# Midomafetamine Capsules (NDA 215455)

Psychopharmacologic Drugs Advisory Committee

June 4, 2024

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# Posttraumatic Stress Disorder (PTSD)

- Follows exposure to actual or threatened death, serious injury, or sexual violence
- Intrusive memories, hyperarousal, and avoidant behavior
- Comorbid mood and substance use disorders common
- High risk for suicidal ideation and behavior
- Limited medication options
  - Two FDA-approved medications: sertraline and paroxetine
  - Response rates rarely exceed 60%
  - Less than 20 to 30% of patients achieve full remission
- Unmet need

# Psychedelic Drug Development

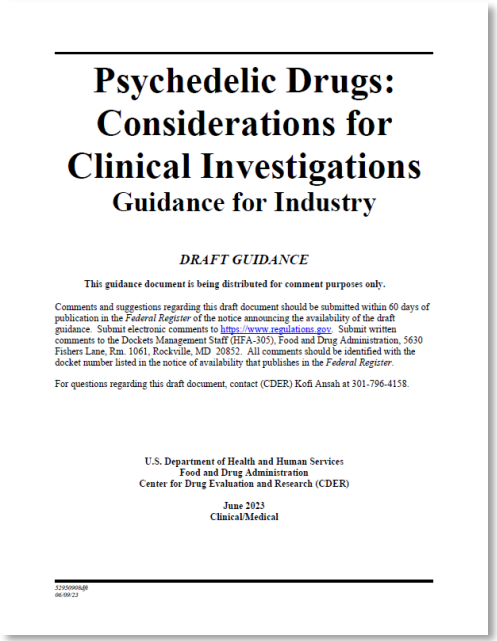
- Surge in interest, particularly for treatment of psychiatric disorders
- When discussing psychedelics:
  - Classic psychedelics (e.g., psilocybin, LSD)
  - Midomafetamine
- Schedule I controlled substances
- Prolonged alterations in mood, perception

# Midomafetamine for PTSD

- Novel treatment paradigm
  - Three sessions of midomafetamine administration
  - Psychological intervention
    - Preparatory sessions before midomafetamine session
    - Medication sessions (with psychological support)
    - Integrative sessions after midomafetamine session
  - 4-month course of treatment
- First of psychedelic drug development program to reach the new drug application stage

# Midomafetamine for PTSD

- Investigational new drug application filed in 2001
- Guidance published in 2023
- First new drug application for this class



**Psychedelic Drugs: Considerations for Clinical Investigations**

**Guidance for Industry**

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Kofi Ansah at 301-796-4158.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**June 2023**
**Clinical/Medical**

# Clinical Trial Data

- Two short-term studies
  - Both positive
  - Clinically-meaningful improvement
- Long-term follow-up assessment
  - Open-label, single-visit
  - Appears that effect may be durable
- However, several factors impact interpretability of these results

# Functional Unblinding

- Acute effects of midomafetamine make it nearly impossible to blind studies
- Designed and conducted as double-blind studies, *but* participants able to accurately guess treatment assignment
- Results in expectation bias

# Mitigating and Assessing Impact of Bias

- Blinded central raters
  - Minimize rater bias
- Unblinding questionnaire
  - Assess extent of participant unblinding
- Follow-up assessments
  - 25% dropout between parent study and follow-up
  - Intercurrent use of non-study drugs
  - Variable interval to follow-up
  - Unblinding of MAPP1 participants

# Role of Psychotherapy

21 CFR 201.57(c)(2)(i)(A): 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), **a statement that the drug is indicated as an adjunct to that mode of therapy**.

- Contribution of psychotherapy has not been characterized
- No comparisons of this therapy to other types of therapy
- No midomafetamine-only arm in clinical studies

# Safety

- Reported adverse events consistent with known effects
- QT assessment incomplete
- Elevations in pulse and blood pressure
- Limited clinical laboratory data
- Adverse events related to abuse potential were not collected if they were deemed positive, favorable, or neutral

# Risk Evaluation and Mitigation Strategy

- Subjective effects can persist several hours
- Patients impaired, in a vulnerable state
- Risks of harm secondary to impairment
- Monitoring necessary to ensure safe use

# Discussion Question 1

- 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

# Discussion Question 2

- Discuss whether the available data are adequate to characterize the safety of midomafetamine for the treatment of PTSD.
  - 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.

# Discussion Question 3

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

# Discussion Question 4

- 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.

# Voting Question 1

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

# Voting Question 2

- 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?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# Midomafetamine Capsules
# (NDA 215455)

## Psychopharmacologic Drugs Advisory Committee

## June 4, 2024

David Millis, MD: Clinical Reviewer, Division of Psychiatry
Olivia Morgan, PhD: Statistical Reviewer, Division of Biometrics I
Victoria Sammarco, PharmD: Risk Management Analyst, Division of Risk Management

# Agenda

I. Introduction: Product and Disease Background
II. Regulatory History and Key Issues
III. Efficacy Analysis
IV. Safety Analysis
V. Risk Management; REMS Recommendations

# INTRODUCTION:
# PRODUCT AND DISEASE BACKGROUND

# Disease Background

- PTSD: disabling condition characterized by intrusive memories, nightmares, hyperarousal, and avoidant behavior following exposure to actual or threatened death, serious injury, or violence (including sexual assault)
- Seriousness:
  - High risk for suicidal ideation and behavior
  - High risk of mood, anxiety, and substance use disorders
- Prevalence:
  - About 5% of US population has PTSD in any given year
  - About 13 million Americans with PTSD

# Product Description

- Generic name: midomafetamine
- Indication: treatment of PTSD in adults
- Chemical structure: similar to amphetamines
- Pharmacological mechanism: acts as a serotonin, norepinephrine, and dopamine reuptake inhibitor and releasing agent
- Route of administration: oral
- Treatment regimen: 3 doses of midomafetamine, taken at least 3 weeks apart, in supervised treatment sessions over a 4-month course of treatment
  - Psychological support during medication administration sessions
  - Regularly scheduled integrative psychotherapeutic sessions in between medication administration sessions
- Setting: outpatient treatment (but medication sessions supervised for duration of effect)

# Current Treatment Options

- Approved pharmacological treatments for PTSD: paroxetine and sertraline (SSRIs)
- Limitations:
  - Response rates rarely exceed 60%
  - Less than 20 to 30% of patients achieve full remission
  - Can take up to 12 weeks to experience treatment effect
  - SSRIs have Boxed Warning for suicidal ideation and behavior
  - Off-label treatment common
- Treatment guidelines suggest psychotherapy as first-line treatment

# Midomafetamine Dosing Regimen

| 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** |

# REGULATORY HISTORY AND KEY ISSUES

# Discussions with Applicant over Study Design: Unblinding Concerns

2001: Investigational new drug application (IND) submitted and allowed to proceed

2016: End-of-Phase 2 Meeting

- Agency expressed concern about possible functional unblinding
  - Physiological effects of the drug versus placebo
  - Expectation bias
- Agency suggested use of active comparators (e.g., niacin, low-dose midomafetamine)
- Applicant responses:
  - Niacin (or other similar drugs) could worsen PTSD symptoms
  - Low-dose midomafetamine exacerbated anxiety in some study participants
  - Inert placebo felt to be preferred strategy, acknowledging limitations
- Agency and Applicant did not reach agreement on adequacy of blind at this meeting

# Functional Unblinding

Concerns with functional unblinding:

- Contributes to expectation bias
  - Both participants or investigators may feel treatment is working if they know they are on drug, or conversely not working if they are on placebo
  - May artificially inflate positive results on drug and deflate placebo response, or affect study dropout rates
  - Investigators may consciously or unconsciously view data, analyze outcomes, or report results differently

# Discussions with Applicant over Study Design: Unblinding Concerns with the SPA

January 2017: MAPP1 protocol submitted as a **special protocol assessment (SPA)**

- SPA = process by which sponsor of an IND attempts to reach agreement with Agency on design of a study intended to support marketing approval

March 2017: SPA No Agreement letter issued

- Disagreed with proposed statistical analyses and choice of secondary endpoint
- Some elements deemed acceptable
  - Plan to minimize bias using *blinded centralized independent rater pool* to administer the primary outcome measure via video interviews
  - Use of midomafetamine-assisted psychotherapy as the treatment arm and "identical psychotherapy with inactive placebo" as control – but with continued caution about adequacy of blinding
  - Definitions of treatment response, loss of diagnosis, and remission on CAPS-5
- Extensive feedback on cardiac safety and abuse liability assessment plans

# Final SPA Agreement

May 2017: meeting to discuss non-agreed SPA and provide advice on revising the request

- Two phase 3 trials with identical designs (MAPP1 and MAPP2) acceptable to support the NDA; a separate SPA for the second trial (MAPP2) would not be necessary
- No need to conduct new animal and human studies of the abuse potential of midomafetamine

June to July 2017: SPA request resubmitted; Agency issued a Special Protocol – Agreement letter

- States that design and planned analysis of studies adequately address objectives necessary to support a regulatory submission
- Agreement does not guarantee that the trial results will be deemed adequate to support approval; this decision can only be addressed during review of the submitted NDA and is based on the adequacy of the overall submission

# Recording of Adverse Events and Abuse Potential Assessment

From March 2017 SPA No Agreement letter:

- "For all Phase 1, 2, and 3 studies, AEs associated with potential abuse or overdose must be documented."
- "For additional details regarding the documentation of AEs, please refer to the 2017 Guidance for Industry: Assessment of Abuse Potential of Drugs."

From the 2017 Guidance:

- "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."
- "At the time of publication of this guidance document, a ranking of relevant AEs as signals of abuse risk is not available, and all AEs are of interest for the Agency to consider in the overall assessment of risk to the public health."

# Applicant's Abuse Potential AE Assessment

From MAPP1 Clinical Study Report:

- "Effects of treatment that were considered to be neutral, positive, or favorable by the participant and the therapist-investigator and, therefore, related to the treatment effect of MDMA in PTSD, were *not* systematically collected as AEs in this study. AEs were defined as any undesirable, unfavorable, inappropriate, or untoward medical occurrence in a participant, including any abnormal sign (e.g., abnormal and clinically meaningful physical exam, laboratory finding, electrocardiogram (ECG) result, or vital sign), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to participation in the research."

# Impact of AE Assessment

Impact of not recording “positive” AEs:

- Data that would help characterize the CNS effects of midomafetamine at the proposed dosage are missing
- Data summarized in the Adverse Reactions section of the drug label are based on the collection of all AEs that occurred during the clinical trials; omission of positive AEs underrepresents the range and frequency of AEs that occurred in the trials
- Data on drug effects that prescribers should monitor for resolution to help decide whether a patient is safe for discharge from a medication session are missing

# Breakthrough Designation and Blinding Survey

August 2017: Breakthrough Therapy Designation granted for midomafetamine for the treatment of PTSD (based on prior phase 1 and phase 2 study results)

October 2020: Agency recommended a Participant Blinding Survey for MAPP2 which was underway; Applicant agreed to conduct the survey

May 2023: Applicant agreed to submit the survey results in the NDA submission

# Safety Assessment and Durability of Effect

September 2022: Breakthrough Therapy Designation advice meeting. Concerns expressed by Agency:

- Inadequacy of the safety database to support an NDA for a chronic condition (does not have ICH-recommended numbers), unless acute short-term treatment shows marked durability of effect
- Inadequacy of proposed exploratory observational study MPLONG for supporting durability of treatment effect; but agreed that results could be submitted for review

May 2023: Pre-NDA meeting; Agency noted that the specific risks to be addressed through the REMS would be a matter of review

# Role of Psychological Intervention

- March 2017 SPA No Agreement Letter:
  - The Applicant proposed that "an appropriate control for MDMA-assisted psychotherapy is an identical course of psychotherapy with inactive placebo, and this will be an appropriate statistical comparator to MDMA-assisted psychotherapy."
  - The Agency responded: "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."
- Neither party during the rest of development otherwise discussed specifics of how the psychotherapy component of the proposed treatment would be described in labeling.
- FDA does not regulate psychotherapy.

# Psychological Intervention in MAPP1 and MAPP2

Goal of intervention in clinical trials varies at different stages of treatment:

- Preparatory sessions (3 sessions)
  - Prior to administration of study drug or placebo
  - Therapeutic goal: to help prepare participant for experiences that may arise during medication session (i.e., psychoeducation/orientation)
- Medication sessions (3 sessions, 8 hours or longer each)
  - Participant receives either midomafetamine or placebo
  - Therapeutic goal: to provide support, following participant's lead to assess the type of support that would be most helpful
- Integrative sessions (9 follow-up sessions)
  - 3 sessions scheduled during the 3-week period following a medication session
  - Therapeutic goal: to help participant describe experiences of medication sessions, particularly experience of remembering the trauma

# Applicant's Proposed Psychological Intervention

Guide for therapists: "MAPS Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder"

- Presents general principles on therapeutic stance: empathy, support, fostering openness to inner experiences that may emerge for the participant, providing a comfortable physical environment
- Therapist is given flexibility to choose therapeutic modalities with which the therapist is familiar
- From this perspective, psychological intervention was not standardized; could vary considerably across therapists

# Psychological Intervention Assessment

Difficult to assess contribution of psychological intervention to treatment effect:

- No treatment arms that employed study drug alone without psychological intervention
- No treatment arms that compared MAPS manualized therapy to other psychotherapeutic approaches

FDA does not regulate psychotherapy:

- The ability to describe concomitant treatment is limited
  - Labeling regulations allow for specification that a drug should be used only in conjunction with another mode of therapy
- REMS can still require elements of safety monitoring

# EFFICACY ANALYSIS: OVERVIEW

# Overview of Study Designs

Phase 3 Studies

- MAPP1: randomized, placebo-controlled, 18-week study; 91 participants with severe PTSD
- MAPP2: randomized, placebo-controlled, 18-week study; 104 participants with moderate or severe PTSD
- MPLONG: exploratory observational study; single visit ≥6 months after end of a previous study to show durability of effect

# Primary Endpoint: CAPS-5

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

- 30-item clinician-reported outcome measure
  - Blinded, centralized independent clinician raters conducted semi-structured interviews to assess key symptoms of PTSD over the last month
- Primary endpoint for MAPP1 and MAPP2: Change from Baseline to Week 18
- Recent adaptations to align with the DSM-5 clinical criteria for PTSD
- Each item gets two ratings:
  - Intensity = minimal, clearly present, pronounced, extreme
  - Frequency = number of times or percentage of time (depending on symptom)
- Intensity and frequency are converted into a single 5-point (0 to 4) severity scale, with higher scores indicating more severe symptoms
- A total severity score generated by summing the individual scores of the first 20 items
- Total severity scores range from 0 to 80
- Administered approximately at Baseline, Week 6, 12, and 18 (primary endpoint)

# Symptoms Covered by CAPS-5

| | |
|---|---|
| [1] Recurrent, intrusive memories | [11] Persistent negative emotional state |
| [2] Recurrent, distressing dreams | [12] Loss of interest in significant activities |
| [3] Flashbacks / dissociative reactions | [13] Detachment / estrangement from others |
| [4] Cued psychological distress | [14] Inability to express positive emotions |
| [5] Cued physiological reaction | [15] Irritability or aggression with minimal provocation |
| [6] Avoiding internal reminders | [16] Reckless behavior |
| [7] Avoiding external reminders | [17] Hypervigilance |
| [8] Dissociative amnesia | [18] Exaggerated startle response |
| [9] Exaggerated negative beliefs about oneself | [19] Problems with concentration |
| [10] Persistent blame of self or others | [20] Sleep disturbance |

# CAPS-5 and Clinical Meaningfulness

Clinical Meaningfulness

- 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.
- The Agency's review of the scale and related literature for the CAPS-5 (looking at how movement of individual items contribute to total score) indicate that 10-point change is included in the range of clinically meaningful within-patient change.

# EFFICACY ANALYSIS: MAPP1 AND MAPP2

# Primary Endpoint: CAPS-5 at Week 18 (mITT Population)

| Variable | MAPP1 | | MAPP2 | |
|---|---|---|---|---|
| | Midomafetamine (N=46) | Placebo (N=44) | Midomafetamine (N=53) | 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 (Week 18) | | | | |
| N | 42 | 37 | 52 | 42 |
| 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. [a] LS Mean, LS mean difference, 95% CI and p-value of treatment effect at Visit 19 were obtained from a mixed models repeated measures (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: CI, confidence interval; CSR, clinical study report; LS, least squares; mITT

**Note** that the functional unblinding may have had some impact on the results

# Clinical Meaningfulness of Results

Results

- MAPP1 and MAPP2 showed a greater than 10-point mean change in both treatment arms on the CAPS-5 at Week 18
  - Around a 24-point mean change on drug
  - And a 13- to 14-point mean change on placebo
- There was around a 9- to 12-point difference between drug and placebo.

# Secondary Endpoint: Sheehan Disability Scale (SDS) at Week 18 (mITT Population)

| Variable | MAPP1 | | MAPP2 | |
|---|---|---|---|---|
| | 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 (Week 18) | | | | |
| N | 42 | 37 | 52 | 42 |
| 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: SDS, Sheehan Disability Scale

# MAPP2 Unblinding Survey (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) |

Source: Clinical Study Report MAPP2 pages 80-81. Safety set: All participants who received any investigational medicinal product. Abbreviations: N, total number of participants in each group; n, total number of participants in each category

# Functional Unblinding

- Functional unblinding of participants in the phase 3 studies (MAPP1 and MAPP2)
  - Unblinding survey conducted in MAPP2 indicates that most MAPP2 participants could guess their treatment arm (especially when on drug)
  - We expect that the same was likely true for MAPP1 participants, even though unblinding survey was not requested for that study
  - No straightforward computational approach to account for functional unblinding in analysis of efficacy results for MAPP1, MAPP2, or MPLONG

# EFFICACY ANALYSIS: MPLONG

# Participant Disposition: N (%)

| Analysis Population | MAPP1 | | | MAPP2 | | |
|---|---|---|---|---|---|---|
| | Midoma-fetamine | Placebo | Total | Midoma-fetamine | Placebo | Total |
| All treated in Parent Study | 46 | 44 | 91 | 53 | 51 | 104 |
| Enrolled in MPLONG | 30 (65.2) | 30 (68.2) | 60 (65.9) | 45 (84.9) | 37 (72.5) | 82 (78.8) |
| MPLONG Effectiveness subset (completed CAPS-5 endpoint) | 27 (58.7) | 29 (65.9) | 56 (61.5) | 44 (83.0) | 37 (72.5) | 81 (77.9) |

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.

MPLONG effectiveness subset: All MAPP1/MAPP2 participants who enrolled in MPLONG and who completed a follow-up PTSD endpoint assessment in the LTFU study. Proportions calculated relative to the number treated in the parent study.

# Study Population

| Study Termination CAPS-5 Total Score (Last Available Assessment) | | | | |
|---|---|---|---|---|
| **Population** | **Statistic** | **Midomafetamine** | **Placebo** | **Total** |
| **Participants from MAPP1 or MAPP2 who enrolled in MPLONG** | N | 75 | 67 | 142 |
| | Mean (SD) | 15.9 (12.6) | 24.9 (12.3) | 20.2 (13.2) |
| **Participants from MAPP1 or MAPP2 not enrolled in MPLONG** | N | 24 | 27 | 51 |
| | Mean (SD) | 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
Participant demographic and baseline characteristics were collected from the parent study.

# Exploratory Analysis of CAPS-5 Scores at Long Term Follow Up (LTFU) Visit 1 (Effectiveness Subset)

| Visit | MAPP1 | | MAPP2 | |
|---|---|---|---|---|
| | Midomafetamine (N=27) | Placebo (N=29) | Midomafetamine (N=44) | Placebo (N=37) |
| Visit 19 (Week 18) in parent study, n | 26 | 29 | 43 | 36 |
| LS mean change from baseline (95% CI) | -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 |
| LS mean change from baseline (95% CI) | -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 14.2-5.3) submitted to eCTD Seq 0047 and MPLONG ISE tables for the MAPP1 subset (Table 14.2-5.6) submitted to eCTD Seq 0054. 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. Note that MAPP1/MAPP2 participants did not have to complete Visit 19 to enroll in MPLONG.

# Interim Use of Other Psychotropic Substances

Some participants received nonstudy interventions during the interim period between parent study and MPLONG including psychotherapy and use of other substances such as MDMA obtained outside of the study, ketamine, 5-methoxy-N,N-dimethyltryptamine (5-MEO-DMT)

| **Participants from MAPP1 and MAPP2** | Midomafetamine (N = 75)[a] | Placebo (N = 67)[a] |
|---|---|---|
| Illicit MDMA, N | 13 | 7 |
| Ketamine use, N | 6 | 6 |
| 5-MEO-DMT use, N | 0 | 1 |
| MDMA, Ketamine or 5-MEO-DMT use, N | 17 | 13 |

[a]Number enrolled in MPLONG

There may be unreported nonstudy drug use in the interim period

# Interim Use of Other Psychotropic Substances

- The Agency conducted exploratory analyses by treating any data collected after interim use of other non-study psychoactive substances as missing, then
  1) repeating the efficacy analysis on effectiveness subset
  2) using the mITT population from MAPP1 and MAPP2 and imputing all missing data (including data treated as missing) under the missing at random assumption
- A limitation of MPLONG is that there may have been some impact of the interim use on the results of the analysis of CAPS-5 scores

# Interim Use of Other Psychotropic Substances

| Difference between LTFU Visit 1 and Visit 19 in LS mean change from baseline (95% CI) | | | | |
|---|---|---|---|---|
| | MAPP1 | | MAPP2 | |
| | Midoma-fetamine | Placebo | Midoma-fetamine | Placebo |
| Estimate using all observed CAPS-5 scores (Effectiveness subset) | -5.51 (-9.95, -1.07) | +0.34 (-3.90, 4.59) | -3.60 (-6.10, -1.09) | -0.69 (-3.43, 2.05) |
| Estimates when treating any data collected after interim use as missing and | | | | |
| (1) repeating the efficacy analysis on Effectiveness subset | -6.14 (-11.25, -1.03) | 0.00 (-4.33, 4.34) | -2.61 (-5.16, -0.05) | -2.01 (-4.86, 0.85) |
| (2) using mITT population and imputing all missing data under the missing at random assumption | -4.93 (-9.32, -0.53) | -0.80 (-5.29, 3.7) | -2.02 (-4.61, 0.57) | -1.91 (-4.64, 0.82) |

# Uncertainties about Efficacy

Functional unblinding

- Difficult to control in clinical trials of psychedelics
- Could influence participant reports of symptom control, but difficult to quantify this effect

Durability of effect of MPLONG

- Exploratory (non-prespecified) study design with limited controls/blinding
- Single follow-up visit, with variability in time to visit
- Concerns about selection bias and interim non-study drug usage

Role of psychological support

- Contribution to overall efficacy cannot be quantified
- No evaluations of midomafetamine without psychological intervention
- Therapists had high level of flexibility in choosing therapeutic modalities within framework of MAPS manual; no evaluations comparing whether changes in therapeutic approach have an influence on efficacy

# SAFETY ANALYSIS

# Adverse Events in Phase 3 Studies

Most frequent adverse events (AEs) in phase 3 trials:

- Headache, bruxism and jaw tightness, decreased appetite, insomnia, nausea, hyperhidrosis, fatigue, dizziness, muscle tightness, feeling cold
- Consistent with prior literature on MDMA and with early-phase evaluations indicating similarity to stimulants and some serotonergic effects
- Duration of AEs appears mostly limited to timeframe of the PK of acute dosing, i.e., 8 hours
- However, time course of AEs perceived as positive is unclear; further discussion later on establishing criteria for safe discharge

# Cardiovascular: Increases in Heart Rate and Blood Pressure

- Blood pressure and heart rate were assessed at baseline, 1.5 hours after first dose of study drug, and at the end of the medication session
- Mean increases in BP and HR at the 1.5-hour assessment in the midomafetamine group
  - BP returned to pre-dose levels by end of medication session
  - HR remained slightly elevated
- Proportion of participants with systolic BP >180 mm Hg: midomafetamine 6.1%, placebo 0.0%
- Risks of rapid elevations in both HR and BP: transient myocardial ischemia, myocardial infarction, CNS hemorrhage, aortic dissection
  - Highest risk for patients with preexisting cardiovascular disease

# Cardiovascular: Proarrhythmic Potential

- Thorough QT study not completed; results would be confounded by known drug-induced HR increase
- Alternative QT assessment is incomplete:
  - Only captured ~1/2 of the therapeutic dose & increased HR limits rate-correction
  - hERG assay did not assess metabolites or appropriate positive controls
- Applicant submitted nonclinical cardiovascular studies, AE reports in phase 2 and phase 3 studies, and literature
  - One AE of cardiac arrhythmia in one phase 2 study
- Overall data insufficient to fully assess these cardiovascular risks
- Known & potential risks would need to be described in labeling

# Suicidal Ideation and Behavior

- Serious adverse events (SAEs) related to suicidal ideation/behavior: small number
  - MAPP1: suicidal ideation in one participant, suicide attempt x 2 in one participant; both in placebo arm
  - MAPP2: no SAEs of suicidal ideation or behavior
- Proportion of participants with AEs related to suicidal ideation and assessed as mild or moderate by investigator were similar between the midomafetamine arms (40%) and placebo arms (43%)
- Participants with no previous history of suicidal behavior did not demonstrate onset of suicidal behavior at any time post-baseline, regardless of treatment arms
- Proportion of participants with baseline Columbia Suicide Severity Rating Scale score ≤3 who experienced increase in C-SSRS to 4 or 5 at any time post-baseline was similar between the midomafetamine arms (4.1%) and the placebo arms (3.2%)
- No evident patterns of increased suicidal ideation or behavior in the immediate 24 to 72 hours after midomafetamine dosing sessions

# Other Psychiatric Symptoms

- AEs that occurred at higher frequencies in participants treated with midomafetamine than those treated with placebo:
  - Anxiety, restlessness, nightmare, intrusive thoughts, nervousness, flashbacks, insomnia, sleep disorder
- Several of these are symptoms consistent with PTSD:
  - Flashbacks, nightmare, intrusive thoughts, sleep disorder
- Some AEs could potentially be related to stimulant or serotonergic properties of midomafetamine
  - Insomnia, sleep disorder, anxiety, restlessness, nervousness

# Psychiatric Adverse Events in Phase 3 Studies

| Psychiatric Disorder System Organ Class<br>Preferred Term | Midomafetamine N=99<br>n (%) | Placebo N=95<br>n (%) |
|---|---|---|
| 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 |

# Thermoregulatory and Osmoregulatory Effects

Thermoregulatory:

- AEs higher in midomafetamine than placebo groups: feeling cold, feeling hot, chills, feeling of body temperature change, temperature intolerance, hyperthermia
- No clinically meaningful differences between midomafetamine and placebo groups in temperature changes

Osmoregulatory:

- AEs higher in midomafetamine than placebo groups: hyperhidrosis, thirst, cold sweat

For both thermoregulatory and osmoregulatory AEs, clinical laboratory evaluations could help assess for any related physiological changes

- i.e., electrolytes, thyroid function studies

# Hepatotoxicity Potential

- With NDA submission, Applicant submitted a report identifying hepatotoxicity as an AE of special interest based on cases of severe liver injury from literature reports of illicit MDMA use
- No AEs related to hepatocellular injury in the development program
- No post-baseline liver function laboratory assessments in phase 3
- Liver function labs collected in one phase 1 and two phase 2 studies
- Risk may be low if used as intended, but should still be characterized

# Abuse Potential

- Review by FDA Controlled Substance Staff of published literature
  - Midomafetamine produces behavioral effects in both animals and humans similar to those produced by Schedule II stimulants such as amphetamine, methamphetamine, cocaine, and methylphenidate
- Epidemiological analysis by FDA Office of Surveillance and Epidemiology
  - Levels of illicit MDMA use in US population are within the range observed for Schedule II stimulant comparators
- Conclusion: midomafetamine has abuse potential that parallels that of the Schedule II stimulants
- There is sufficient published literature indicating abuse potential that FDA did not require Applicant to perform a dedicated human abuse potential study.
- AEs related to abuse potential were not systematically collected during phase 3 studies.

# Safety Risk: Patient Impairment

- AEs reflecting drug effects perceived as positive, favorable, or neutral were not collected
  - Known sensory, mood, cognitive effects can last for several hours
  - No trial-specific data to inform characterization of nature and time course of impairment for the proposed dosing regimen
- Discharge readiness in phase 3 studies per investigator judgment
- Risk Evaluation and Mitigation Strategy (REMS) is needed to mitigate potential harms associated with impairment

# Uncertainties About Safety

- Based on adverse event reporting, safety profile is consistent with known effects of midomafetamine
- Some safety concerns not adequately assessed:
  - Cardiovascular safety: arrhythmia risk and QT prolongation
  - Hepatotoxicity
  - Abuse-related effects
  - Discharge criteria after medication session
- Safety database may be adequate to assess risks based on proposed time-limited dosing regimen, but more data may be needed to support chronic-intermittent use if longer-term treatment is deemed necessary

# RISK MANAGEMENT; REMS RECOMMENDATIONS

# Initial Plan for Addressing Safety Concerns

**To be addressed separately from REMS:**

- Potential for hepatotoxicity
  - LFTs only at screening; literature case reports of hepatotoxicity with illicit MDMA use
  - Can further characterize through a post-marketing study
- Known elevations of blood pressure and heart rate by midomafetamine
  - Ensure return of blood pressure and heart rate to a safe level (if elevated) prior to discharge from medication session
  - Risk of adverse cardiovascular sequelae is higher for patients with pre-existing cardiovascular disease
  - Will address through labeling

**To be addressed through a REMS:**

- Potential for harm associated with impairment after midomafetamine exposure
  - Need to ensure safety of patients prior to discharge from medication session


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# Risk Management for Midomafetamine

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# Presentation Overview

- Risk Evaluation and Mitigation Strategies (REMS) overview
- Risk for which a REMS is being considered
- Agency's proposed risk management

# RISK EVALUATION AND MITIGATION STRATEGIES (REMS) OVERVIEW

# REMS Overview

- A REMS is a drug safety program that FDA can require for certain drugs.
- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require application holders to develop and comply with REMS programs if determined necessary to ensure the benefits of a drug outweigh the risks.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- FDA has authority to require a REMS pre-approval or post-approval.

# A REMS Can Include…

- Medication Guide or Patient Package Insert
- Communication Plan for 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)
- Implementation System
- Timetable for submission of assessments*



*applies only to NDAs and BLAs

# REMS May Include ETASU

These are not mutually exclusive and can be used in combination to support safe use

- Certification and/or specialized training of healthcare providers who prescribe the drug
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug only in certain healthcare settings
- Drug is dispensed/administered only with evidence of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in a registry

# RISK FOR WHICH A REMS IS BEING CONSIDERED

# Effects Associated with Midomafetamine

Effects associated with illicit MDMA that are also associated with midomafetamine[1,2]:

- reduction of inhibition
- an openness to suggestion
- a range of intense emotions
- altered sensory perception
- impaired ability to perceive and predict motion

These effects may impair a patient's judgement which may lead to serious harm such as

- hospitalization
- death
- events that could result in hospitalization, death or with significant negative consequences



1. Lykos Therapeutics. Proposed Prescribing Information for Rysanso, March 14, 2024.
2. *What are the effects of MDMA?* (National Institute on Drug Abuse 2021)

# Rationale for Agency's Proposed REMS

- Patient impairment from midomafetamine administration is expected; therefore, safeguards must be in in place to mitigate serious harm from this impairment

- Midomafetamine was studied under strict controls in clinical development which included:
  - monitoring in a controlled setting for an extended period, including overnight stays after most medication sessions
  - two therapists were required to be present during medication sessions
  - patients were instructed not to drive until the following day after medication administration

If approved, a REMS will be necessary to ensure the benefits of midomafetamine outweigh the risk of serious harm resulting from patient impairment.

# AGENCY'S PROPOSED RISK MANAGEMENT

# Agency's Proposed REMS Requirements

The REMS would include the following requirements:

- the drug be dispensed only in certain healthcare settings
- the drug be dispensed to patients with documentation of safe-use conditions
- each patient using the drug be subject to monitoring
- each patient using the drug be enrolled in a registry

In addition, the REMS would also include:

- implementation system to assist with operationalization of the REMS
- timetable for submission of assessments

# Agency's Proposed REMS Goal

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

# Serious Harm of Interest

Including but not limited to:

- Events resulting in hospitalization or death
- Events
  - that could put patients at risk of hospitalization or death (e.g., walking into traffic, driving)
  - with significant negative consequences (e.g., sexual assault, financial coercion)
- Worsening of psychological disorders that cause disability or that may lead to hospitalization or death (e.g., extreme anxiety, exacerbation of PTSD)
- Suicidal ideation and behavior

# Agency's Proposed REMS

Wholesaler

must only ship drug to certified healthcare settings

Certified Healthcare Setting

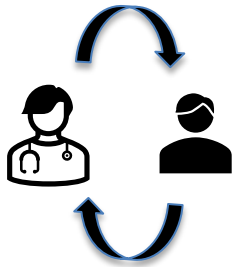
{setting must able to dispense controlled substances}

REMS Administrator

setting reports after each medication session

Prescribing

Drug Administration and Patient Monitoring



Healthcare Setting Follow Up with Patient after Medication Sessions

# Agency's Proposed REMS: Healthcare Setting Requirements

Policies and procedures are in place to ensure safe use (not exhaustive):

- a prescriber is available during midomafetamine administration and monitoring
- at least two healthcare providers are onsite (one of which must be a licensed healthcare provider) to monitor the patient's medical (including vital signs) and psychological status for at least eight hours or until the patient is stable to be discharged
- emergency action plans are in place to escalate care if needed based on the patient's medical or psychological status
- plans are in place in case the patient requires longer monitoring
- the patient is stable to be discharged from the healthcare setting
- the patient is released to an accompanying adult after each medication session

All relevant staff must be trained and agree to follow all established processes and procedures to comply with all REMS requirements

# Agency's Proposed REMS: Patients

Patients will be enrolled in the REMS, which entails:

- they will receive counseling on the
  - potential effects and risks of midomafetamine
  - need to be monitored for at least eight hours
  - need to leave the medication session with an accompanying adult
  - not to drive or operate machinery until at least the next day
  - need to follow up with the healthcare setting after medication sessions
- they agree to participate in the REMS registry

# Agency's Proposed REMS: Registry

Purpose: to better characterize the risk of serious harm resulting from patient impairment.

- Data will be used to determine whether changes to monitoring and other safe use conditions are needed

Data collected will include but not be limited to:

- signs and symptoms of mental or physical distress experienced by the patient
- onset and duration of short-term effects
- monitoring duration
- if care needed to be escalated
- safety after medication sessions including the occurrence of events indicative of serious harm from patient impairment from midomafetamine administration

Limitations:

- Patients may be lost to follow-up which can lead to incomplete data collection
- REMS registry can only be used to characterize the serious risk the REMS is intended to mitigate

# Agency's Proposed REMS: REMS Assessment

- Assessment of the REMS will include:
  - measures to assess if the REMS is functioning as intended
  - measures that indicate whether the REMS is mitigating serious harm from patient impairment from midomafetamine administration

- Assessment of the REMS will occur regularly. These findings will inform if any modifications to the REMS are necessary.
  - additional data sources such as through post-marketing requirements may be needed to fully characterize the risk and inform REMS modifications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