Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
June 4, 2024

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room.

Topic: The Committee discussed new drug application 215455, for midomafetamine (MDMA) capsules, submitted by Lykos Therapeutics, for the proposed indication of treatment of post-traumatic stress disorder. The Committee was asked to discuss the overall benefit-risk profile of the product, including the potential public health impact.

These summary minutes for the June 4, 2024 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on July 26, 2024.

I certify that I attended the June 4, 2024 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Frimpong, PharmD	Rajesh Narendran, MD
Designated Federal Officer, PDAC	Chairperson, PDAC

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
June 4, 2024

The Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 4, 2024. FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Lykos Therapuetics. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong, PharmD (Designated Federal Officer). There were approximately 1,570 people in attendance. There were 32 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The Committee discussed new drug application 215455, for midomafetamine (MDMA) capsules, submitted by Lykos Therapeutics, for the proposed indication of treatment of post-traumatic stress disorder. The Committee was asked to discuss the overall benefit-risk profile of the product, including the potential public health impact.

Attendance:
Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Rajesh Narendran, MD (*Chairperson*); Kim O. Witczak (*Consumer Representative*)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Jessica K. Jeffrey, MD, MPH, MBA; Sonia L. Krishna, MD, FAPA, DFAACAP; Patrick S. Thomas, Jr., MD, PhD

Psychopharmacologic Drugs Advisory Committee Member Present (Non-Voting): Carla M. Canuso, MD (*Industry Representative*)

Temporary Members (Voting): Maryann Amirshahi, PharmD, MD, MPH, PhD; Melissa Decker Barone, PsyD *(via video conferencing platform)*; John B. Hertig, PharmD, MS, CPPS, FASHP, FFIP; Paul E. Holtzheimer, MD *(via video conferencing platform)*; Elizabeth Joniak-Grant, PhD (*Patient Representative*); Mary E. Rebo, PharmD, MBA, CPPS

FDA Participants (Non-Voting): Peter Stein, MD; Teresa Buracchio, MD; Tiffany R. Farchione, MD; Jean Kim, MD; Peiling Yang, PhD; Cynthia LaCivita, PharmD

Designated Federal Officer (Non-Voting): Joyce Frimpong, PharmD

Open Public Hearing Speakers: Brian Dempsey (Wounded Warrior Project); Robert M. Grant; Russell Hausfeld; Casey Tylek; Nese Devenot; Michael Abrams (Public Citizen); Jonathan Alpert (American Psychiatric Association); Ifetayo Harvey (People of Color Psychedelic Collective); Kayla Greenstein; Brett Waters (Reason for Hope); Brian Pace; Joe Welker; Beau Witka; Derandoria (Deran) Young (Black Therapist Rock and Veterans Mental Heal Leadership Coalition); Naomi Mathis (Disabled American Veterans); Jonathan Lubecky; Sehrish Sayani; Pedram Daraeizadeh; Manish Agrawal (Sunstone Therapies); Sasha Sisko; Adriane Fugh-Berman and Quaid Guarino, MS (PharmedOut); Matthew J. Baggott; Nick Browne; Loree Sutton; Meaghan Buisson (statement read by Sarah Grosh); Scott Chesney; Cristina Pearse; Ari Polivy; Ron Blake; Katherine Cassell (Veterans of the Foreign Wars of the United States); Lori Tipton; Debbie Plotnick (Mental Health America)

The agenda was as follows:

Call to Order and Introduction of Committee	**Rajesh Narendran, MD** Chairperson, PDAC
Conflict of Interest Statement	**Joyce Frimpong, PharmD** Designated Federal Officer, PDAC
FDA Opening Remarks	**Tiffany R. Farchione, MD** Director Division of Psychiatry (DP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Lykos Therapeutics**
Introduction	**Amy Laverdiere, MBA** Program Lead Lykos Therapeutics
Unmet Need	**Jerry Rosenbaum, MD** Director Center for the Neuroscience of Psychedelics Massachusetts General Hospital Research Institute Stanley Cobb Professor Psychiatry Harvard Medical School
Efficacy	**Berra Yazar-Klosinski, PhD** Chief Scientific Officer Lykos Therapeutics
Safety	**Alia Lilienstein, MD, MPH** Senior Medical Director Lykos Therapeutics

APPLICANT PRESENTATIONS (CONT.)

Clinician Perspective	**Kelley O'Donnell, MD, PhD** Director of Clinical Training NYU Langone Center for Psychedelic Medicine Research Assistant Professor of Psychiatry NYU School of Medicine
Benefit-Risk	**Berra Yazar-Klosinski, PhD**
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Introduction: Product and Disease Background	**David Millis, MD** Clinical Reviewer DP, ON, OND, CDER, FDA
Regulatory History and Key Issues	**David Millis, MD**
Efficacy Analysis	**Olivia Morgan, PhD** Statistical Reviewer Division of Biometrics I (DBI) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Safety Analysis	**David Millis, MD**
Risk Management for Midomafetamine	**Victoria Sammarco, PharmD, MBA** Risk Management Analyst Division of Risk Management (DRM) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Clarifying Questions to FDA	

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURMENT

Questions to the Committee:

1. **DISCUSSION**: Discuss the evidence of effectiveness for midomafetamine for the treatment of post-traumatic stress disorder (PTSD). 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

    Committee Discussion: *Committee members commented that functional unblinding and expectation bias may have played a role in the efficacy results. Some suggested that a larger sample size would have been better to understand the issues. Some members also stated that the expectation bias and functional bias in itself could account for what was seen in the clinical trial in the short term. Regarding durability, many committee members stated that there were too many confounders involved to tease the small data set apart. Regarding psychological intervention, committee members suggested the study should have been structured as a two-by-two factor design and some expressed concerns that the therapist unblinding and the therapist power of suggestibility could have influenced the results. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION**: 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.

    Committee Discussion: *Committee members suggested additional data to include, but not limited to, comorbid populations. Committee members also mentioned the risks of boundary violations, hyponatremia, and cited the lack of lab data, and the lack of QTc/cardiac data. Others stated that the abuse liability was felt to be inadequate and concerns about diversion were raised, but some committee members stated that this could be addressed in phase 4 studies. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSIO**N: Discuss the potential for patient impairment to occur with midomafetamine and the potential for serious harm that may result due to the impairment.

    Committee Discussion: *Committee members stated that there was risk of patient impairment that could last longer than what was studied and that a REMS would be needed to mitigate this risk. Others expressed concerns regarding the down titration of other psychotropic drugs, as it could add to a patient's impairment risk. Some suggested an overnight stay would be better. Committee members wanted greater clarity on*

monitoring and discharge criteria for patients (e.g., heartrate, blood pressure, and other safety precautions). Please see the transcript for details of the Committee's discussion.

4. **DISCUSSION**: 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.

   Committee Discussion: *Many Committee members agreed that the risk was not fully characterized. To minimize this risk, Committee members suggested the following: two licensed therapists, training by an independent outside group rather than the sponsor, adequate medical training for the therapist so they are aware of the cardiovascular and medical risks that may occur, the presence of a medical staff onsite, safety reporting mechanisms outside of the treatment centers, and the addition of more comprehensive ECG, laboratory, and vital sign data. Duration of impairment should also be more fully characterized. Please see the transcript for details of the Committee's discussion.*

5. **VOTE**: Do the available data show that the drug is effective in patients with posttraumatic stress disorder?

   Vote Result: Yes: 2 No: 9 Abstain: 0

   Committee Discussion: *A majority of the panel voted "No", that the data did not show that midomafetamine was effective in patients with PTSD. Many stated that the functional unblinding, the lack of management of expectation bias and selection bias limited the interpretability of the efficacy analyses. Those who voted "Yes", did note that there were concerns for the functional unblinding and expectation bias which could have reduced the effect size that were reported; however, they could not overlook the fact the effect sizes were large. Please see the transcript for details of the Committee's discussion.*

6. **VOTE**: 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?

   Vote Result: Yes: 1 No: 10 Abstain: 0

   Committee Discussion: *A majority of the Committee agreed that the benefits of midomafetamine with FDA's REMS do not outweigh its risks for the treatment of patients with PTSD. Many Committee members commented that there needed to be more efficacy and safety data. The one Committee member who voted "Yes", stated that the REMS, while not perfect, is on the right track to address the safety concerns. In addition, this member commented on the need for new PTSD treatment options for this population. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:45 PM