AEs coded with the following PTs: completed suicide, intentional overdose, intentional self-injury, self-injurious ideation, suicidal ideation, suicide attempt, suicide threat, suspected suicide, suspected suicide attempt, and any PTs containing the term "suicidal." In addition, suicidal ideation scores of 4 or 5 on the C-SSRS were considered AESIs.

SAEs related to suicidal ideation and suicide attempt were discussed previously. In the pooled database of participants from MAPP1 and MAPP2, the number of participants with AESIs related to suicidal ideation and assessed as mild or moderate by the investigator were similar between the midomafetamine and placebo treatment arms (midomafetamine, 40 [40%]; placebo, 41 [43%]). Two participants with AESIs related to suicidal ideation and assessed as severe by the investigator were both in the placebo arms of MAPP1.

Participants in both the midomafetamine treatment group and the placebo group who had no previous history of suicidal behavior did not demonstrate the onset of suicidal behavior at any time post-baseline. The number of participants with baseline C-SSRS scores ≤3 who experienced an increase in C-SSRS score to 4 or 5 at any time postbaseline was similar between the midomafetamine treatment group (4/98 [4.1%]) and the placebo group (3/93 [3.2%]). There were no evident patterns of increased suicidal ideation or behavior in the immediate 24 to 72 hours after midomafetamine dosing sessions.

5. Other psychiatric symptoms

   AEs that occurred at higher frequencies in participants treated with midomafetamine than those treated with placebo were: anxiety, restlessness, bruxism, nightmare, intrusive thoughts, nervousness, flashbacks, insomnia, and sleep disorder.

   a. Several of these, including flashbacks, nightmare, intrusive thoughts, and sleep disorder, are symptoms consistent with PTSD.
   b. AEs such as insomnia, sleep disorder, anxiety, restlessness, and nervousness could potentially be related to the stimulant properties of midomafetamine.

6. Thermoregulatory and osmoregulatory effects

   a. Thermoregulatory AEs of feeling cold, feeling hot, chills, feeling of body temperature change, temperature intolerance, and hyperthermia were higher in participants treated with midomafetamine than those treated with placebo.

   b. There were no clinically meaningful temperature changes or differences between midomafetamine and placebo participants in temperature in the clinical trials.

c. The clinical significance of the observed thermoregulatory AEs is not clear. Similar thermoregulatory symptoms are known to occur with midomafetamine in the literature.

d. Osmoregulatory AEs of hyperhidrosis, thirst, and cold sweat were higher in participants treated with midomafetamine than those treated with placebo.

e. The clinical significance of the observed osmoregulatory AEs is not clear. Similar osmoregulatory symptoms are known to occur with midomafetamine in the literature.

7. Hepatotoxicity

a. The Applicant selected hepatotoxicity as an AESI based on cases of severe liver injury from literature reports of illicit midomafetamine use.

b. In the midomafetamine clinical trials, there were no AEs related to hepatocellular injury. However, predose and postdose liver function studies were conducted in just one phase 1 study and two phase 2 studies and were not assessed in the phase 3 studies.

Liver function studies were conducted for Study MP-1 (N=23), Study MP-2 (N=14), and Study MPKF (N=16). Abnormal results were obtained for nine participants across the three studies. However, any patterns of change in liver function results are difficult to identify because the three studies had different designs, different durations, different drug exposures, and different tests completed (ALT only in MP-1; ALT and bilirubin in MP-2; AST, ALT, and ALP in MPKF). This issue will be discussed in more detail under Safety Issue #2.

3.3.3 Safety Issues in Detail

3.3.3.1 Key Safety Issue: Is the Safety Database Adequate to Characterize the Safety of Midomafetamine?

Size of the Safety Database

A total of 426 participants were exposed to midomafetamine in the Applicant's trials. The Applicant obtained the right for their safety database to include safety data from 50 participants exposed to midomafetamine in National Institute on Drug Abuse (NIDA) studies. These data create a safety database of 476 participants.

The E1A Guideline (March 1995) proposes exposures for the assessment of drugs intended for the long-term treatment of non-life-threatening conditions (i.e., 1500 participants overall, 300 to 600 participants for 6 months, 100 participants for 1 year); however, that guideline would not apply to PTSD, which is a serious and life-threatening condition and to the currently proposed dosing regimen that is limited to three sessions of midomafetamine administration. If the submitted data support the proposed dosing regimen for midomafetamine, the safety database submitted by the Applicant may be adequate.

It is also important to note that there is extensive published literature from several decades on the use of MDMA. The Agency cannot rely on the published literature for the safety assessment for this particular program; however, the literature has been used to inform some aspects of this safety review.

Clinical Laboratory Data are Limited

For Studies MAPP1 and MAPP2, the NDA submission includes a minimal set of labs conducted to screen participants for eligibility. Predose and postdose laboratory assessments were not conducted. The

submitted lab file includes results only for drug screen, hepatitis C, beta HCG, C-reactive protein, and carotid ultrasound. Other clinical labs collected for screening, including liver function tests, are in source documents at the clinical trial sites and were not entered into the laboratory data file submitted with the NDA. No predose or postdose hematology, electrolytes, BUN, creatinine, liver function studies, metabolic panel, urinalysis, or other labs were obtained on the days of the medication sessions.

The Applicant had identified hepatotoxicity as an AESI based on literature reports of severe liver injury with illicit midomafetamine use. The Applicant did not observe AEs suggestive of liver injury in any of the studies in the clinical development program. However, in the absence of laboratory assessment, it is not possible to explore any early trends indicating early drug-induced liver injury that may present prior to clinically observable liver-related AEs.

The Applicant submitted a Hepatotoxicity Safety Signal Evaluation Report based on data from one phase 1 trial (Study MPKF) and two phase 2 trials (MP-1 and MP-2) in which liver function tests were conducted. Only one participant experienced a shift from "normal" to "high" values in any liver function test (and only up to 43 on AST which is not a severely elevated value).

Concerns about changes in laboratory parameters are somewhat mitigated if the treatment paradigm is restricted to acute drug administration only, as the patient's total drug exposure will be for a limited duration of time with about 3 weeks between drug doses. Overall, review of the available laboratory data did not reveal any clear pattern of increases in liver function test results after administration of midomafetamine; but as noted, the data were insufficient for a more complete assessment. However, there were other AEs reported in the placebo-controlled trials, including thermoregulatory, osmoregulatory, and muscle-related AEs that could represent acute drug effects.

If this application were to be approved, a postmarketing requirement for additional safety assessments, including pre- and post-treatment laboratory assessment (e.g., hematology, electrolytes, comprehensive metabolic panel, liver function tests) could be considered.

Cardiovascular Safety

The clinical and nonclinical data regarding intrinsic arrhythmia risk (QTc-interval prolongation and torsade de pointes) from the development program are inadequate based on the FDA guidance for industry, *QT/QTc Interval Prolongation and Proarrhythmic Potential* (October 2012). Although the reviewed data do not show prolongation of the QTc interval, these data are confounded by the marked increase in heart rate associated with the drug.

At present, it remains unclear if midomafetamine has intrinsic proarrhythmic potential, conditional arrhythmia risk (defined as the potential to trigger arrhythmia in those who are vulnerable or predisposed), or both. Conditional risk is possible given that amphetamine-class compounds induce sympathomimetic activation which may trigger arrhythmias. There was one exacerbation event of pre-existing ventricular ectopy discussed earlier in the SAE section.

The second cardiovascular safety concern is that midomafetamine results in significant increases in both heart rate (HR) and systolic blood pressure (SBP). The FDA guidance for industry, *Assessment of Pressor Effects of Drugs* (February 2022), notes that large drug-induced BP elevations are relevant for all drugs, even those designed for short-term use. Drugs like midomafetamine that have both positive chronotropic (high HR) and pressor effects (high SBP) exhibit the greatest rate pressure product, which is

a risk criterion defined as HR multiplied by SBP. Rapid elevations in rate pressure product may cause transient myocardial ischemia and myocardial infarction, as well as other cardiovascular events dependent on hemodynamic stress (e.g., central nervous system hemorrhage and aortic dissection). Although myocardial oxygen consumption is difficult to measure directly, rate pressure product is a strong correlating value which predicts morbidity and mortality (i.e., risk of ischemic events, etc.) in patients with known or occult cardiovascular disease. This concern is not solely theoretical, given that prior illicit use with MDMA has been associated with myocardial infarction, central nervous system hemorrhage, and aortic dissection—all of which may be triggered by hemodynamic stress. However, no such major events occurred in the development program, albeit with a limited safety database.

Midomafetamine Effects Perceived as Positive Were Not Recorded

In a communication on March 9, 2017, the Agency advised the Applicant that: "For all Phase 1, 2 and 3 studies, [adverse events] associated with potential abuse or overdose must be documented." The Agency also referred to its *Guidance for Industry: Assessment of Abuse Potential of Drugs* (January 2017) for additional details regarding the documentation of adverse events. However, the Applicant's summary of the abuse potential of midomafetamine in the NDA submission includes the following statement: "Effects of treatment that were considered to be neutral, positive, or favorable by the participant and the therapist and study physician and, therefore, likely related to the treatment effect of midomafetamine in PTSD, were not systematically collected as AEs."

The Applicant collected AEs that were categorized as positive, neutral, or favorable beginning March 15, 2023, as part of the study MAPPUSX. However, that data of limited utility for this review due to a lack of a placebo control and because the subject pool is a small fraction of the subjects in the entire development program.

Drug effects that may have been perceived as positive, such as euphoria, stimulation, or somnolence, could indicate drug-liking and would be important for the assessment of whether the studies revealed any risk for abuse potential. Drug effects perceived as positive would also be important in the assessment of the safety risks for midomafetamine and the determination of drug effects that prescribers should monitor for resolution to help decide whether a patient is safe for discharge from the medication session. This issue is discussed further in Section 3.3.4.2.2.

There are limitations in understanding all drug effects during drug therapy due to the limited AE data collection in the clinical trials. Moreover, data that are summarized under section 6 ADVERSE EVENTS of the drug label are typically based on the collection of all AEs that occurred during clinical trials. This contrasts with the more limited AE data collection rationale used by the Applicant in midomafetamine trials, which inherently underrepresents the range and frequency of CNS AEs occurring in these clinical trials.

3.3.4 Abuse Potential and Related Safety Issues

For regulatory purposes, the assessment of abuse potential is considered to be a safety issue. MDMA (the commonly used abbreviation referring to the illicit version of midomafetamine used for nonmedical purposes) has been used for abuse purposes by individuals in the United States for over 40 years and is a Schedule I drug under the Controlled Substances Act (CSA). If the NDA for midomafetamine is approved, the abuse potential of the drug would be described in Section 9 (Drug Abuse and Dependence) of the drug label. An NDA approval for midomafetamine would also necessitate a rescheduling action for

MDMA by the Drug Enforcement Agency to a schedule, to be determined, permitting use by prescription based on an FDA analysis of preclinical and clinical abuse-related studies, as well as an epidemiological evaluation of available data on nonmedical use[2] of MDMA and comparator drugs.

In a meeting between the Applicant and FDA on May 11, 2017, FDA informed the Applicant that no new animal or human studies evaluating the abuse potential of midomafetamine would be required, given that midomafetamine has been extensively investigated preclinically and clinically in National Institutes of Health-funded studies (including self-administration, drug discrimination, conditioned place preference, and human abuse potential studies). Thus, FDA concluded that data from these published studies could inform the abuse potential assessment of midomafetamine for the abuse potential section of the NDA review, in addition to an evaluation of abuse-related adverse events and an epidemiological assessment of illicit MDMA abuse.

The epidemiological evaluation also provides context for considering the potential public health impacts of an approved midomafetamine product as part of the overall benefit-risk assessment (Section 3.3.5).

3.3.4.1 Abuse Potential Assessments of Midomafetamine in Animals

Animal abuse-related studies are primarily conducted in order to predict whether a novel drug will have abuse potential in humans. However, the knowledge that humans use midomafetamine for its rewarding effects predated the initiation of animal abuse-related studies, which were conducted to better understand the drug's pharmacological and behavioral properties.

Animal behavioral studies that contribute to the evaluation of abuse potential have been conducted with midomafetamine for four decades. These published studies include self-administration, conditioned place preference, and drug discrimination, as summarized briefly below. The Applicant did not conduct any of the numerous animal studies with midomafetamine that are published in the scientific literature. Given that the studies have remarkable consistency in demonstrating that midomafetamine produces responses that are rewarding or are similar to other known drugs of abuse, they will not be described in great detail with regard to individual methodology or specific variations in outcomes.

3.3.4.1.1 Self-Administration Studies

A self-administration study evaluates whether a test drug has rewarding properties that may be indicative of abuse potential. In a self-administration study, animals are trained to press a bar a fixed number of times in order to receive an intravenous dose of the test drug. The more that an animal self-administers the test drug compared to vehicle, the greater likelihood there is that humans will also seek out the drug for its rewarding effects.

[2] FDA has established standard regulatory definitions of *misuse* and *abuse*, and some data sources in this review combine these into a composite outcome that we call nonmedical use. *Misuse* refers to intentional use, for therapeutic purposes, of a drug in a way other than prescribed or by an individual for whom it was not prescribed. *Abuse* refers to intentional, non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. We acknowledge the concerns about stigma associated with the term *abuse* and the challenges public health surveillance systems can have in distinguishing the motivation for people's behaviors to categorize them neatly.

Published self-administration studies with midomafetamine have been conducted in both nonhuman primates and in rodents. There is remarkable consistency among these studies in the demonstration that midomafetamine produces self-administration across various species in numerous laboratories.

Midomafetamine was evaluated in self-administration studies with comparison to Schedule I or II stimulants, including drugs such as amphetamine, methamphetamine, cocaine, cathinones (3,4-methylenedioxypyrovalerone (MDPV), methcathinone, methylone, pentylone, butylone, and mephedrone, α-pyrrolidinopentiophenone (αPVP)) and isomers of midomafetamine (S-(+)-midomafetamine and R-(−)- midomafetamine). Midomafetamine typically maintained self-administration to a degree that was slightly lower than that produced by the comparators. However, this does not necessarily mean that midomafetamine has a lower abuse potential than the comparators. Self-administration of a drug can be influenced by experimental factors such as individual drug dose, drug infusion rate, and the time interval between drug administrations.

Overall, data from the self-administration studies in nonhuman primates and in rodents provide abundant evidence that midomafetamine produces rewarding effects. These data strongly suggest that humans would also experience midomafetamine as rewarding. Data from human abuse potential studies and epidemiological evaluations confirm that humans do use midomafetamine for its rewarding responses (see Sections 3.3.4.2.1 and 3.3.5).

3.3.4.1.2 Conditioned Place Preference Studies

A conditioned place preference (CPP) study is another method of analyzing if a test drug has rewarding properties. In this study, an animal is evaluated for whether it is more likely to spend time on the side of a cage where it previously received a test drug, compared to the other side of the cage where it previously received vehicle. If the animal seeks out the drug side of the cage, it is concluded that the test drug has rewarding properties that the animal would like to experience again.

Numerous rodent studies consistently show that midomafetamine produces CPP. Thus, similar to the self-administration study data, the CPP data strongly suggest that humans would also experience midomafetamine as rewarding. Data from human abuse potential studies and epidemiological evaluations confirm that humans do use midomafetamine for its rewarding responses (see Sections 3.3.4.2.1 and 3.3.5).

3.3.4.1.3 Drug Discrimination Studies

Drug discrimination is an experimental method of determining whether a test drug produces effects that are similar to another drug with a specific pharmacological mechanism of action. Animals are first trained to bar-press on one lever when they feel the effects of a training drug, and to bar-press on the other lever when they feel no drug effects (after vehicle administration). Then the animal is challenged with the test drug and if the animal bar-presses on the training drug lever, the test drug is said to "generalize" to the training drug. Full generalization is 75 to 80% bar pressing on the training drug lever, suggesting that the two drugs produce very similar effects based on a similar mechanism of action. Partial generalization between the test drug and the training drug, when it is in the 60 to 75% range, may suggest that there is some overlap in the mechanism of action between the two drugs that produces limited similarity in drug effects.

In drug discrimination studies, when rodents are trained to discriminate midomafetamine from vehicle, a variety of Schedule I and II stimulants (amphetamine, methamphetamine, cocaine, methylphenidate, and certain cathinones) and Schedule I psychedelics (lysergic diethylamide [LSD], 2,5-dimethoxy-4-

methylamphetamine [DOM], 2,5-dimethoxy-4-iodoamphetamine [DOI], and mescaline) produce full or partial generalization to the midomafetamine cue. Conversely, when rodents are trained to discriminate one of these Schedule I and II stimulants or psychedelics from vehicle, midomafetamine produces full or partial generalization to the stimulant or psychedelic cue.

Overall, the drug discrimination data suggest that midomafetamine produces drug effects in animals that are a combination of the effects of both stimulants and psychedelics. In human abuse potential studies, midomafetamine produces effects that have been likened to both stimulants and psychedelics (Section 3.3.4.2.1).

3.3.4.1.4 Intracranial Self Stimulation Studies

The Applicant submitted a summary of intracranial self-stimulation (ICSS) studies conducted in animals with midomafetamine. ICSS is a method in that evaluates whether a test drug produces rewarding properties that alter the sensitivity of the hedonic pathways in the brain, as a measure of the drug's abuse potential. In the ICSS model, rats are trained to bar-press for rewarding electrical stimulation to the brain. Although rats will not work for low levels of electrical current, they will if certain drugs of abuse are given as a pretreatment before testing begins. This occurs because the positive effects of certain drugs of abuse increase the rats' sensitivity to lower levels of reward.

For regulatory purposes, ICSS currently has limitations regarding its applicability in assessing abuse potential compared to self-administration, conditioned place preference, and drug discrimination. Although ICSS has been studied with certain stimulants and opioids, fewer studies have been conducted with other classes of drugs in order to establish the reliability of responses. More critically, false negatives have occurred when known drugs of abuse in a variety of drug classes (such as zolpidem and ketamine) are tested with ICSS. Thus, studies evaluating midomafetamine with ICSS will not be described because the data from these studies are difficult to interpret, especially given the wide methodological designs represented in the studies.

3.3.4.2 Abuse Potential Assessments of Midomafetamine in Humans

The evaluation of the abuse potential of midomafetamine in humans includes an assessment of human abuse potential (HAP) studies, AEs that are indicative of abuse potential, and epidemiological databases. The assessment of epidemiological data related to abuse potential is described in Section 3.3.5.

3.3.4.2.1 Human Abuse Potential Studies

Epidemiological data establish that midomafetamine is a drug of abuse, and there is extensive literature available that describes a number of abuse-related assessments (e.g., drug-liking) after exposure to midomafetamine in the clinical setting. Typically, a HAP study evaluates the abuse-related subjective responses (e.g., "drug liking" and "high") produced by a range of doses of a test drug, in comparison to placebo and a comparator drug with similar behavioral effects and/or a similar mechanism of action that is scheduled under the CSA. Participants in a HAP study are typically individuals who have experience with drugs that are similar to that of the test drug.

The Applicant did not conduct any HAP studies and instead provided a summary of HAP studies that are published in the scientific literature. Given that these HAP studies have remarkable consistency in demonstrating that midomafetamine produces responses that are rewarding or are similar to known

drugs of abuse, the published studies will not be described in detail with regard to individual methodology or specific variations in outcomes.

The most important aspect of the Applicant's literature review of published HAP studies is the comparative studies between midomafetamine and another known substance of similar mechanism with well documented abuse, such as amphetamines. The Applicant provided a literature search through PubMed from 2000 through April 4, 2023, looking for the following keywords: "methylenedioxymethamphetamine" or "MDMA" in combination with the following search terms: "HAP" or "abuse potential" or "abuse liability" or "drug liking." Filters were set to select for clinical trials, meta-analyses, and randomized controlled trials. FDA performed a similar search with no additional comparative studies identified.

The most relevant comparisons were included in this summary with assessments similar to an FDA-required HAP study. These studies directly compared midomafetamine with approved drugs with abuse potential (e.g., *d*-amphetamine, methamphetamine, methylphenidate). Each reference submitted by the Applicant was reviewed independently by FDA.

Midomafetamine Comparison With Amphetamine

HAP studies consistently show that midomafetamine 125 mg either produced a significantly higher peak rating for "drug liking" compared with *d*-amphetamine 40 mg (Cami et al. 2000). Additionally, midomafetamine across numerous dose ranges (e.g., 1.5 mg/kg, 2 mg/kg, 125 mg) produced numerically higher ratings for "drug liking" and "good drug effect" when compared with d-amphetamine at different dose ranges depending on study (Tancer and Johanson 2003). In studies that utilized the Profile of Mood States (POMS), midomafetamine 125 mg either was the only drug that separated from placebo on peak effects on "elation" and "positive mood" scales (Cami et al. 2000), or it showed similar peak effects on "arousal," "elation," "positive mood," and "vigor" scales compared with 40 mg *d*-amphetamine (Johanson et al. 2006).

Midomafetamine 125 mg dose also produced greater positive mystical-type experiences compared to amphetamine 40 mg. On the Five-Dimensional Altered States of Consciousness (5D-ASC) measure of "blissful state," midomafetamine produced higher ratings than d-amphetamine and placebo. In the same study, an assessment with the Mystical Experience Questionnaire (MEQ) showed statistically greater positive mood responses with midomafetamine compared to *d*-amphetamine on scales such as "positive mood," "transcendence of time/space," "positive mood," and "ineffability" (Holze et al. 2020). Additionally, midomafetamine showed higher numeric scores on MEQ dysphoria scales compared to placebo, whereas amphetamine did not produce scores higher than placebo (Cami et al. 2000).

Midomafetamine Comparison With Methamphetamine

When midomafetamine was compared to methamphetamine in a HAP study, midomafetamine 100 mg showed a significantly greater peak effect for ratings of "high" compared with methamphetamine 40 mg, and a higher rating for "good drug effect" for midomafetamine when compared to methamphetamine 20 mg (Kirkpatrick et al. 2012). In this same study, midomafetamine also showed a greater peak rating for "bad drug effect" when compared to methamphetamine.

Midomafetamine Comparison With Methylphenidate

Several HAP studies show that midomafetamine (75 mg to 125 mg) demonstrated significantly greater peak ratings for "drug liking" and "drug high" compared to methylphenidate (40 mg to 60 mg) (Hysek et al. 2014). Within these studies, midomafetamine also showed a significantly greater rating for "good drug effect," as well as greater ratings for "oceanic boundlessness" and "blissful state" on the 5D-ASC, when compared to methylphenidate.

Additional indirect comparative literature was provided by the Applicant and reviewed by the FDA. A comprehensive review by Vollenweider (2001) of separate clinical studies of midomafetamine, psilocybin, and ketamine compared the respective subjective effects of these drugs in healthy volunteers. The author concluded that psilocybin and S-ketamine produced a loss of ego boundaries, whereas midomafetamine produced changes in affective state (e.g., happiness, enhanced mood) with only a slight increase in "depersonalization." The Applicant suggests this shows the abuse-related subjective effects of midomafetamine could be considered less than those produced by S-ketamine. However, it should be noted this conclusion was not a direct comparison between the two drugs and the studies reviewed were not specifically evaluating abuse potential.

Conclusions From the Clinical Abuse Potential Literature Review

In HAP studies, midomafetamine appears to produce similar or increased subjective effects indicative of abuse potential (e.g., drug liking) when compared to FDA-approved Schedule II stimulant drugs in both naïve and experienced midomafetamine users. The preponderance of evidence from the HAP studies suggest that midomafetamine has equal or greater abuse potential than relevant comparators such as amphetamine, methamphetamine, and methylphenidate. Although beyond the scope of this section, midomafetamine not only appears to produce similar subjective effects to other psychostimulants but also possess what some authors referred to as "empathogenic" effects such as happiness and openness. This is relevant given that empathogenic effects are desirable and may contribute to its abuse potential. However, some data also suggest that certain subjective effects (e.g., dysphoria) were more substantial in midomafetamine than comparator stimulant drugs.

3.3.4.2.2 Abuse-Related Adverse Events From Applicant's Clinical Studies

The assessment of central nervous system (CNS) adverse events is conducted by an Applicant to evaluate the safety of the drug under development. This safety assessment includes the evaluation of abuse potential. As stated in the FDA guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017):

> "All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes…
>
> "The presence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential. If euphoria-related AE(s) are reported, it will be important to further characterize the profile of the abuse-related signals to determine if the drug is similar to other known drugs of abuse (a stimulant, sedative, hallucinogen, etc.)…
>
> "The Agency's interest extends to information about the timing of the AEs and the narratives from case report forms (CRFs), which are important in interpretation of the drug effects."

As communicated to the Applicant on March 9, 2017:

> "For all Phase 1, 2 and 3 studies, AEs associated with potential abuse or overdose must be documented. Case narratives of each of these AEs need to be provided, especially for any patient with serious AEs (SAEs). Cases involving purported lack of compliance or patients who discontinue participation without returning the study medication must be fully described. For additional details regarding the documentation of AEs, please refer to the 2017 Guidance for Industry: *Assessment of Abuse Potential of Drugs*. It warrants noting that, since your face-to-face EOP2 meeting with the Agency, CSS finalized this previous draft guidance.
>
> "The incidence of abuse-related AEs in comparison to placebo in trials should be reported by study, population, dose, and displayed in tabular format. Tables should be created for abuse-related higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE."

However, in the NDA, the Applicant stated that they did not collect as adverse events any "effects of treatment that were considered to be neutral, positive, or favorable by the participant and the therapist and study physician, and therefore, likely related to the treatment effect of [midomafetamine] in PTSD." This is not consistent with FDA advice provided to the Applicant in 2017 regarding the collection of adverse events in clinical studies.

Thus, the Applicant excluded the majority of adverse events typically included with an abuse potential evaluation. Although the Applicant did include an analysis of such events starting February 23, 2023, as part of the open-label extension study MAPPUSX, this evaluation is very limited in its ability to characterize the adverse event profile specific to abuse potential with midomafetamine. Within this limited analysis, there were eight cases of feeling relaxation, three cases of euphoric mood, one hallucination and one case of intentional product misuse. Although only a very limited collection of abuse-related AEs, there is a clear signal of abuse potential based on the reported AEs. Most notably, feeling of relaxation was present in 18.6% of participants dosed starting February 23, 2023, in the open-label extension study.

Table 15. Preferred Terms Related to Abuse Potential for Participants Dosed After February 23, 2023 in Study MAPPUSX

Preferred Term	Number of Participants With Event (%)
Feeling of relaxation	8 (18.6%)
Euphoric mood	3 (7%)
Derealization	2 (4.7%)
Time perception altered	2 (4.7%)
Thinking abnormal	1 (2.3%)

Source: Table 14.3.2.2.2.1.2 of the MAPPUSX report.

3.3.4.3 Summary of Animal and Human Abuse Potential Study Data

The data from published animal and human studies that evaluated the abuse potential of midomafetamine show that it produces signals of abuse potential that are similar to Schedule II comparators. Human abuse potential studies show that the midomafetamine produces euphoria and stimulation, which demonstrates that it produces CNS adverse events that are relevant to the safety assessment of this drug, including its abuse potential.

3.3.5 Epidemiologic Data on Patterns of Use and Harms Associated with Illicit MDMA

This section provides a summary of the frequency and patterns of illicit MDMA nonmedical use[3] and related harms from several epidemiologic data sources and published literature to further inform the assessment of midomafetamine abuse potential and consideration of abuse as a safety issue. In addition, we characterized adverse events in cases of single-substance illicit MDMA use, which may suggest additional safety signals warranting investigation. We recognize that inferences that can be drawn in this regard are limited, because important details are often lacking in these cases, particularly about the exact substances and doses involved. FDA reviewed epidemiological analyses and literature on harms associated with illicit MDMA nonmedical use provided by the Applicant in their submission.[4] FDA also conducted independent analyses of available data sources and an independent scoping literature review of published epidemiologic studies and case reports describing illicit MDMA nonmedical use and related harms. Our independent database analyses included methamphetamine, amphetamine, and methylphenidate as comparators for context. We included a summary of the most relevant analyses below and considered the complete set of epidemiologic analyses in the application review and recommendations for drug scheduling. Methods for the complete analyses and literature assessment can be found in Section 6.2.1.

Based on nationally representative general population surveys, past-year MDMA nonmedical use in adolescents and adults is fairly low,[5][6] generally ≤1% and similar to that of methamphetamine, slightly lower than amphetamine, and slightly higher than methylphenidate nonmedical use. Nonmedical use of MDMA and the selected stimulant comparators has decreased among adolescents in the past decade.[7] For example, nonmedical use of amphetamines decreased from 7.4% in 2010 to 2.1% in 2023, Adderall from 6.5% to 1.7%, MDMA from 4.5% to 0.7%,[8] and Ritalin from 2.7% to 0.6% among 12th graders. In populations entering or being assessed for substance use disorder treatment,[9][10] reported recent abuse of MDMA was also low (<2%), similar to amphetamine, higher than methylphenidate, and considerably lower than methamphetamine.

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[3] We preferentially used the term "nonmedical use" when describing surveillance data to reflect the variation in definitions that encompass abuse across data sources and to avoid stigmatizing language. We used the term "abuse" when the data presented were specifically restricted to abuse, as captured in some data sources. Since all MDMA use captured in surveillance data sources to date is illicit, we referred to any MDMA use or other illicit drug use (e.g., LSD, cocaine) as nonmedical use to use consistent terminology for MDMA and contextual comparators that are available by prescription but may be used nonmedically.

[4] Abuse Potential Summary and Proposal and Rationale Related to Drug Scheduling of Midomafetamine (API: 3,4 methylenedioxymethamphetamine [MDMA])

[5] Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2015-2022.

[6] Researched Abuse, Diversion, and Addiction-Related Surveillance Survey of Non-Medical Use of Rx Drugs, 2018-2023

[7] Monitoring the future (MTF) panel study annual report, 2010-2023. https://monitoringthefuture.org/wp-content/uploads/2023/07/mtfpanel2023.pdf

[8] In 2014, survey question was edited to include additional forms of MDMA ("molly") in the description. This version of the question was used in subsequent years.[9] Researched Abuse, Diversion, and Addiction-Related Surveillance Treatment Center Program, 2018-2022

[9] Researched Abuse, Diversion, and Addiction-Related Surveillance Treatment Center Program, 2018-2022

[10] NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version, 2018-2022

Most available measures of morbidity and mortality indicate that harms associated with use of illicit MDMA are considerably lower than with methamphetamine, fairly similar to amphetamine, and higher than with methylphenidate. From 2012 to 2022, 7614 abuse-related exposure cases involving MDMA were captured from calls to U.S. poison centers[11] for medical advice on a drug exposure event. Most of these exposure cases resulted in moderate medical outcomes (56.2%). Methamphetamine tended to have more severe medical outcomes than MDMA, particularly for fatal events (8.2% versus 0.7%), but a higher proportion of single-substance MDMA abuse cases had major medical outcomes (10.4%) than for amphetamines (5.0%) or methylphenidate (2.9%). In 2011 (the last year of data available from a data source of ED visits provided by the Applicant), MDMA was involved in 7.2 visits per 100,000 U.S. population, compared to 51.3 visits per 100,000 U.S. population for methamphetamine/amphetamines.[12]

Available data indicate that MDMA is involved in fewer fatal overdoses than methamphetamine or amphetamine but more than methylphenidate. From 2010 to 2017, there were 693 MDMA-involved overdose deaths nationally, compared to 33,505 involving methamphetamine, 6154 involving amphetamine (including 4354 without mention of methamphetamine, a parent drug of amphetamine), and 254 involving methylphenidate.[13] In more recent data from 35 states and D.C. (3Q 2019 to 4Q 2022),[14] there were 882 MDMA-involved deaths, compared to 53,590 methamphetamine-involved deaths, 18,288 amphetamine-involved deaths (including 3333 without methamphetamine), and 130 methylphenidate-involved overdose deaths. Similar to amphetamine (7.7%) and methylphenidate (3.1%), only a small proportion of fatal overdoses involving MDMA were single-substance (7.3%), while a higher percentage of methamphetamine overdoses were single substance (21.4%).

Documented Harms Associated with Illicit MDMA Use and Gaps Remaining in our Understanding of Safety Outcomes

FDA identified adverse events associated with illicit MDMA use by evaluating (1) the Applicant's Abuse Potential Summary section, (2) structured clinical effect data from single-substance MDMA abuse cases and narratives from fatal single-substance MDMA exposure cases from poison centers (2012 through 2022),[15] (3) structured information available from toxicologist consultations for single-substance MDMA exposure cases (2010 through 3Q 2023),[16] and (4) a scoping literature review.[17] We also searched the FDA Adverse Event Reporting System and did not identify any single-substance exposure reports involving MDMA.

The Applicant's abuse potential summary section included a table describing health outcomes and adverse events associated with confirmed MDMA use, and an accompanying narrative review

[11] America's Poison Centers National Poison Data System, 2012-2022
[12] Drug Abuse Warning Network, 2011
[13] National Center for Health Statistics, Drug Involved Mortality, 2010-2017
[14] Centers for Disease Control and Prevention, State Unintentional Drug Overdose Reporting System, 3Q2019-4Q2022
[15]America's Poison Centers National Poison Data System, 2012-2022[16] Toxicology Investigators Consortium Core Registry
[16] Toxicology Investigators Consortium Core Registry
[17] Due to the limitations of the literature search described in the Applicant's Abuse Potential Summary section, FDA conducted a scoping review of health outcomes and adverse events associated with illicit MDMA use.

highlighted the possibility of physical dependence, tolerance, and withdrawal with MDMA use, as well as the possibility of rare serious adverse events associated with acute overdose of MDMA (e.g., hyperthermia, hyponatremia, rhabdomyolysis, acute renal failure, seizure, cardiovascular events, disseminated intravascular coagulation, hemorrhage, psychiatric problems, hepatotoxicity, and death).

In general, FDA's evaluation of poison center case data, toxicologist consultation case data, and our scoping literature review identified a similar pattern of adverse events as described in the Applicant's abuse potential summary. Analysis of single-substance MDMA abuse poison center cases found that the most common related clinical effects were tachycardia, agitation, hypertension, confusion, hallucinations/delusions, vomiting, mydriasis, diaphoresis, and nausea. From our other data sources, we identified cases of multiorgan toxicity occurring in the context of broader acute syndromes associated with MDMA (e.g., serotonin syndrome, hyperthermia, hyponatremia).

Conversely, FDA identified reports of adverse events associated with illicit MDMA use that the Applicant has not sufficiently addressed in the proposed labeling or provided rationale for not including in the proposed labeling in their application. These include specific cardiovascular outcomes of myocardial infarction, cerebral hemorrhage, aortic dissection, arrhythmias (including ventricular dysrhythmias), cardiac arrest, and sudden death whereas the OVERDOSAGE section of the Applicant's proposed labeling only broadly refers to "cardiovascular adverse events." Respiratory adverse events (e.g., hypoxia, respiratory distress, respiratory arrest, and pulmonary edema) were also identified in our review but are not included in the Applicant's proposed labeling. In addition, while hepatoxicity is noted as a potential complication of hyperthermia in the Applicant's Abuse Potential Summary, it is not included in the proposed labeling. Our scoping literature review identified cases of hepatic injury with delayed onset and in the absence of other toxic syndromes, although these cases lacked confirmatory testing for MDMA. The WARNINGS AND PRECAUTIONS section of the Applicant's proposed labeling broadly refers to neuropsychiatric and physiologic effects, and "the possible emergence or exacerbation of psychiatric symptoms" in patients with PTSD. Other neuropsychiatric adverse events we identified included amnesia, anxiety, agitation, psychosis, depressed level of consciousness, and delirium. Finally, the scoping review identified cases where MDMA was used to perpetrate sexual assault.

Key Data Limitations

Although illicit MDMA has been used for decades and information on use patterns and safety outcomes related to illicit MDMA can help inform potential risks for a prescription midomafetamine product, there are many limitations to interpreting these data in the context of therapeutic use of a prescription product. First, adverse outcomes related to illicit MDMA nonmedical use often occur in the context of polysubstance use, making it difficult to isolate the effects of MDMA, specifically. Even in cases where MDMA was used in a single-substance setting, the purity and dosage of the MDMA product consumed is usually not known (i.e., lacked confirmatory testing), and in some cases substances that are believed to be MDMA might include non-MDMA ingredients that could substantially impact clinical effects and outcomes. The demographics and clinical comorbidities of the population that uses illicit MDMA is likely different from the population who would potentially use the prescription midomafetamine product. In addition, the use circumstances and setting of use of illicit MDMA and prescription midomafetamine will differ greatly.

Summary of Information on Illicit MDMA Use and Associated Harms

MDMA is used as an illicit substance in the general population at a low frequency similar to illicit methamphetamine, slightly lower than amphetamine nonmedical use, and slightly higher than methylphenidate nonmedical use. MDMA is infrequently noted as a drug of abuse in treatment admissions for substance use disorder. Medical outcomes of poison center cases associated with illicit MDMA use tend to be less severe than those associated with methamphetamine, slightly more severe than for amphetamine nonmedical use, and substantially more severe than methylphenidate nonmedical use. MDMA-involved deaths almost always involved other substances, and MDMA was involved in more overdose deaths than methylphenidate but substantially fewer than amphetamine or methamphetamine.

The Applicant's evaluation of the published literature appears to have gaps with respect to evaluation of potential safety outcomes based on experience with illicit MDMA. FDA identified adverse events associated with illicit MDMA use by evaluating case narratives of fatal single-substance cases from poison centers, toxicologist consultations for single-substance MDMA exposures, and an independent scoping literature review. We identified adverse events associated with illicit MDMA use, including specific cardiovascular, respiratory, hepatic, and neuropsychiatric outcomes, as well as various laboratory abnormalities, whereas the Applicant has only addressed them broadly. We also identified cases where MDMA was used to perpetrate sexual assault. Interpretation is difficult, however, because use of other substances may accompany illicit MDMA use, the purity and dosage of the MDMA product consumed is usually not known, and what is believed to be MDMA might include non-MDMA ingredients that could substantially impact clinical effects and outcomes.

3.4 Risk Mitigation

Midomafetamine effects may result in a temporary reduction of inhibition, an openness to suggestion, and a range of intense emotions. Other known effects of midomafetamine include a heightened and/or altered awareness of sensory input, physical surroundings, and passage of time. Based on midomafetamine's pharmacology and mechanism of action, patients may be at risk for serious harm resulting from patient impairment.

In the clinical program, midomafetamine was studied under strict controls. Participants were administered midomafetamine under medical supervision and were monitored by two therapists for eight hours in a controlled setting with most participants additionally staying overnight at a study site. There were also exclusion criteria that prevented participants with certain concurrent mental health disorders or lack of social support from receiving midomafetamine. Participants had to agree to not drive until the following day post medication administration. There were no clear objective criteria for discharge and participants were discharged at the discretion of the therapists.

We are particularly concerned that serious harm could result while patients are impaired. Serious harm due to patient impairment may include, but are not limited to, events resulting in hospitalization or death, events that put patients at risk for hospitalization or death, and events with significant negative consequences. Also, because the onset, duration, and exact nature of the short-term effects of midomafetamine were not captured in the clinical program, the safety profile and requirements for appropriate monitoring require further characterization. We are also concerned about worsening of psychological disorders that cause disability or that may lead to hospitalization or death, and suicidal behaviors and ideation.

3.4.1 Risk Evaluation and Mitigation Strategy (REMS)

REMS Background

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical manufacturers to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond labeling. The elements of a REMS can include: a Medication Guide or package insert, a communication plan to healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, elements to assure safe use (ETASU), and an implementation system. All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared by the Applicant and reviewed by FDA.

ETASU can include one or more of the following requirements:

Healthcare providers who prescribe the drug have training or experience or are specially certified

Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified

The drug be dispensed only in certain healthcare settings

The drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory results

Each patient using the drug be subject to monitoring

Each patient using the drug be enrolled in a registry

ETASU can impose burdens on the healthcare system and potentially impact patient access to treatment; therefore, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

Must be commensurate with specific serious risk(s) listed in the labeling.

Cannot be unduly burdensome on patient access to the drug.

To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

The Agency has provided feedback to the Applicant regarding the REMS between 2017 and before NDA submission in 2023.

Agency's Proposed REMS

If midomafetamine is approved, a REMS will be necessary to ensure the benefits outweigh the risks of serious harm resulting from patient impairment from midomafetamine administration. Patient impairment is an expected effect from midomafetamine administration and there must be safeguards to mitigate serious harm from patient impairment, similar to the risk mitigation in the clinical trials, to support patient safety.

The REMS will consist of ETASU, an implementation system and a timetable for submission of assessment. The Agency is proposing a REMS that is comprised of the following ETASU:

the drug can only be dispensed in certain healthcare settings,

the drug be dispensed to patients with evidence or other documentation of safe-use conditions,

each patient using the drug be subject to monitoring, and

each patient using the drug be enrolled in a registry.

The proposed REMS goal is to mitigate the risks of serious harm resulting from patient impairment from midomafetamine administration by ensuring that patients are managed in a medically supervised healthcare setting during and after midomafetamine administration.

The serious harms of interest include but not are not limited to: events resulting in hospitalization or death, events that put patients at risk for hospitalization or death, events with significant negative consequences, worsening of psychological disorders that cause disability or that may lead to hospitalization or death, and suicidal behaviors and ideation.

Midomafetamine dispensing and administration will be restricted only to certain healthcare settings certified in the REMS. As a condition of certification in the REMS, healthcare settings that dispense midomafetamine will be required to enroll each patient prior to treatment initiation. The enrollment will inform patients about the risk of impairment and the serious harm that may result, the need to report adverse events, and the patient agrees to be discharged to an accompanying adult and not drive or operate heavy machinery in the immediate period after the medication session. The healthcare settings are required to develop and put in place policies and procedures to ensure: (1) a prescriber is available during midomafetamine administration and monitoring and to determine if second dose is held for safety or tolerability concerns, (2) at least two healthcare providers are onsite, one of which must be a licensed healthcare provider, to monitor patients' medical (including vital signs) and psychological status for at least eight hours and until patient is stable to be discharged; (3) emergency action plans are in place to escalate care if needed; (4) plans are in place in case the patient requires longer monitoring; (5) the patient is stable to be discharged from the healthcare setting; (6) and that patient is released to an accompanying adult after each medication session, and (7) follow-up with patients after discharge from each medication session.

The proposed REMS also includes a patient registry to better characterize the risk of serious harm that may result from patient impairment. Patients will be assessed during midomafetamine administration and monitoring, and after discharge from each medication session. Data collected through the registry may better inform us of the signs and symptoms of mental or physical distress experienced by the patient while monitored, onset and duration of short-term effects, and whether care needed to be escalated. In addition, information regarding patient safety between treatments will be collected including events that result in increased risk due to impaired judgement, or worsening of psychological disorders that cause disability, hospitalization, or death. Registry data will also be used to determine whether changes to monitoring and other safe use behaviors in the REMS are needed.

A REMS Assessment Plan will be developed to evaluate the proposed midomafetamine REMS. The REMS design will impact the selection of metrics and data sources, which will be used to inform whether the REMS is functioning as intended and assess whether the REMS is meeting its risk mitigation goals.

3.4.2 Postmarketing

Due to the small size of safety database, limited availability of clinical data, and no recording of midomafetamine effects perceived as positive in the clinical trial development, we are also considering a postmarket requirement and enhanced pharmacovigilance to further characterize the safety risk described in Section 3.3, if approved.

4 Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Posttraumatic stress disorder (PTSD) is a psychiatric disorder that may occur following exposure to actual or threatened death, serious injury, or sexual violence. It is characterized by: – Intrusion symptoms (i.e., recurrent dreams or intrusive memories about the event, dissociative reactions in which the individual feels or acts as if the traumatic event were recurring, intense physiological reactions or psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event); – Persistent avoidance of memories, thoughts, feelings, or external reminders associated with the traumatic event; – Negative alterations in mood and cognition associated with the traumatic event (i.e., inability to experience positive emotions, inability to remember an important aspect of the traumatic event, distorted cognitions or guilt about the cause or consequences of the traumatic event); and – Marked alterations in arousal and reactivity (i.e., hypervigilance, exaggerated startle response, angry outbursts with little or no provocation, poor concentration, insomnia). • Patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning that result in high healthcare utilization and diminished quality of life. • Per the National Institute of Mental Health, an estimated 3.6% of U.S. adults had PTSD in the past year, with higher past-year prevalence in women (5.2%) than men (1.8%).	PTSD is a serious psychiatric condition occurring frequently in the U.S. population, with significant morbidity and downstream personal and societal effects.

	Evidence and Uncertainties	Comments to the Advisory Committee
Current Treatment Options	• The current standard of care for PTSD involves certain modalities of psychotherapy (such as cognitive-behavioral therapy [CBT] or eye movement desensitization and reprocessing [EMDR]) either alone or in combination with pharmacotherapy. • There are only two currently approved pharmacotherapeutic treatments for PTSD, sertraline and paroxetine, both approved in 2000. No new medications have been approved for PTSD since then.	Despite PTSD's increased prominence and high prevalence as a major psychiatric disorder, no new pharmacotherapeutic treatments have been approved in almost 25 years. The two approved drugs also require chronic daily dosing.
Benefits	• Two phase 3 studies MAPP1 and MAPP2 were conducted as 18-week randomized, double-blind, placebo-controlled trials in 91 and 104 participants each respectively with PTSD, after participants took three dosing sessions each of midomafetamine in conjunction with additional psychological support sessions on other days before and after dosing. • In both trials, participants in the midomafetamine arm experienced statistically significantly greater improvement in PTSD symptoms at Week 18 based on the primary endpoint of mean change from baseline and difference from placebo on the CAPS-5. In MAPP1, there was an estimated -11.86 (95% confidence interval [CI]: -17.41, -6.32; p<0.0001) point larger reduction from baseline in mean CAPS-5 scores for participants randomized to midomafetamine compared to those randomized to placebo. In MAPP2, there was an estimated -8.91 (95% CI: -13.70, -4.12; p=0.0004) greater reduction in CAPS-5 scores from baseline for participants in the midomafetamine arm compared to those on placebo. The mean numerical score reductions on midomafetamine by Week 18 were -24.50 and -23.69 for MAPP1 and MAPP2 respectively (-12.64 and -14.78 on placebo). According to the literature, overall score reductions of at least 10 points on the CAPS-5 may be considered clinically meaningful (Varker et al. 2020). • For both MAPP1 and MAPP2, the prespecified secondary efficacy endpoint was the change in the Sheehan Disability Scale (SDS) score from baseline to Visit 19 (Week 18). The Type I error rate in both studies was controlled using a hierarchical testing strategy where the difference in SDS scores would only be formally tested if the difference in CAPS-5 scores was statistically significant (which is the case here). Results of both studies showed a statistically significant difference between the	MAPP1 and MAPP2 were both statistically positive for efficacy on the FDA-agreed upon primary endpoint of the CAPS-5 at Week 18, as well as a prespecified secondary endpoint of the SDS change from baseline. Overall mean score reductions on the CAPS-5 for MAPP1 and MAPP2 were considered clinically meaningful. MPLONG also notes likely durability of effect even at least 6 months after completion of treatment. Also, there is additional support indicating a similar efficacy pattern from the open-label studies MP16 and MAPPUSX. These results, if able to be taken at face value, would indicate the effectiveness of a drug that can be administered just 3 times over 18 weeks and have durability of effect of at least 6 months afterwards. However, given the functional unblinding that occurred during the placebo-controlled trials, the contribution of likely expectation bias cannot be discounted while it also cannot be quantified. The consistency of results though over time in MPLONG (and some continued improvement even in the placebo arms) may signify a greater possibility that there is a drug treatment effect that is longer-lasting and larger than would be seen with expectation bias alone. Also, the contribution of psychotherapeutic support sessions to the overall efficacy results cannot be fully quantified or understood, as there were no factorial design studies conducted to verify the contribution of those sessions alone with or without drug; the types of therapy

	Evidence and Uncertainties	Comments to the Advisory Committee
	midomafetamine arm and the placebo arm in reduction in SDS scores (-1.36 (-2.46, -0.25) and -1.20 (-2.26, -0.14) mean change from baseline for MAPP1 (with p-value 0.0167) and MAPP2 (with p-value 0.0271) respectively). • However, a major concern with the placebo-controlled studies as conducted was that functional unblinding occurred (likely due to the marked experiential effects of midomafetamine relative to placebo) as well as concerns about potential investigator or participant expectation bias. These concerns were verified by a survey given to MAPP2 participants with around 80 to 90% of participants who received midomafetamine correctly guessing their treatment arm. • An observational extension study, MPLONG, evaluated 60 participants from MAPP1 (unblinded) and 82 from MAPP2 (still blinded) at a single follow-up visit at least 6 months afterwards on the CAPS-5. A similar mean difference from placebo was maintained in the drug groups from both studies (-14.7 in MAPP1 and -11.96 in MAPP2) at the long-term timepoint. There was also continued mean score improvement from Week 18 to the long-term timepoint in all arms except the placebo arm of MAPP1. However, this data is also challenging to interpret given variable durations of follow-up and the use of interim potentially therapeutic interventions in some individuals. • The treatment sessions were bracketed by what the Applicant termed 1 preparatory before and another 3 integrative therapy sessions on days after the dosing sessions. The MAPS therapy manual gives broad guidelines on the conduct of medication sessions, such as the physical environment and supportive therapist stance. The therapist is given considerable flexibility in the selection of specific therapeutic modalities, so we cannot consider the therapy sessions standardized as conducted across the trials. •	that were conducted are also not standardized across the trials per the MAPS manual. Based on CAPS-5 scores, it appears there is evidence of a significant treatment effect of midomafetamine versus placebo after 3 dosing sessions, by Week 18, that may persist for 6 months or more. These benefits, if verified, of midomafetamine for people with a serious condition such as PTSD could be of substantial clinical importance.
Risks and Risk Management	• The most frequent adverse events (AEs) of midomafetamine in the phase 3 trials MAPP1 and MAPP2 were headache, bruxism and jaw	The overall safety profile for midomafetamine appears consistent with prior literature and earlier phase data for this drug that has some similarities to stimulant-class

	Evidence and Uncertainties	Comments to the Advisory Committee
	tightness, decreased appetite, insomnia, nausea, hyperhidrosis, fatigue, dizziness, muscle tightness, and feeling cold. • Midomafetamine causes a period of significant impairment that lasts at least 8 hours and requires professional observation during that time in a safe setting. The Applicant did not provide data on specific discharge criteria or appear to use systematic symptom assessments to determine readiness for discharge during their trials. • Midomafetamine is associated with changes in cardiovascular indices such as increased heart rate and blood pressure. Significant elevations in mean blood pressure and heart rate were observed. The mean increase in systolic blood pressure was 17 mm Hg and the mean increase in diastolic blood pressure was 7 mm Hg. A greater proportion of midomafetamine-treated patients manifested blood pressure exceeding 140/90 mm Hg (67.7 versus 22.1%, risk difference 45.6 (95% CI 33.1-58) and Severe hypertension (SBP >180 mm Hg) occurred in 6.1 of midomafetamine-treated patients versus 0.0% in placebo, risk difference 6.1 (1.4-10.8). The latter may be most relevant regarding potential triggering of cardiovascular events as drug exposure will be intermittent. In addition, the mean heart rate after session 3 increased by 23 bpm. After the session, heart rate values remained elevated by about 10 bpm compared with predose values. The risk of cardiovascular events from elevated blood pressure and heart rate cannot be determined given the small size of the safety database. One serious AE of cardiac arrhythmia (ventricular extrasystoles) occurred in a participant on drug during a phase 2 study MP-8 resulting in hospitalization, but baseline electrocardiogram noted pre-existing ventricular ectopy, which was likely exacerbated by the drug. • Although there were concerns that suicidal ideation and behavior (SI/B) could be exacerbated by drug withdrawal or other drug-related concerns, we detected no signal for SI/B for participants on drug versus placebo, or correlating with withdrawal period timing. There were three serious AEs in MAPP1 and MAPP2 relating to SI/B, all occurring on placebo.	drugs. Most of the drug's AEs appear limited to the timeframe of the pharmacokinetics of acute dosing, i.e., 8 hours, including cognitive and behavioral impairments that will require professional observation and appropriate discharge evaluation. Although there are concerns that some of the drug's effects require more detailed data collection to fully characterize them, most of this data collection could likely be safely deferred to postmarketing required studies if we determine that short-term dosing is all that is necessary for durable treatment of PTSD (i.e., at least 6 months to 1 year). As there was not collection of laboratory assessments during MAPP1 and MAPP2, a postmarketing requirement for additional safety assessments, including pre- and post-treatment laboratory assessment (e.g., hematology, electrolytes, comprehensive metabolic panel, liver function tests) could be considered. A risk evaluation and mitigation strategy is being considered to mitigate the risks of serious harm resulting from patient impairment from midomafetamine administration by ensuring that patients are managed in a medically supervised healthcare setting during and after midomafetamine administration.

	Evidence and Uncertainties	Comments to the Advisory Committee
	• The data from published animal and human studies evaluated the abuse potential of midomafetamine, as well as epidemiologic data regarding midomafetamine nonmedical use, show that it produces signals of abuse potential that are similar to Schedule II comparators. • Thermoregulatory and osmoregulatory changes occurred in participants taking midomafetamine (which is a known issue with the drug from past literature); the overall clinical significance of these events could not be determined due to the lack of laboratory data although generally they seemed to resolve after dosing ended. • Hepatotoxicity was noted as an AE of special interest due to limited case reports in past literature; however, laboratory data was not collected in the phase 3 studies. No acute AEs related to liver function were noted during those studies. • Although the International Council for Harmonisation offers recommendations on the size of database to characterize safety of drugs intended for chronic administration, these are not applicable if we determine that short-term dosing is sufficient for longer-term efficacy. • The Applicant did not appropriately document CNS-related AEs (particularly ones that detect 'positive' or drug-liking effects such as euphoria) as previously advised by our Controlled Substance Staff.	

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6 Appendix

6.1 Additional Summaries of Efficacy Results for MPLONG

Table 16. Tipping Point Analysis for Durability of CAPS-5 Total Scores in MPLONG With Shift Parameter Applied to Participants From Midomafetamine Group With Reported Interim Midomafetamine, Ketamine, or DMT Use for Participants from MAPP2

Shift Parameter for Participants in Midomafetamine Group With Interim Use	Estimated LS Mean Change From Baseline in CAPS-5 Total Score for Participants in Midomafetamine Arm at Visit 19 (95% CI)	Estimated LS Mean Change From Baseline in CAPS-5 Total Score for Participants in Midomafetamine Arm at LTFU V1 (95% CI)	Estimated Difference From Visit 19 to LTFU V1 in LS Mean Change From Baseline in CAPS-5 Total Score (95% CI)
0	-23.84 (-27.03, -20.65)	-25.86 (-29.61, -22.11)	-2.02 (-4.61, 0.57)
1	-23.85 (-27.04, -20.66)	-25.75 (-29.51, -21.98)	-1.90 (-4.50, 0.70)
3	-23.85 (-27.04, -20.66)	-25.51 (-29.31, -21.71)	-1.66 (-4.28, 0.96)
5	-23.86 (-27.04, -20.67)	-25.27 (-29.10, -21.44)	-1.42 (-4.06, 1.23)
10	-23.86 (-27.05, -20.68)	-24.66 (-28.60, -20.72)	-0.79 (-3.53, 1.94)
20	-23.87 (-27.05, -20.69)	-23.38 (-27.58, -19.19)	0.49 (-2.50, 3.48)

Source: FDA Statistical Analyst.

Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; CI, confidence interval; DMT, dimethyltryptamine; ISE, integrated summary of efficacy; LS, least squares; TFU, long-term follow-up; V, visit

Table 17. Tipping Point Analysis for Durability of CAPS-5 Total Scores in MPLONG With Shift Parameter Applied to Participants From Midomafetamine Group With Reported Interim Midomafetamine, Ketamine, or DMT Use for Participants From MAPP1

Shift Parameter for Participants in Midomafetamine Group With Interim Use	Estimated LS Mean Change From Baseline in CAPS-5 Total Score for Participants in Midomafetamine Arm at Visit 19 (95% CI)	Estimated LS Mean Change From Baseline in CAPS-5 Total Score for Participants in Midomafetamine Arm at LTFU V1 (95% CI)	Estimated Difference From Visit 19 to LTFU V1 in LS Mean Change From Baseline in CAPS-5 Total Score (95% CI)
0	-24.44 (-28.06, -20.81)	-29.36 (-34.17, -24.56)	-4.93 (-9.32, -0.53)
1	-24.44 (-28.07, -20.82)	-29.20 (-34.02, -24.38)	-4.76 (-9.17, -0.35)
3	-24.46 (-28.08, -20.84)	-28.87 (-33.72, -24.02)	-4.41 (-8.84, 0.02)
5	-24.47 (-28.10, -20.85)	-28.52 (-33.40, -23.64)	-4.05 (-8.50, 0.41)
10	-24.51 (-28.13, -20.89)	-27.59 (-32.55, -22.63)	-3.08 (-7.61, 1.45)
20	-24.57 (-28.19, -20.96)	-25.57 (-30.78, -20.36)	-1.00 (-5.79, 3.80)

Source: FDA Statistical Analyst.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5; CI, confidence interval; DMT, dimethyltryptamine; ISE, integrated summary of efficacy; LS, least squares; TFU, long-term follow-up; V, visit

6.2 Methods for FDA's Independent Epidemiologic Data Analyses and Scoping Literature Review

6.2.1 Overview

We examined multiple data sources to describe nonmedical use and related harms associated with MDMA, relative to other stimulants. These data sources collect information from various populations: the general population, people seeking medical treatment for adverse effects of nonmedical use, people who have received consultative evaluations from medical toxicology physicians during the course of their care, and people entering treatment for substance use disorder. We present major features of each data source in . We provide a more detailed description of each data source and our analytic approach in the sections below. Quantitative analyses were performed independently by two analysts to ensure accuracy of results, with any discrepancy resolved by a detailed review of the analytic approach and reconciliation of any differences. In addition, we supplemented these analyses with qualitative review to further describe the circumstances of, and clinical outcomes associated with, use of MDMA. We also conducted a scoping literature review of epidemiologic studies and case reports and case series for health outcomes following illicit MDMA use. The methods described here represent the complete set of epidemiological analyses conducted that were considered for the application review and drug scheduling recommendations. We included a summary of results from the most relevant analyses in Section 3.3.5.

Table 18. Overview of Data Sources to Assess MDMA Nonmedical Use and Compared to Other Stimulants of Interest

Characteristic	Population and Data Sources Used	Use(s) of Data Source(s)
Scale and relative frequency of nonmedical use cases involving 3,4-methylenedioxy methamphetamine (MDMA) and comparators	General population National Survey on Drug Use and Health (NSDUH), 2015-2022 Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) Nonmedical Use of Prescription Drugs (NMURx) Survey, 2018-2023	Estimated number and prevalence of individuals in the general U.S. population reporting nonmedical use of MDMA and comparator stimulants
	High school and college students Monitoring the Future (MTF), 2010-2023	Estimated number and prevalence of students in U.S. secondary schools reporting nonmedical use of MDMA and comparator stimulants
	Individuals/healthcare providers seeking medical advice after abuse-related exposure National Poison Data System (NPDS) exposure cases from Poison Centers (PC)s, 2012-2022*	Exposure case counts and characteristics documented by PCs involving abuse of MDMA and comparators
	People entering or being assessed for treatment for opioid or substance use disorders (OUD/SUD) RADARS Treatment Center Program (TCP), 2017-2023* Inflexxion National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Addiction Severity Index-Multimedia Version® (ASI-MV®), 2017-2023*	Proportion of patients entering or being assessed for treatment for OUD/SUD reporting past thirty-day abuse of specific MDMA and comparator simulants
	Toxicologist consultations for exposures involving MDMA and comparators Toxicology Investigators Consortium (ToxIC) Core Registry cases, January 1, 2010, through September 30, 2023	Exposure case counts involving misuse/abuse of MDMA and comparators
Route of abuse for MDMA and comparator stimulants	Individuals/healthcare providers seeking medical advice after abuse-related exposure NPDS exposure cases to PCs, 2012-2022*	Proportion of cases with specific routes of abuse for single-substance exposure cases involving the drug
	People entering or being assessed for treatment for OUD/SUD Inflexxion NAVIPPRO™ ASI-MV®, 2022-2023*	Proportion of respondents endorsing abuse of a specific drug via specific routes among people entering or being assessed for SUD treatment NAVIPPRO™
	Toxicologist consultations for exposures involving MDMA ToxIC Core Registry cases, January 1, 2010, through September 30, 2023	Number of MDMA single-substance and polysubstance exposure cases by route

Characteristic	Population and Data Sources Used	Use(s) of Data Source(s)
Morbidity associated with abuse or nonmedical use, involving MDMA and comparators	Individuals seeking/healthcare providers medical advice after abuse-related exposure NPDS exposure cases to PCs, 2012-2022*	Number of cases and severity of outcomes for abuse cases with related clinical effects
	Toxicologist consultations for exposures involving MDMA ToxIC Core Registry cases, January 1, 2010, through September 30, 2023	Clinical characteristics and outcomes of single-substance MDMA exposures
	FDA Adverse Event Reporting System (FAERS), January 1, 2013, through December 31, 2023	Qualitative review of single-substance exposure reports involving MDMA
Overdose mortality involving MDMA and comparators	Deaths involving drug substances National Vital Statistics System-Morality (NVSS-M) Drug-Involved Mortality (DIM), 2010-2017 Centers for Disease Control (CDC) State Unintentional Drug Overdose Reporting System (SUDORS), 2019-2022	Counts of drug overdose deaths classified as either intentional, unintentional, or undetermined intent
	Deaths in single-substance exposure cases involving MDMA ToxIC Core Registry cases, January 1, 2010, through September 30, 2023	Clinical characteristics of fatal single-substance MDMA exposures
	Deaths in single-substance exposure cases involving MDMA NPDS exposure cases to PCs, 2012-2022*	Qualitative review of fatality abstracts for direct cases of single substance exposures involving MDMA with a fatal outcome assessed as undoubtedly responsible†

Source: Reviewer generated.

* Provides data on exposures resulting from abuse.

† In NPDS data, fatal cases may be marked as direct or indirect. Direct report cases are those which were reported directly to the receiving PC and are typically more complete than indirect cases. Indirect report cases may have been obtained by a PC through other means (e.g., review of local medical examiner cases), generally have less accompanying information, and seldom have fatality abstracts available for review. Fatality abstracts include an assessment for the relative contribution to the fatality for each substance involved.

6.2.2 Comparator Drugs

In consultation with the Center for Drug Evaluation and Research's Controlled Substances Staff, we selected the following comparator drugs:

Schedule II: amphetamine, methamphetamine, and methylphenidate.

These stimulant comparators were chosen because of their pharmacologic similarities to MDMA. Depending on the drugs and groupings available in the data source, we included specific prescription stimulants, such as amphetamine/dextroamphetamine (e.g., Adderall), and methylphenidate (e.g., Ritalin), as comparators. We included all formulations of each comparator available in the respective data source as the exact formulations captured differed between databases.

Comparisons of Estimates of Nonmedical Use and Related Outcomes

In this review, we compare estimates of nonmedical use and related outcomes as descriptive comparisons rather than formal statistical comparisons (i.e., p-values for differences in estimates or examination of overlapping 95% confidence intervals); apparent differences in estimates may not be statistically significant. Furthermore, conventional statistical hypothesis testing is complicated by use of

multiple comparator drugs across multiple outcomes in a diversity of data sources. P-values are based on probability, and the probability of a Type 1 error (incorrectly concluding that a finding is significant when it actually only occurred by chance) increases with an increasing number of tests. Given the many comparators and outcome measures, we believe that a qualitative synthesis of descriptive data are the most appropriate approach for the purpose of this review.

6.2.3 Epidemiologic Analysis Methods

We conducted a descriptive analysis of multiple data sources to describe the extent of nonmedical use and related adverse outcomes associated with MDMA, relative to other stimulants. We describe below quantitative analyses of structured data for MDMA and comparator stimulants in the United States as well as a more detailed qualitative review of cases that describe the circumstances of, and clinical outcomes associated with, use of MDMA.

6.2.3.1 NSDUH

The National Survey on Drug Use and Health (NSDUH) is an annual survey of the U.S. general population, with stratified probability sampling to enable calculation of national estimates. Since 2015, NSDUH has elicited information on lifetime and past year use of ecstasy and other stimulants. We consider use of the term "ecstasy" in the NSDUH to be synonymous with our use of "MDMA."

We extracted available data on ecstasy and comparators from the 2015-2022 NSDUH detailed tables posted publicly on the SAMHSA website.[18] We reported national estimates in terms of numbers of individuals and percent of the total population reporting any lifetime, past-year, or past-month nonmedical use of ecstasy, methamphetamine, amphetamines, methylphenidate, and/or prescription stimulants.[19] Although prescription methamphetamine products are available in the United States, utilization of these drugs in clinical practice is rare (Bokhari and Fournier 2013), thus we considered all use of methamphetamine and ecstasy nonmedical. We chose to include the prescription stimulant group comparator because data for methylphenidate and amphetamine were not available for all the outcomes of interest in the NSDUH. Finally, we limited analyses to results reflecting nonmedical use of prescription stimulants and did not include legitimate medical use.

Due to the COVID-19 pandemic and methodological changes to the survey, NSDUH data from 2020 and the period from 2021 through 2022 are not comparable to previous years or to each other.

6.2.3.2 RADARS® NMURx

The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System conducts the Nonmedical Use of Prescription Drugs (NMURx) survey, which is a serial, cross-sectional, online survey of the general adult population to elicit information on the nonmedical use of drugs (prescription, nonprescription, unapproved, and illicit). Every 6 months, it recruits 30,000 respondents through a survey panel company in which respondents voluntarily register to complete surveys for modest compensation.

[18] Reports and Detailed Tables from the National Survey on Drug Use and Health (NSDUH). 2022. https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health

[19] Prescription stimulants include amphetamine, methylphenidate, weight loss stimulants, Provigil, and all other prescription stimulants, thus, counts for prescription stimulants will not equal the sum of individuals reporting nonmedical use of amphetamine, methylphenidate, or other individual prescription stimulants.

From the NMURx, we included data on past-year nonmedical use of MDMA, amphetamine, non-pharmaceutical amphetamine, methamphetamine, and methylphenidate. NMURx defines a case of prescription drug nonmedical use as: use in a way not directed by your healthcare provider including 1) without a prescription 2) greater amounts, more often or longer than directed, 3) used it for the experience or feeling it caused, and 4) changed it before use by crushing, chewing, dissolving, or heating.

RADARS provided FDA with NMURx results from 2018 through 2023 under an existing contract with FDA. Using data collected on semi-annual surveys, RADARS calculated the nationally weighted number of individuals reporting nonmedical use of MDMA and stimulant comparators and the prevalence of nonmedical use. There are limitations to the NMURx weighting scheme based on the limited demographic and health-status variables used to represent the distribution of these variables in the general adult U.S. population, ages 18 years and older.

6.2.3.3 MTF

Monitoring the Future (MTF) is a nationally representative, annual cross-sectional survey of adolescents and adults, college and high school students and graduates, intended to monitor emerging substance abuse problems and understand the effectiveness of policy and intervention efforts. The survey captures self-reported information on drug use behaviors among students in the 8th, 10th, and 12th grades, college students, and adults up to 30 years of age. We extracted nonmedical use data for MDMA, amphetamines,[20] methamphetamine, crystal methamphetamine, Adderall, and Ritalin from MTF annual reports from 2010 through 2023.

6.2.3.4 NPDS

The National Poison Data System (NPDS) is a database managed by the America's Poison Centers. America's Poison Centers is a nationwide network of Poison Centers (PCs) that receive calls from individuals, healthcare professionals, and other interested persons in the general U.S. population regarding exposures to prescription drugs and other substances. We searched NPDS for closed cases of human exposure to MDMA in the United States and territories, 2012 to 2022, by using America's Poison Centers product codes for MDMA and excluding cases that had medical outcomes classified as "confirmed non-exposure." We requested product codes for MDMA from America's Poison Centers and used these codes in our analysis. In addition, we also analyzed the comparator drugs[21] amphetamine, methamphetamine, and methylphenidate. We used a combination of NPDS generic codes and IBM Micromedex® Solutions product codes to identify these comparator cases.

At the time of extraction, America's Poison Centers had completed its standard processes for outcome adjudication and quality control for all these data and had locked the data to ensure reliability. Search parameters used for MDMA and selected comparators are summarized in .

[20] Includes Adderall and all other amphetamines

[21] includes CII prescription stimulants and illicit stimulants

Table 19. NPDS Search Parameters—MDMA and Comparators

Report Name	MDMA, Amphetamines: Case Log (Product Code) Methylphenidate, Methamphetamine: Case Log (Generic Code/Product Code)
Date of query	01/25/2024
Date range for query	1/1/2012 to 12/31/2022†
NPDS version	20.2.3
Drugs of interest	MDMA, amphetamines, methamphetamine, methylphenidate
Formulation	All formulations
Case type	Exposure
Case status	Closed
Species	Human
Product code filter	Contains at least one
Generic and product codes‡	**Redacted**
Age range	All
Geography	50 U.S. states, Washington D.C., and five territories (American Samoa, Guam, Norther Mariana Islands, Puerto Rico, and the U.S. Virgin Islands)
Confirmed non-exposures	Excluded
Polysubstance exposures	Included
Reason for exposure	All

Source: Reviewer generated.
† 2022 is the most recent year for which cases in NPDS were locked at the time of the analysis. At the end of each calendar year, America's Poison Centers gives the Poison Centers approximately 6 months to close out any cases that remain open before the database for that year is locked. Once a database is locked, no further changes to any cases can be made by a poison center.
‡ For case-level analyses of exposure narratives, FDA evaluated only MDMA product exposure cases where MDMA was undoubtedly responsible for the death.
Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; NPDS, National Poison Data System

We analyzed data from cases involving human exposure to MDMA and comparators. In select analyses, we restricted to cases classified by America's Poison Centers as reason for exposure, "*intentional abuse,*" which we call *abuse* since it aligns with the FDA regulatory definition. We evaluated the cases using categories defined by America's Poison Centers. Two independent analysts performed quantitative analyses to ensure the accuracy of our results.

6.2.3.5 RADARS TCP

RADARS® Treatment Center Program (TCP) consists of the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients Program (SKIP) which collect information on past-month drug abuse from patients entering both private and public opioid addiction treatment programs across the United States. FDA obtained surveillance data from RADARS® TCP's 6-month reports through an ongoing contract with the Rocky Mountain Poison and Drug Center (RMPDC).

We examined trends in the number and percentage of respondents endorsing past-month abuse of MDMA, methamphetamine, and prescription stimulants from 2018 through 2022 from all sites that contributed survey data during the study period.

We used results of analyses in which RADARS® excluded careless responses, i.e., surveys with 24 or more opioid item endorsements or endorsements of nine or more consecutive items were deemed careless responses.

6.2.3.6 NAVIPPRO™

The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Addiction Severity Index-Multimedia Version® (ASI-MV®) is a computer-administered version of Addiction Severity Index (ASI) assessment via patient self-report. NAVIPPRO™ ASI-MV® collects data from a sample of adults

seeking treatment or being assessed for substance use disorder treatment at participating facilities across the United States. FDA obtained surveillance data collected from the NAVIPPRO™ ASI-MV®'s six-month reports through an ongoing contract with Inflexxion.

We first examined the number and percent of respondents endorsing past-month abuse of MDMA, illicit methamphetamine, prescription amphetamine, prescription methamphetamine, and prescription methylphenidate in each calendar year from 2018 through 2022.

We then analyzed the number and percent of respondents endorsing past-month abuse and routes of abuse for MDMA and stimulant comparators from January 2021 through December 2022.

To improve comparability of these data between years, we restricted our analysis of the number and percentage of respondents endorsing abuse of MDMA and comparators to sites reporting results from at least one assessment per quarter from 2018 through 2022. We compared overall trends between data from all sites and consistent sites and found similar trends. We examined the percent of respondents endorsing past-month abuse and route of administration from 2021 through 2022, using data from all sites.

6.2.3.7 NVSS-M and DIM

The drug-involved mortality (DIM) data consist of National Vital Statistics System, Mortality (NVSS-M) data linked with information extracted from the literal text fields from death certificates that reflect mentions of drugs involved in the death. DIM data also contain information on cause of death, manner, circumstances, and other factors contributing to the death.

Data Analysis

We used the most recent years available in the DIM dataset, January 1, 2010 to December 31, 2017, to identify drug overdose deaths with International Classification of Diseases, Tenth Revision (ICD-10) underlying cause-of-death codes X60 to X64 (intentional poisoning), X40 to X44 (accidental self-poisoning) and Y10 to Y14 (undetermined poisoning), hereafter referred to as *overdose deaths,* for U.S. residents where MDMA or selected comparators (i.e., amphetamine, methylphenidate, methamphetamine) were mentioned in the literal text as contributing to the death.

Information on the list of *principal variants*3F[22] that were used to identify mentions of drugs in this analysis are provided in .

[22] Principal variant refers to an umbrella term that enables aggregate counts for all search terms that referred to the same substance (*Drug-Involved Mortality Restricted Data* (National Center for Health Statistics Research Data Center 2018)).

Table 20. National Vital Statistics System—Drug-Involved Mortality (DIM) Algorithm for Case Identification and Principal Variants*

Month/year of query	February 2024
Date range for query	January 01, 2010 – December 31, 2017 (years available for query)
ICD-10 underlying cause-of-death	For identifying poisoning deaths Accidental self–poisoning: X40-X44 Undetermined poisonings: Y10-Y14 Intentional poisoning: X60-X64 For identifying intentional vs. unintentional or undetermined poisoning Intentional poisoning: X60-X64 Accidental self–poisoning: X40–X44 or undetermined poisonings: Y10-Y14
MDMA	Principal Variant: MIDOMAFETAMINE
MDMA+MDA (sensitivity analysis)	Principal Variant: MIDOMAFETAMINE or Principal Variant: TENAMFETAMINE
Amphetamine	Principal Variant: AMPHETAMINE or Principal Variant: AMBIGUOUS and ambiguous_variant_3 = AMPHETAMINE or Principal Variant: DEXTROAMPHETAMINE or Principal Variant: LISDEXAMFETAMINE
Methylphenidate	Principal Variant: METHYLPHENIDATE or Principal Variant: DEXMETHYLPHENIDATE
Methamphetamine	Principal Variant: METHAMPHETAMINE
Amphetamine second definition (sensitivity analysis)	Include: Principal Variant: AMPHETAMINE or Principal Variant: AMBIGUOUS and ambiguous_variant_3 = AMPHETAMINE or Principal Variant: DEXTROAMPHETAMINE or Principal Variant: LISDEXAMFETAMINE Exclude: Principal Variant: METHAMPHETAMINE

Source: DIM Documentation. Drug-Involved Mortality Restricted Data: https://www.cdc.gov/rdc/b1datatype/datafiles/Drug-Involved-Mortality-Data-Documentation.pdf.

* Principal variant: A principal variant is an umbrella term that enables aggregate counts for all search terms that referred to the same substance. The substances mentioned in the death certificate literal text were assumed to be involved in the death unless contextual information in the literal text suggested otherwise.

Abbreviations: MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; ICD-10, International Classification of Diseases, Tenth Edition

We tabulated number of deaths with documented involvement of these products by substance (single versus multiple substances), and by underlying cause-of-death categories (intentional, unintentional, or undetermined poisoning).

We also further evaluated deaths with documented involvement of these products by underlying cause-of-death categories (intentional poisoning versus unintentional or undetermined poisoning), stratified by year (from 2010 to 2017) and by total overdose deaths and single-substance overdose deaths.

Single- versus multiple-substance involvement was defined by the number of unique principal variants that were involved in death. Specifically, identification of one unique principal variant mention with involvement classified the case as single-substance involvement, while multiple, principal variant mentions with involvement classified the case as multiple-substance involvement.[23]

[23] We used variable "count_PV_involved" in DIM data to quantify the number of unique specific substance involved deaths (i.e., count_PV_involved= 1 corresponded to single-substance and count_PV_involved >1 corresponded to multiple-substance)

We also conducted two sensitivity analyses. The first sensitivity analysis was to provide a range of MDMA-involved deaths by including MDA.[24] Although MDA is a separate drug, it is also a metabolite of MDMA. The second sensitivity analysis provided a second definition for amphetamine. This is because methamphetamine is metabolized into amphetamine and overdose deaths involving amphetamine without restriction on methamphetamine involvement may be an overestimate of amphetamine-involved deaths. These two definitions of amphetamine deaths, with and without restriction on methamphetamine involvement, provide a range of amphetamine-involved deaths.

All analyses were performed independently by two analysts to optimize accuracy of results, with any discrepancy resolved by detailed review of processes.

6.2.3.8 SUDORS

The Centers for Disease Control and Prevention (CDC) fund 49 states and the District of Columbia to abstract information from death certificates and medical examiner and coroner reports, including toxicology results, on drug overdose deaths of unintentional or undetermined intent through State Unintentional Drug Overdose Reporting System (SUDORS). Detailed information is abstracted from all unintentional and undetermined intent drug overdose deaths and entered into a web-based system to describe decedent demographics, circumstances that preceded the fatal overdose (e.g., prior history of overdose, recent release from an institutional setting), circumstances occurring during or immediately preceding the overdose (e.g., presence of potential bystanders), as well as some limited medical history (e.g., mental health diagnoses, treatment for substance use disorder), and response to the overdose (e.g., naloxone administration). In addition, SUDORS contains information on drugs detected during postmortem toxicology testing as well as those determined by a medical examiner or coroner to have caused death.

The CDC provided FDA with the number of overdose deaths involving MDMA, amphetamine, methamphetamine, and methylphenidate from quarter (Q) 3 2019 to Q4 2022. MDMA deaths in SUDORS include deaths involving MDA. To ensure comparability over time, CDC provided these data for a selection of jurisdictions that reported data throughout the entire study period (35 states and the District of Columbia).[25] Drug involvement includes deaths in which the medical examiner or coroner listed the specified drug(s) as causing death on the death certificate, in the medical examiner/coroner report, or in the postmortem toxicology report. We analyzed counts and percentages for 1) all deaths and 2) single-substance deaths involving MDMA and stimulant comparators. Similar to the DIM analysis, we analyzed SUDORS data with a second definition for amphetamine that excludes methamphetamine.

6.2.3.9 ToxIC Core Registry

The Toxicology Investigators Consortium (ToxIC) Core Registry is a multicenter toxicosurveillance and research network established in 2010.[26] The ToxIC Core Registry contains data from patients manifesting toxicologic symptoms from intentional and unintentional exposure at over 50 participating centers in

[24] MDA, also known as tenamfetamine or 3,4-methylenedioxyamphetamine

[25] Alaska, Arizona, Colorado, Connecticut, Delaware, District of Columbia, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Tennessee, Utah, Vermont, Virginia, and Washington.

[26] Toxicology Investigators Consortium (ToxIC) Core Registry. American College of Medical Toxicology; 2023. Available from: https://www.acmt.net/toxic/

the United States and several international locations. All patients entered into the ToxIC Core Registry have been formally evaluated and treated by a medical toxicologist. Medical toxicology physicians enter patient data into the ToxIC Core Registry, including substance(s) involved, demographics, encounter circumstances, toxidrome, signs and symptoms, treatment, and outcomes.

FDA searched the ToxIC Core Registry database from January 1, 2010, through September 30, 2023[27], using the strategies described in and .

Table 21. ToxIC Core Registry Search Strategy for Cases With MDMA

Date of search	January 23, 2024	
Time period	January 1, 2010, through September 30, 2023*	
Selected fields	All fields	
Filters	**Filter (OR)**	**Selection**
	exp_pa1_psycho1 "Primary Agent #1 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa2_psycho2 "Primary Agent #2 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa3_psycho3 "Primary Agent #3 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa4_psycho4 "Primary Agent #4 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa5_psycho5 "Primary Agent #5 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa6_psycho6 "Primary Agent #6 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa7_psycho7 "Primary Agent #7 Psychoactive"	=Methylenedioxymethamphetamine
	exp_pa1_sympa1 "Primary Agent #1 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine, Ecstasy)
	exp_pa2_sympa2 "Primary Agent #2 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine, Ecstasy)
	exp_pa3_sympa3 "Primary Agent #3 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine,Ecstasy)
	exp_pa4_sympa4 "Primary Agent #4 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine,Ecstasy)
	exp_pa5_sympa5 "Primary Agent #5 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine,Ecstasy)
	exp_pa6_sympa6 "Primary Agent #6 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine,Ecstasy)
	exp_pa7_sympa7 "Primary Agent #7 Sympathomimetic"	=MDMA (methylenedioxy-N-methamphetamine, Ecstasy)

Source: Reviewer generated.

* Most recent data available from the ToxIC Core Registry.

[27] Most recent data available from the ToxIC Core Registry.

Table 22. ToxIC Core Registry Search Strategy for Single-Substance Cases With Comparator Drugs

Date of search	February 22, 2024	
Time period	January 1, 2010, through September 30, 2023*	
Selected fields	All fields	
Filters	**Filter (OR)**	**Selection**
	exp_pa1_sympa1 "Primary Agent #1 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa2_sympa2 "Primary Agent #2 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa3_sympa3 "Primary Agent #3 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa4_sympa4 "Primary Agent #4 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa5_sympa5 "Primary Agent #5 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa6_sympa6 "Primary Agent #6 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	exp_pa7_sympa7 "Primary Agent #7 Sympathomimetic"	=methylphenidate OR =dexmethylphenidate OR =methamphetamine OR =amphetamine OR = dextroamphetamine OR = lisdexamfetamine OR =mixed amphetamine salts
	Filter (AND)	**Selection**
	exp_pa2_class2 "Primary Agent #2 Class"	=

Source: Reviewer generated.

* Most recent data available from the ToxIC Core Registry.

6.2.3.10 FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

FDA searched the FAERS database from January 1, 2013, through December 31, 2023, with the strategy described in .

Table 23. FAERS Search Strategy

Date of search	January 30, 2024
Time period of search	January 1, 2013, through December 31, 2023
Search type	RxLogix Quick Query
Product terms	PAIs: midomafetamine, midomafetamine hydrochloride
MedDRA search terms (ver. 26.1)	All

Source: Reviewer generated.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PAI, pharmaceutical active ingredient

6.2.4 Scoping Literature Review

The objectives of the scoping literature review were to 1) gain a broader understanding of the observational literature on MDMA use and health outcomes and 2) assess the degree to which case reports/case series and large-population epidemiologic studies on illicit MDMA use may inform harms from therapeutic or nonmedical use of MDMA.

We searched both PubMed and Embase on January 18, 2024. The search included articles published between January 1, 2008, through January 18, 2024. Search strings included various terms for MDMA, misuse and abuse terminology, and excluded studies where exposure was investigator assigned (i.e., randomized clinical trials) and animal studies. Two reviewers screened 4273 nonduplicate articles captured from the PubMed and Embase searches for observational epidemiologic and case studies that examine patterns of MDMA use and safety outcomes resulting from MDMA use. We further screened articles to retain U.S. and international articles with study designs of case reports, case series, cohort studies, cross-sectional studies, ecologic studies, and case-control studies. Screeners excluded conference abstracts, clinical trials, editorial, letters, animal or laboratory studies describing knowledge, attitudes, perspectives or beliefs, and studies of efficacy outcomes. Screeners scanned reference lists of review articles for potentially relevant titles.

There were 235 observational epidemiologic articles and 100 case reports or case series articles identified for further abstraction. For the epidemiologic studies, reviewers abstracted the study design and high-level description of the results pertaining to the MDMA associated health outcome. The epidemiologic studies were mainly cross-sectional studies, mostly of survey data and/or describing patterns of MDMA use in a population. Therefore, we did not move forward with a more detailed abstraction of the epidemiologic studies. For the case reports and case series, after excluding non-English language articles, we were left with 92 articles containing 124 cases. We reviewed details of each case when available, including demographic information, MDMA dosing information and exposure window. In addition, we evaluated adverse events associated with MDMA intake with approximate time to onset, concomitant substance use, relevant medication and medical history, and outcomes

(e.g., death, hospitalization, disability). We coded each adverse event to MedDRA (version 26.1) and analyzed relatedness of adverse events to MDMA use along with status in the Applicant's proposed draft labeling.