NDA 215455

COMPLETE RESPONSE

Lykos Therapeutics
Attention: Berra Yazar-Klosinski, PhD
Chief Scientific Officer
3141 Stevens Creek Blvd #40547
San Jose, CA 95117

Dear Dr. Yazar-Klosinski:

Please refer to your new drug application (b) (4) or midomafetamine capsules.

We also acknowledge receipt of your amendment dated (b) (4), which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

COMPLETE RESPONSE ISSUES

We have concluded that your application does not provide substantial evidence of effectiveness or establish the safety of your product to support the approval of midomafetamine for the treatment of posttraumatic stress disorder (PTSD). We have identified several issues with the application that preclude its approval.

1. You did not collect important information on events that the participant, therapist, or study physician considered "positive" or "favorable." This information is necessary for FDA to assess signals of abuse potential and patient impairment in the clinical trials in order to adequately describe the drug effects in labeling and inform appropriate monitoring for the safe use of midomafetamine. In addition, FDA inspections also identified several unreported adverse events for at least two sites, which increase our concerns about the reliability of the safety data.

   FDA had advised in our (b) (4), communication that "For all Phase 1, 2 and 3 studies, AEs associated with potential abuse or overdose must be documented," and we referred you to our guidance for industry, Assessment of Abuse Potential of Drugs (2017) for recommendations regarding how to appropriately document

adverse events associated with abuse potential even if they are considered desirable (e.g., euphoria-related experiences, mood changes). During the sponsor inspection, FDA identified that the definition of an adverse event (AE) in the MAPP2 training information and the safety manual were not consistent with the MAPP2 protocol. Specifically, the training (e.g., All-Site Community Meeting slide presentations) and the safety manual provided by the sponsor to the study sites described an AE as "any undesirable, unfavorable, inappropriate, or untoward medical occurrence in a patient while participating in a clinical trial… NOT positive or favorable effects." However, the MAPP2 protocol defined an AE as "any medical occurrence in a participant, including any abnormal sign (e.g., abnormal and clinically significant physical exam finding, laboratory finding, 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." The systematic training of not reporting "positive" or "favorable" effects as AEs raises concerns over the reliability of the safety data. All AEs, including "positive" effects, should have been identified and reported. As you were specifically advised, regardless of whether a participant, therapist, or physician may find a drug experience to be neutral, positive, or favorable, events that are relevant to the abuse potential of a drug or potential for impairment should have been captured and reported in the safety and abuse potential summary in the NDA. Because such events were not captured and reported, the studies failed to adequately characterize the safety of midomafetamine, its acute effects, the duration of impairment, or signals of abuse potential within these studies. This information is necessary to appropriately label and provide recommendations for the safe use of midomafetamine.

Overall, based on this failure to collect important information on "positive" or "favorable" events, and the unreported adverse events identified by FDA at the study sites, there are substantial concerns about the reliability of the safety data which limit our ability to adequately assess the safety of midomafetamine for the treatment of PTSD.

2. You have not demonstrated that the effect observed with midomafetamine is durable beyond the 18-week end-of-study assessments (8 weeks after the last dose of midomafetamine) in MAPP1 and MAPP2. As PTSD is a chronic condition, any drug indicated for the treatment of PTSD is expected to provide a durable treatment effect. Given the proposed dosing regimen of midomafetamine of a limited duration of three treatment sessions, it is critical to understand whether the treatment benefit is durable beyond the Week 18 assessment to inform the appropriate use of midomafetamine for labeling of the drug.

   There are multiple design issues with MPLONG which render the data inadequate to establish the durability of effect from MAPP1 and MAPP2. MPLONG consisted of only a single visit. Additionally, there was marked variability in the timing of those visits, with a wide range of 6 months to up to 2 years of follow-up. Only a portion of

participants from MAPP1 and MAPP2 enrolled into MPLONG, and there is a potential for bias due to self-selection for participation in MPLONG. Importantly, many participants used potentially therapeutic interventions in the interim period between completing MAPP1 or MAPP2 and the MPLONG assessment. Given these issues, the data from the MPLONG study do not provide evidence of a durable treatment effect.

Overall, the data contained in your application fails to establish how MDMA should be used to treat this chronic disease, whether treatment with a single treatment cycle is adequate or if retreatment is necessary. Information as to how the drug should be managed over the course of a chronic disorder is essential in the directions to health care providers in labeling.

3. Although the MAPP1 and MAPP2 protocols allowed for enrollment of participants with prior experience taking midomafetamine, approximately 40% of the enrolled participants reported prior use of midomafetamine, which is much higher than the background use of midomafetamine in the proposed indicated population with PTSD, and higher than what would be expected based on available data. Notably, FDA analyses of data from the 2022 National Survey on Drug Use and Health found that, in individuals with past-year moderate or severe mental illness, the lifetime prevalence of MDMA use was 16.2% and 20.5%, respectively. Additionally, the inspections conducted as part of this review detected very high rates of failures during the "prescreening" process prior to the formal screening (i.e., screening procedures and informed consent). Together these two factors suggest the possibility of selection bias, with the enrolled population not being representative of the general PTSD population. Not only does this potentially limit generalizability, it also raises the possibility of expectation bias given that participants who have prior experience with midomafetamine are more likely to recognize the effects of midomafetamine (i.e., leading to functional unblinding) and anticipate a treatment benefit. These limitations impact the interpretability of MAPP1 and MAPP2 and, together with failure of MPLONG to provide evidence of a durable treatment effect, preclude the ability to establish substantial evidence of effectiveness.

We believe that the most efficient path to address the clinical issues above would be to conduct a new clinical trial to assess the durability of effect and adequately characterize the safety of midomafetamine. The most informative design would be a randomized, double-blind study which includes the initial treatment sessions followed by blinded long-term follow-up with pre-specified criteria for retreatment, if needed. Your study design should incorporate elements that address the following identified complete response issues:

a) Demonstrate durability of effect

- Continue to follow participants in a blinded manner after the acute treatment period

- Incorporate prespecified criteria for recurrence of PTSD symptoms and potential retreatment of participants who meet these criteria, with follow-up assessments collected. These criteria should take into account symptom ratings as well as whether the participant seeks additional treatment outside the study

- Follow up assessments scheduled at least monthly

b) Minimize potential for bias

- Exclude or minimize the number of participants with prior use of MDMA or other psychedelics

- Incorporate an assessment of participant expectancy at baseline

- Assess both participant and rater/therapist unblinding at the end of the study

- Consider the inclusion of a low-dose midomafetamine arm as a control

c) Adequately characterize the safety of midomafetamine

- Capture all abuse-related adverse events, regardless of perceived emotional valence. Refer to the FDA guidance for industry Assessment of Abuse Potential of Drugs (2017) for recommendations regarding how to appropriately document adverse events associated with abuse potential. You should make every effort to characterize the nature, onset, and resolution of these events.

- Develop standardized criteria to assess participants' readiness for discharge following completion of the treatment session, which should include both psychological and physiological assessments.

Given the serious nature of the concerns raised about the reliability of the safety data, and also acknowledging comments made during the open public hearing of the advisory committee and in the public docket raising concerns about study conduct and the adequacy of collection of adverse event information, we recommend that you consider an independent third-party data audit of all study records and reports, including the recordings of the treatment sessions, to identify unreported or under-reported adverse events. As the review of any future resubmission would still consider data from MAPP1 and MAPP2, addressing these issues could provide greater assurance of the robustness of the findings from these studies. If you choose to conduct such an audit, we recommend discussing the goals and design of the audit with the Agency prior to its

initiation. We also note that, although initial inspections have been completed for the submission, some inspection-related activities are still ongoing.

ADDITIONAL COMMENTS

We have identified data gaps in your application that are not approvability issues at this time, and that could have been addressed with post-marketing requirements had your application been approved. Your application did not include laboratory data (e.g., liver analytes, electrolytes) from the phase 3 studies and the cardiac safety assessment was incomplete. We would expect these gaps to be addressed in a resubmission. Any subsequent studies to assess the efficacy and safety of midomafetamine will need to include the following:

1. Incorporate routine laboratory assessment at baseline and post-dose (e.g., liver analytes, electrolytes)

2. Assess vital signs (blood pressure and heart rate) at baseline, after each dose of study drug, and at the end of the medication session. Incorporation of these assessments into a dedicated cardiac pharmacodynamic study (see below) may also be considered rather than embedding in the larger trial.

We also note that the in vitro hERG assessment is inadequate to support an integrated risk assessment for midomafetamine. We recommend the evaluation of major metabolites on hERG current. We recommend utilization of appropriate positive controls (see best practice considerations in the new ICH S7B Q & A, section 2.1), as previously communicated in the May 13, 2021, Type B Guidance Written Response Only minutes.

Further, we recommend a dedicated pharmacodynamic (ECG) study using continuous Holter monitoring that, at a minimum, covers the proposed therapeutic dose of midomafetamine and preferably high clinical exposure as described in the guidance for industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2005). The design of the ECG study will depend upon whether the study will use an active comparator, which may lead to an increase in heart rate.

Although the following are not considered approvability issues, we recommend that they be addressed in your clinical trial:

1. Characterize the extent to which psychotherapy in the treatment contributes to the treatment benefit and if psychotherapy is necessary for a potential treatment benefit of midomafetamine to inform labeling.

    a) The MAPS-based regimen may not be generalizable to all types of psychotherapy practices. We recommend using an evidence-based standard of

care psychotherapy in lieu of the MAPS-developed psychotherapy in any future studies.

b) Consider a factorial study design that includes an arm with no psychotherapy.

2. Improve the diversity of your study population. For proposed recommendations regarding study diversity, refer to our recently published draft guidance for industry, *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*.

Finally, there are other gaps in the application that, although not approvability issues, could be addressed with additional studies. You should consider including the following data in a future resubmission:

1. Drug-drug interaction study: We recommend that you consider assessing the potential for an interaction between midomafetamine and SSRI drugs to determine if a taper of SSRIs is necessary prior to initiation of treatment midomafetamine.

2. PK study in patients with impaired hepatic function: Midomafetamine is primarily metabolized in the liver. The impaired liver function is anticipated to increase the systemic exposures of midomafetamine. Therefore, we recommend that you conduct a PK study in patients with hepatic impairment. We note that you plan to conduct a PK study in participants with moderate hepatic impairment as a post-marketing phase 4 study (MPKH).

3. PK study in patients with renal impairment: Based on the available data, midomafetamine appears to be minimally excreted through renal pathway. Therefore, the PK of midomafetamine is not likely to be altered in patients with mild to moderate renal impairment (estimated glomerular filtration rate (eGFR <60 mL/min). However, given that uremic toxin could affect the hepatic disposition of midomafetamine in patients with severe renal impairment (eGFR: <30 mL/min), the review team recommends a reduced design renal impairment study for midomafetamine in patients with severe renal impairment.

4. Clinical lactation study: When lactating women with PTSD use midomafetamine, there is a potential for midomafetamine to get excreted into the breast milk. Therefore, it is important to conduct a milk-only clinical lactation study to understand the extent of midomafetamine that is excreted into breast milk.

5. Pre- and post-natal development study: After reviewing the data available from your conducted reproductive toxicology studies and data found in the literature, we have determined that there is a gap in the characterization of the risk of midomafetamine treatment during pregnancy on the development of the CNS and other developing systems. We acknowledge that, at the End of Phase 2 meeting on (b) (4) , the Division stated that a pre- and postnatal development (PPND) study would

not be needed if the intended clinical use for midomafetamine remained acute and a pregnancy test will be conducted before each session. However, because literature suggests there may be an effect of MDMA on the developing brain, and based on the lack of reliable pregnancy data in humans, we recommend that you conduct a PPND study to characterize the risk of in utero exposure to midofmafetamine to these developing systems that have not been adequately evaluated in the other conducted reproductive studies (e.g., embryofetal development).

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

PROPRIETARY NAME

Please refer to correspondence dated (b) (4), which addresses the proposed proprietary name, (b) (4) This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated (b) (4) and last amended on (b) (4) which contains elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for midomafetamine capsule, if it is approved, to ensure that the benefits of the drug outweigh the risk of serious harm resulting from patient impairment. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

    - Present tabulations of the new safety data combined with the original application data.

    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

08/08/2024 02:39:42 PM