**Consensus Statement:**
**Experts Endorse MDMA-assisted Therapy for PTSD**

**Re:** Lykos Therapeutics NDA #215455, Midomafetamine (MDMA) for use in the treatment of PTSD

**To Whom It May Concern:**

We, the undersigned researchers and clinicians, are writing to express our professional assessment of the treatment for PTSD using midomafetamine (MDMA) that is under consideration by the U.S. Food and Drug Administration. On the basis of the safety and efficacy data we have seen, assuming the integrity of the data is validated by the relevant regulators, and in light of the very urgent and widespread unmet need for effective treatments for PTSD, we believe that midomafetamine (MDMA) is now approvable for use with therapy in the treatment of PTSD, given suitable safeguards and post-approval monitoring.

This assessment is based on the references listed below, including the published peer-reviewed phase 3 clinical trial data for midomafetamine (MDMA) assisted therapy, the recent Institute for Clinical and Economic Review (ICER) report on those clinical trials, the sponsor's brief for the FDA-convened Psychopharmacologic Drugs Advisory Committee, and that committee's June 4, 2024 deliberations. We also note over four decades of research with MDMA and what can be inferred about the safety profile of MDMA from its widespread use.

**Rationale: Urgency**
We face a severe global mental health crisis, including an estimated 13 million Americans who are suffering from PTSD. Current therapies for PTSD fail to achieve remission in over half of patients who are treated. U.S. military veterans are taking their lives at an average rate of more than 17 per day. *The need for a more effective therapy for PTSD is urgent.*

**Rationale: Efficacy**
The phase 3 clinical trials of midomafetamine-assisted therapy for PTSD have shown substantial evidence of efficacy with a consistency of results across the fifteen different study sites and across various patient subgroups that provides additional confidence in the reliability of the primary finding.

Although concerns have been raised about functional unblinding and expectancy effects in the phase 3 trials, these are common issues with testing psychoactive medications. We believe that these concerns do not rise to a level that would call the main clinical trial findings into question. In our assessment, the findings provide ample evidence of the efficacy of midomafetamine-assisted therapy for PTSD:

- **CAPS-5 Score Improvements in Patients with PTSD:** The phase 3 trials have demonstrated a clinically meaningful reduction in PTSD symptoms, as measured by CAPS-5 (Clinician-Administered PTSD Scale for DSM-5) scores, in participants with moderate to severe PTSD who received midomafetamine-assisted therapy compared to those who received placebo plus therapy. The reduction was statistically significant with

substantial evidence of efficacy. At the primary study endpoint across two phase 3 trials, 87% of participants in the midomafetamine group experienced a clinically meaningful response, 69% no longer met the diagnostic criteria for PTSD, and 40% achieved remission. In contrast, 66% of participants in the placebo-plus-therapy group had a clinically meaningful response, 41% did not meet diagnostic criteria, and 14% achieved remission. The CAPS-5 was administered by remote, blinded, independent assessors.

On average, participants in the midomafetamine group experienced approximately a two-fold greater reduction in CAPS-5 scores compared to the placebo-plus-therapy group.

- **Durable Remission of PTSD Symptoms:** Long-term follow-up data from both phase 3 studies suggest that remission persists for at least 6 months after the treatment, with 39% of the midomafetamine group still in remission, compared to 11% of the placebo-plus-therapy group. This is a particularly notable finding given that patients in both studies had suffered from PTSD for an average of 15 years.

- **Additional Improvements in Patients**: Improvements were also observed in the key secondary endpoint – scores on the Sheehan Disability Scale (SDS), including reductions in functional impairment associated with PTSD, as well as exploratory endpoints of depression symptoms, as measured by the Beck Depression Inventory (BDI-II). The midomafetamine-assisted therapy group showed significantly greater reductions in both SDS and BDI-II scores compared to the placebo-plus-therapy group.

**Rationale: Safety**
Midomafetamine-assisted therapy has been shown in clinical trials to be generally safe and well tolerated. This is an acute course of therapy with very limited total drug exposure (the sponsor's phase 3 protocol included three midomafetamine sessions only).

MDMA has been studied for over four decades – it was used in psychotherapy from the late 1970s until 1985, when it was placed in Schedule I for reasons unrelated to its clinical safety or efficacy. The United Nations Office on Drugs and Crime has estimated that worldwide, over 20 million people use MDMA annually. Even in unsupervised, non-medical settings, serious adverse events are rare. Medical use of approved midomafetamine (MDMA) will be supervised by licensed healthcare providers. There were no serious adverse events indicative of cardiovascular or hepatic risk in the phase 3 trials, and any such medical concerns that remain can be addressed via safety surveillance and post-approval studies.

Psychotherapy, which is understood to be a vital component of the treatment, also presents risk, which MDMA can increase. We are aware of one instance of harmful therapist misconduct in a phase 2 trial of MDMA and a public allegation of harmful therapist misconduct in a phase 3 trial. Naturally, the sponsor, the FDA, and the field must take this risk very seriously. Post-approval, the delivery of this treatment will likely be governed by a combination of state licensing boards,

payers, and professional associations. The sponsor's guidelines for delivery of midomafetamine-assisted therapy, including ethical standards and other measures to minimize the risk of therapist misconduct, should be reviewed to ensure their sufficiency, particularly given the unique nature of therapy with midomafetamine (MDMA).

**Conclusion**

While we agree with many of the issues raised by the FDA advisory committee, given the data we have reviewed and the urgency of the need, our assessment is that the benefits of midomafetamine-assisted therapy outweigh the risks and that midomafetamine is now approvable. The use of midomafetamine-assisted therapy should include a Risk Evaluation and Mitigation Strategy (REMS) that can be adjusted as real-world safety and efficacy data emerge.

*Signed:*

*Note: Titles and institutional affiliations are listed for identification purposes only.*

**Statement coordinator: Robert Jesse**

**Brian Anderson M.D., M.Sc.**[1]
Assistant Professor, Psychiatry
*UCSF School of Medicine*
Assistant Professor, Psychiatry

**Yvan Beaussant, M.D., M.Sc.**
Instructor in Medicine, Department of Psychosocial Oncology and Palliative Care
*Dana-Farber Cancer Institute*
*Harvard Medical School*

**Harriet de Wit, Ph.D.**
Professor, Department of Psychiatry and Behavioral Neuroscience
*University of Chicago*

**Paul Hutson, PharmD, M.S.**[2]
Distinguished Professor
Director, Transdisciplinary Center for Research in Psychoactive Substances
*University of Wisconsin-Madison School of Pharmacy*

**Franklin King IV, M.D.**[1]
Director of Training and Education
*Massachusetts General Hospital Center for Neuroscience of Psychedelics*
Instructor in Psychiatry, *Harvard Medical School*

**Jennifer Mitchell, Ph.D.**[2]

**Consensus Statement:**
**Experts Endorse MDMA-assisted Therapy for PTSD**

Professor in the Departments of Neurology and Psychiatry & Behavioral Sciences
*UCSF School of Medicine*
Associate Chief of Staff for Research and Development, *San Francisco VA Medical Center*

**Christopher R. Nicholas, Ph.D.**[2]
Associate Professor, Transdisciplinary Center for Research on Psychoactive Substances
*University of Wisconsin School of Medicine and Public Health*

**David Nutt, D.M., F.R.C.P., F.R.C.Psych, F.B.Ph.S, F.Med.Sci., D.Laws**
Edmond J. Safra Professor of Neuropsychopharmacology
*Imperial College London*
Winner, Nature John Maddox Prize 2013

**David E. Presti, Ph.D.**
Teaching Professor of Neuroscience
*University of California, Berkeley*

**Charles L. Raison, M.D.**
Professor of Human Ecology and Psychiatry, Department of Psychiatry
*University of Wisconsin-Madison School of Medicine and Public Health*

**Kristin Raj, M.D.**
Clinical Associate Professor of Psychiatry

**Barbara O. Rothbaum, Ph.D.**[1,2]
Professor in Psychiatry; Director, Veterans Program and the Trauma and Anxiety Recovery Program; Paul A. Janssen Chair in Neuropsychopharmacology; Associate Vice Chair of Clinical Research
*Emory University School of Medicine*

**Scott Shannon, M.D.**[2]
Assistant Clinical Professor, Department of Psychiatry
*University of Colorado*
Distinguished Fellow, *American Academy of Child and Adolescent Psychiatry*
Founder*, Wholeness Center*
Past President *American Holistic Medical Association*
Past President, *American Board of Integrative Holistic Medicine*
Founding CEO, *Board of Psychedelic Medicine and Therapies*

**Christopher S. Stauffer, M.D.**[1,2]
Associate Professor of Psychiatry
*Oregon Health & Science University*

**Consensus Statement:**
**Experts Endorse MDMA-assisted Therapy for PTSD**

**Bessel van der Kolk, M.D.**[2]
Professor of Psychiatry
*Boston University School of Medicine*
President, *Trauma Research Foundation*

**Nolan Williams, M.D.**

**Manish Agrawal, M.D.**[2]
Co-Founder and CEO
*Sunstone Therapies*

**Jonathan Book, M.D.**
Former Chief Medical Officer
*Magellan Health Services*

**George R. Greer, M.D.**
President
*Heffter Research Institute*
Past President, *Psychiatric Medical Association of New Mexico*
Distinguished Life Fellow, *American Psychiatric Association*

**Henry Harbin, M.D.**
Board Member, *BrainFutures*
Former CEO, *Magellan Health Services*
Commissioner of President Bush's Commission on Mental Health (2003)

**Kristine Panik, M.D.**
Psychiatrist, UC Berkeley Student Health Services
*University of California, Berkeley*

**Dan H. Rome, M.D.**
Chief Medical Officer
*Enthea Benefits PBC*

*Disclosures:*
*[1] Has received support and/or funding from Lykos for independent investigator-initiated research.*
*[2] Has served as a researcher and/or clinician on the Phase 3 trials referenced in this statement or on other Lykos-sponsored research.*

---

## REFERENCES

Mitchell, J.M., Bogenschutz, M., Lilienstein, A. *et al.* (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature Med,* 27(6), 1025–1033. https://doi.org/10.1038/s41591-021-01336-3

Mitchell, J.M., Ot'alora G., van der Kolk, B. *et al.* (2023). MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Med,* 29(10), 2473–2480. https://doi.org/10.1038/s41591-023-02565-4

ICER. Accessed July 5, 2024. Post-Traumatic Stress Disorder: An assessment of MDMA-assisted therapy.

U.S. Food and Drug Administration. Accessed July 5, 2024. Sponsor Briefing Document: Midomafetamine (MDMA) Capsule with Psychological Intervention.

U.S. Food and Drug Administration. Accessed July 5, 2024. Participation Information: June 4, 2024 Meeting of the Psychopharmacologic Drugs Advisory Committee Meeting.

U.S. Food and Drug Administration. Accessed July 5, 2024. June 4, 2024 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)