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Testimony before the FDA Psychopharmacologic Drug Advisory Committee Meeting

NDA/BLA# 215455

Drug name: midomafetamine (Lykos Therapeutics)

June 4, 2024

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I'm Michael Abrams of Public Citizen's Health Research Group. I have no financial conflicts of interest in this matter.

The committee today is mainly evaluating the treatment-associated experiences of 173[1] participants who took part in the placebo-controlled efficacy studies, and 476[2] individuals whose data were used to consider (the psychedelic drug) midomafetamine (MDMA, "molly," "ecstasy") as psychotherapy-enabling treatment for PTSD.

The two pivotal randomized clinical trials were functionally unblinded (essentially open-label) and thus likely biased towards favorable drug effects. Patients and therapists likely knew who received the drug (and who received placebo), and anecdotes suggest that some therapists abused that knowledge to manipulate patient beliefs.[3] Despite reluctantly 'green lighting' these trials,[4] the FDA's briefing materials state:

> "…the contribution of the likely expectation bias cannot be discounted while it also cannot be quantified."

For the primary outcome[5] in both trials, statistical estimates of a 9-point difference in one trial and a 12-point difference in the other favoring the drug treatment did not, or only barely, achieved the 10-point difference the FDA (and the sponsor) agreed represents the low end of meaningful improvement in PTSD-related symptoms.[6]

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[1] U.S. Food and Drug Administration. Briefing document: NDA/BLA# 215455. Drug name: midomafetamine (Lykos Therapeutics). Psychopharmacologic Drugs Advisory Committee Meeting. June 4, 2024. https://www.fda.gov/media/178984/download. Accessed June 1, 2024. P. 25.

[2] *Ibid.* P. 39.

[3] Goldhilld O. What to watch for in crucial FDA meeting on MDMA therapy for PTSD. *STAT+*. May 31, 2024.

[4] The agency previously proposed at least two active controls conditions (low dose drug and niacin); both that were rejected by the sponsor.

[5] The 80-point, DSM, CAPS-5 assessment

[6] U.S. Food and Drug Administration. Briefing document: NDA/BLA# 215455. Drug name: midomafetamine

Moreover, the pivotal trials were confounded by the inclusion (in both treatment arms) of imprecisely-defined, multi-hour psychotherapy sessions.[7] To quote the FDA briefing materials again:

"the contribution of psychotherapeutic support sessions to the overall efficacy results cannot be fully quantified or understood…" even as the results show that both drug- and placebo-exposed patients improved markedly, though variably.[8][9]

Adverse effects that were markedly more prevalent (at least 5% more) with drug treatment than placebo included:

- Dry eyes, nystagmus, and blurry vision
- Gastrointestinal disturbances
- Thermoregulation disturbances
- Acute blood pressure increases and chest discomfort
- Muscle tightness
- Headache, dizziness, paresthesia, and tremor
- Psychiatric symptoms, such as insomnia and restlessness

And, of course, the abuse and dependence potential of the treatment are well-established in human and animal studies. Thus, as the FDA briefing materials state, it is particularly concerning that "the applicant did not appropriately document central nervous system-related adverse events," as advised by the agency's controlled substances staff.[10]

Based on the available evidence, and considering the many deficiencies of this drug application, the known benefits of midomafetamine to treat post-traumatic stress disorder are insufficient to outweigh the many risks.

Public Citizen's Health Research Group thus urges the committee to vote "No" on the voting questions, and to recommend to the FDA that midomafetamine not be approved.

(Lykos Therapeutics). Psychopharmacologic Drugs Advisory Committee Meeting. June 4, 2024. https://www.fda.gov/media/178984/download. Accessed June 1, 2024. P. 34.

[7] *Ibid.* P. 39.

[8] Scores of 24- and 14- CAPS-5 points, respectively, with standard deviations of 12-points, following study engagement.

[9] U.S. Food and Drug Administration. Briefing document: NDA/BLA# 215455. Drug name: midomafetamine (Lykos Therapeutics). Psychopharmacologic Drugs Advisory Committee Meeting. June 4, 2024. https://www.fda.gov/media/178984/download. Accessed June 1, 2024. P. 27.