Erratum to FDA Briefing Document

Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

June 4, 2024

This errata contains corrections to FDA's briefing information for the June 4, 2024, PDAC Meeting. The meeting will discuss new drug application 215455, for midomafetamine (MDMA) capsules, submitted by Lykos Therapeutics, for the proposed indication of treatment of post-traumatic stress disorder.

1) Page 17, third paragraph, last sentence

"The main design elements of the studies are shown in ."

Revised text (additions in bolded and underlined font):

"The main design elements of the studies are shown in **Table 1**."

2) Page 19, first sentence after last bullet

"Additional key exclusion criteria for MAPP2 were: Had used ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first medication session; or had previously participated in a MAPS-sponsored MDMA clinical trial."

Revised text (deletions in strikethrough font):

"~~Additional key exclusion criteria for MAPP2 were:~~ Had used ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first medication session; or had previously participated in a MAPS-sponsored MDMA clinical trial."

3) Page 20, first paragraph

"The CAPS-5 is a 20-item clinician-reported outcome measure in which a blinded, centralized independent clinician rater conducted a semistructured interview to assess key symptoms of PTSD over the last month. CAPS-5 served as the primary endpoint for MAPP1 and MAPP2 studies (and the open-label MP16 study). The CAPS-5 was designed to align with the DSM-5 clinical criteria for PTSD. Each item has a response option from 0 to 4, with a score of 4

indicating the highest severity. A total severity score is then created by summing the individual scores. The total severity score range is 0 to 80, with a higher score indicating more severe PTSD symptoms."

Revised text (additions in bolded and underlined font and deletions in strikethrough font):

"The CAPS-5 is a **30-item**~~20-item~~ clinician-reported outcome measure in which a blinded, centralized independent clinician rater conducted a semistructured interview to assess key symptoms of PTSD over the last month. CAPS-5 served as the primary endpoint for MAPP1 and MAPP2 studies (and the open-label MP16 study). The CAPS-5 was designed to align with the DSM-5 clinical criteria for PTSD. Each item has a response option from 0 to 4, with a score of 4 indicating the highest severity. A total severity score is then created by summing the individual scores **of the first 20 items**. The total severity score range is 0 to 80, with a higher score indicating more severe PTSD symptoms."

4) Page 20, last paragraph, first sentence

"The medication regimen used in the four 18-week studies consisted of three sessions of midomafetamine administration and is summarized in ."

Revised text (additions in bolded and underlined font):

"The medication regimen used in the four 18-week studies consisted of three sessions of midomafetamine administration and is summarized in **Table 2**."

5) Page 21, third paragraph, last sentence

"See for an overview of the study structure for MAPP1 and MAPP2."

Revised text (additions in bolded and underlined font):

"See **Figure 1** for an overview of the study structure for MAPP1 and MAPP2"

6) Page 23, first paragraph, third sentence

"The Sponsor allocated 2% of the alpha (0.0001) to the unblinded sample size re-estimation to account for any possible downward bias in the variance estimate."

Revised text (additions in bolded and underlined font and deletions in strikethrough font):

"The Sponsor allocated **<u>0.2%</u>** ~~2%~~ of the alpha (0.0001) to the unblinded sample size re-estimation to account for any possible downward bias in the variance estimate."

7) Page 24, second paragraph, second sentence

"The study enrolled participants who had received at least one dose of midomafetamine in Study MAPP1, MAPP2, MP16, or MAPPUSX; however, the Agency's analyses of MPLONG data presented in this briefing document only include participants from MAPP1 and MAPP2."

Revised text (additions in bolded and underlined font and deletions in strikethrough font):

"The study enrolled participants who had received at least one dose of **<u>investigational medical product (drug or placebo)</u>** ~~midomafetamine~~ in Study MAPP1, MAPP2, MP16, or MAPPUSX; however, the Agency's analyses of MPLONG data presented in tfhis briefing document only include participants from MAPP1 and MAPP2."

8) Page 24, third paragraph, third sentence

"The study protocol included a review of adverse events, a single administration of the C-SSRS, and a single administration of the primary efficacy assessment tool used in the parent study."

Revised text (additions in bolded and underlined font and deletions in strikethrough font):

"The study protocol included a review of **<u>medical history</u>** ~~adverse events~~, a single administration of the C-SSRS, and a single administration of the primary efficacy assessment tool used in the parent study."

9) Page 25, last paragraph

"The number of participants who enrolled, who were included in different analysis populations, and who completed MAPP1, MAPP2, and enrolled in MPLONG is shown in ."

Revised text (additions in bolded and underlined font):

"The number of participants who enrolled, who were included in different analysis populations, and who completed MAPP1, MAPP2, and enrolled in MPLONG is shown in **<u>Table 3</u>**."

10) Page 27, first paragraph, last sentence

"The results for both studies are presented in ."

Revised text (additions in bolded and underlined font):

"The results for both studies are presented in **Table 5**."

11) Page 28, first full paragraph, first sentence

" displays the estimated mean changes from baseline in CAPS-5 total score throughout the three assessment visits (approximately 6 weeks, 10 weeks, and 18 weeks from baseline)."

Revised text (additions in bolded and underlined font):

"**Figure 2** displays the estimated mean changes from baseline in CAPS-5 total score throughout the three assessment visits (approximately 6 weeks, 10 weeks, and 18 weeks from baseline)."

12) Page 29, first paragraph, last sentence

"The results for both studies are shown in ."

Revised text (additions in bolded and underlined font):

"The results for both studies are shown in **Table 6**."

13) Page 30, last paragraph

"The demographic and baseline characteristics of the mITT population from MAPP1 and MAPP2 stratified by whether or not participants enrolled in MPLONG are shown in ."

Revised text (additions in bolded and underlined font):

"The demographic and baseline characteristics of the mITT population from MAPP1 and MAPP2 stratified by whether or not participants enrolled in MPLONG are shown in **Table 7**."

14) Page 31, last paragraph, second sentence

" shows data for participants who entered MPLONG from either MAPP1 or MAPP2."

Revised text (additions in bolded and underlined font):

"**Table 8** shows data for participants who entered MPLONG from either MAPP1 or MAPP2."

15) Page 32, second sentence

"MAPP1 was conducted prior to both MAPP2 and the start of MPLONG, so participants from MAPP1 tended to have a longer period of time between completing the parent study and their LTFU Visit 1 in MPLONG ()."

Revised text (additions in bolded and underlined font):

"MAPP1 was conducted prior to both MAPP2 and the start of MPLONG, so participants from MAPP1 tended to have a longer period of time between completing the parent study and their LTFU Visit 1 in MPLONG (**Figure 3**)."

16) Page 34, second paragraph, first sentence

"Based on the results of this tipping point analysis, the interim use of ketamine, 5-MEO-DMT, or illicit MDMA use in the interim period may have had some impact on the estimate at the LTFU visit (,)."

Revised text (additions in bolded and underlined font):

"Based on the results of this tipping point analysis, the interim use of ketamine, 5-MEO-DMT, or illicit MDMA use in the interim period may have had some impact on the estimate at the LTFU visit (**Table 16**, **Table 17**)."

17) Page 35, last paragraph, second sentence

"Data from the survey, shown in , indicated that study participants could guess their treatment arm assignment with a high degree of accuracy."

Revised text (additions in bolded and underlined font):

"Data from the survey, shown in **Table 9**, indicated that study participants could guess their treatment arm assignment with a high degree of accuracy."

18) Page 38, second paragraph, second sentence

"As discussed in Section 3.2.1, 62% of randomized participants in MAPP1 and 78% of randomized participants in MAPP2 were included in the MPLONG effectiveness subset ()."

Revised text (additions in bolded and underlined font):

"As discussed in Section 3.2.1, 62% of randomized participants in MAPP1 and 78% of randomized participants in MAPP2 were included in the MPLONG effectiveness subset (**Table 3**)."

19) Page 38, third paragraph

"There were several differences between patients who enrolled in MPLONG and those who did not. First, patients who enrolled generally had a lower CAPS-5 total score at parent study termination compared to those who did not enroll ()."

Revised text (additions in bolded and underlined font):

"There were several differences between patients who enrolled in MPLONG and those who did not. First, patients who enrolled generally had a lower CAPS-5 total score at parent study termination compared to those who did not enroll (**Table 7**)."

20) Page 40, second paragraph

"See for SAEs that occurred during the midomafetamine development program."

Revised text (additions in bolded and underlined font):

"See **Table 10** for SAEs that occurred during the midomafetamine development program."

21) Page 41, third paragraph, first sentence

" presents the TEAEs leading to treatment discontinuation in the placebo-controlled phase 3 studies MAPP1 and MAPP2."

Revised text (additions in bolded and underlined font):

"**Table 12** presents the TEAEs leading to treatment discontinuation in the placebo-controlled phase 3 studies MAPP1 and MAPP2."

22) Page 41, last paragraph, last sentence

"AEs occurring in the combined MAPP1 and MAPP2 set in ≥2% of participants and at frequencies greater than placebo are presented in organized by system organ class."

Revised text (additions in bolded and underlined font):

"AEs occurring in the combined MAPP1 and MAPP2 set in ≥2% of participants and at frequencies greater than placebo are presented in **Table 13** organized by system organ class."

23) Page 44, last bullet

"Significant elevations in mean blood pressure and heart rate were observed (). The mean change across both studies in SBP was 17 mm Hg and DBP 7 mm Hg and the mean heart rate after session 3 increased by 23 bpm. Mean systolic and diastolic blood pressures tended to return to predose levels; however, pulse rates remained elevated by approximately 10 bpm."

Revised text (additions in bolded and underlined font):

"Significant elevations in mean blood pressure and heart rate were observed (**Figure 4**). The mean change across both studies in SBP was 17 mm Hg and DBP 7 mm Hg and the mean heart rate after session 3 increased by 23 bpm. Mean systolic and diastolic blood pressures tended to return to predose levels; however, pulse rates remained elevated by approximately 10 bpm."

24) Page 45, first sentence

"Outlier analysis () demonstrated a greater proportion of MDMA-treated patients who manifested blood pressure at or above 140/90 mm Hg (68% versus 22%, risk difference 45.6 (95% CI 33.1 to 58), and severe hypertension with SBP >180 mm Hg 6.1 versus 0.0%, risk difference 6.1 (1.4 to 10.8)."

Revised text (additions in bolded and underlined font):

"Outlier analysis (**Table 14**) demonstrated a greater proportion of MDMA-treated patients who manifested blood pressure at or above 140/90 mm Hg (68% versus 22%, risk difference 45.6 (95% CI 33.1 to 58), and severe hypertension with SBP >180 mm Hg 6.1 versus 0.0%, risk difference 6.1 (1.4 to 10.8)."

25) Page 71, last paragraph, third sentence

"We present major features of each data source in ."

Revised text (additions in bolded and underlined font):

"We present major features of each data source in **Table 18**."

26) Page 75, last paragraph, last sentence

"Search parameters used for MDMA and selected comparators are summarized in ."

Revised text (additions in bolded and underlined font):

"Search parameters used for MDMA and selected comparators are summarized in **Table 19**."

27) Page 77, last paragraph

"Information on the list of *principal variants*3F[22] that were used to identify mentions of drugs in this analysis are provided in ."

Revised text (additions in bolded and underlined font):

"Information on the list of *principal variants*3F[22] that were used to identify mentions of drugs in this analysis are provided in **Table 20**."

28) Page 80, last paragraph

"FDA searched the ToxIC Core Registry database from January 1, 2010, through September 30, 2023 , using the strategies described in and ."

Revised text (additions in bolded and underlined font):

"FDA searched the ToxIC Core Registry database from January 1, 2010, through September 30, 2023 , using the strategies described in **Table 21** and **Table 22**."

29) Page 82, second paragraph

"FDA searched the FAERS database from January 1, 2013, through December 31, 2023, with the strategy described in ."

Revised text (additions in bolded and underlined font):

“FDA searched the FAERS database from January 1, 2013, through December 31, 2023, with the strategy described in **Table 23**.”