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Major Milestone for Psychedelic-Assisted Therapy: Lykos Therapeutics Submits New Drug Application to the FDA for MDMA-Assisted Therapy for PTSD

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On Dec. 12, 2023, the Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation (MAPS PBC) announced their submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for MDMA (midomafetamine) in combination with psychotherapy for the treatment of post-traumatic stress disorder (PTSD). (Press Release, Lykos Therapeutics, "MAPS PBC Announces Submission of New Drug Application to the FDA for MDMA-Assisted Therapy for PTSD" (Dec. 12, 2023). This marks the first NDA submission for any psychedelic-assisted therapy and is a major milestone for the medicinal psychedelics industry.

Subsequently, on Jan. 5, 2024, MAPS PBC announced a name change/rebranding to Lykos Therapeutics, as well as the successful close of an oversubscribed Series A financing of over $100 million, which will help fund the regulatory approval and pre-launch steps for MDMA-assisted therapy for PTSD. (Press Release, Lykos Therapeutics, "MAPS Welcomes New Investors, Name Change for MAPS Public Benefit Corporation" (Jan. 5, 2024).

MDMA, often grouped in the category of psychedelics, is a synthetic psychoactive compound classified as an entactogen, meaning it induces emotional states such as openness and oneness. Mental health professionals were already using MDMA in combination with psychotherapy to treat patients in the 1970s, but in 1985, the U.S. Drug Enforcement Administration (DEA) categorized MDMA (also known as ecstasy) as a Schedule I drug under the Controlled Substances Act precluding its medical use.

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In the 2000s, renewed interest in this compound led to a marked increase in investigational placebo-controlled studies of MDMA-assisted therapy for PTSD. In 2017, the FDA granted MDMA-assisted therapy for PTSD "breakthrough therapy" status—a designation

designed to speed up the development and review of medications for serious conditions where preliminary clinical evidence has suggested the medication may show substantial improvement over available therapy on a clinically significant endpoint(s). (Press Release, MAPS, "FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Therapy for PTSD, Agrees on Special Protocol Assessment for Phase 3 Trials" (Aug. 26, 2017).

MAPS PBC (now known as Lykos Therapeutics) conducted six Phase 2 and two Phase 3 studies evaluating the use of MDMA-assisted therapy for PTSD. The two pivotal Phase 3 studies (MAPP1 and MAPP2) were randomized, double-blind, placebo-controlled trials in 90 and 104 subjects, respectively, with PTSD. (Jennifer M. Mitchell et al., "MDMA-Assisted Therapy for Severe PTSD: a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study", 27 Nature Med. 1025, 1025-33 (2021) and Jennifer M. Mitchell et al., "MDMA-Assisted Therapy for Moderate to Severe PTSD: a Randomized, Placebo-Controlled Phase 3 Trial", 29 Nature Med. 2473, 2473-80 (2023).) Therapy involved three preparatory sessions followed by three treatment cycles over a three-month period with each treatment cycle including one medication session (where the patient self-administered MDMA under the supervision of a healthcare provider(s) who also delivered psychotherapy) and three integration sessions.

Both studies met the primary endpoint measuring PTSD symptomology by the change from baseline to 18 weeks in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and a secondary endpoint of improvement in functional impairment associated with PTSD as assessed by the change from baseline to 18 weeks in the Sheehan Disability Scale (SDS). In both studies, no serious adverse events were reported in the group which received MDMA-assisted therapy.

In a press release, Amy Emerson, CEO of Lykos Therapeutics, stated: "The filing of our NDA is the culmination of more than 30 years of clinical research, advocacy, collaboration and dedication to bring a potential new option to adults living with PTSD, a patient group that has experienced little innovation in decades." (Lykos Therapeutics, Dec. 12, 2023, supra.)

Lykos Therapeutics asked the FDA for priority review of their NDA. The FDA will decide within 60 days if the NDA will be accepted for review and if it will be a priority or standard review (six months or 10 months, respectively).

An approval by the FDA of MDMA-assisted therapy for PTSD would also require the DEA to change the Schedule I classification of Lykos Therapeutics' formulation of MDMA so that it can be used as a prescription medication. This is because Schedule I is reserved for drugs with a high abuse potential but no accepted medical use. Drugs with abuse potential that do have accepted medical use—or, in other words, are FDA-approved products—are placed into Schedule II, III, IV or V depending on their relative abuse potential and degree to which they induce dependence.

The drug scheduling process includes multiple steps and federal agencies. The Controlled Substance Staff within the FDA performs an eight-factor analysis (8FA) of the abuse-related data submitted in the NDA and, together with input from the National Institute on Drug Abuse (NIDA) staff, makes scheduling recommendations. (U.S. Department of Health and Human Services, FDA and Center for Drug Evaluation and Research, "Assessment of Abuse Potential of Drugs: Guidance for Industry", FDA (Jan. 2017).

The Department of Health and Human Services (HHS) considers the 8FA and recommendations and then transmits the 8FA and scheduling recommendations to the DEA, which makes the final rescheduling decision.

Questions and Implications if FDA Grants Approval of MDMA-Assisted Therapy

Many questions remain as to what MDMA-assisted therapy will look like if approved. Because the FDA is responsible for regulating the drug component, it is unclear how the therapy component will be regulated and how it will be addressed in the labeling.

Similarly, it remains unclear what therapist training will entail. Lykos Therapeutics has started designing their own therapist training program, but a shortage of mental health professionals may limit accessibility to this medication. ("Education", Lykos Therapeutics (last visited Jan. 22, 2024) and "Health Workforce Shortage Areas", Health Resources and Services Administration (data as of Jan. 20, 2024)).

It is also unclear what standards and requirements the FDA will put in place for prescribers and whether the FDA will require a Risk Evaluation and Mitigation Strategy (REMS) as an additional level of patient safety.

The cost of the medication is still another unknown, while the cost of the therapy component would likely vary as well. It remains unclear whether, and the extent to which, insurance companies will cover MDMA-assisted therapy.

Implications for those in the psychedelic space are far-ranging. As Amy Emerson stated: "If approved, MDMA-assisted therapy would be the first psychedelic-assisted therapy, which we hope will drive additional investment into new research in mental health." (Lykos Therapeutics, Dec. 12, 2023, supra). Stakeholders in the medicinal psychedelic space see this NDA submission as a major milestone and a catalyst for the development and potential approval of other psychedelic medications.

The next NDA submission may be for psilocybin-assisted therapy, as Compass Pathways has initiated its Phase 3 program for their proprietary formulation of synthetic psilocybin (COMP360) in combination with psychological support for treatment-resistant depression. (Press Release, Compass Pathways, "Compass Pathways Initiates UK Component of Global Phase 3 Study of Psilocybin Treatment in Treatment-Resistant Depression, and Launches New Research Center", (Nov. 15, 2023). Some researchers are looking into developing compounds targeting similar receptors as those targeted by psychedelics, but without the hallucinogenic properties.

Everyone will be watching closely to see how the FDA approaches review of Lykos Therapeutics' NDA, but lessons can already be gleaned, including the unprecedented use of an ethnically diverse subject population in the second Phase 3 study (MAPP2), where 26.9% of subjects identified as Hispanic/Latino and 33.7% identified as other than White. (Jennifer M. Mitchell et al., 2023, supra).

Notwithstanding the still-unanswered questions, given the pace of development and regulatory review of medicinal psychedelics, healthcare facilities and mental health professionals interested in providing this therapy will likely need to begin planning in order to hit the ground running if MDMA-assisted therapy for PTSD gains FDA approval, as is expected.

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