STATISTICAL METHODS ANALYSIS PLAN

Statistical Analysis Plan v1.0

Addendum to SAP



A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms

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STATISTICAL ANALYSIS PLAN

Version 1.0

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STATISTICAL ANALYSIS PLAN

Final Version 1.0

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SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol version 6.0 (26Jul2023). The following table details the changes made to the SAP.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
1.0	All	Initial document	

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1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analysis to be performed for the study, MMED008 entitled "A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms." [redacted] has been engaged by Mind Medicine, Inc. (the 'sponsor') to develop the SAP and carry out the statistical analysis described in this SAP, including production of all tables, figures and listings. This SAP denotes the final analysis of the study, and does not include any formal interim analysis.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to determine the dose-response signal and assess the dose-response relationship of 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) as measured by the change in Hamilton Anxiety Rating Scale (HAM-A) Total Score from Baseline to Week 4.

2.1.2 Secondary Objectives

The key secondary objective of the study is to determine the dose-response signal and asses the dose-response relationship of the 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to Week 8. Other secondary objectives are:

- To determine the dose-response signal and assess the dose-response relationship of the 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) as measured by the change in HAM-A Total Score from Baseline to End of Study,
- To determine whether MM-120 (25, 50, 100 or 200 µg freebase-equivalent) improves functionality and quality of life measures in subjects with anxiety symptoms, including improvements in the following:
    - Depressive symptoms
    - Anxiety symptoms
    - Functional disability
    - Quality of life
    - Sleep
    - Sexual function

2.1.3 Safety Objectives

The safety objectives of the study are to assess the safety and tolerability of the 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) after oral administration in subjects with anxiety symptoms.

2.1.4 Exploratory Objectives

Exploratory objectives of the study include:

- To explore dose response on drug effects, altered perception and mystical experience,
- To explore the effect of MM-120 on direct and indirect health-care resource utilization (HCRU) and associated costs (for later analysis, not part of this SAP),
- To explore whether genetic polymorphisms are related to pharmacodynamics,
- To assess blind integrity and to examine whether guess rates are associated with outcomes such as AEs or mood/anxiety symptoms.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of the study will be the change in HAM-A Total Score from Baseline to Week 4.

2.2.2 Secondary Endpoints

The key secondary endpoint is change in HAM-A Total Score from Baseline to Week 8.

Other secondary endpoints are:

- Change in HAM-A Total Score from Baseline to End of Study
- Change from Baseline to Day 2 (where applicable), Week 1, Week 2, Week 4, Week 8, and End of Study in the following measures:
  - For depressive symptoms
    - Montgomery-Asberg Depression Rating Scale (MADRS)
  - For anxiety symptoms
    - Clinical Global Impression - Severity (CGI-S)
    - Clinical Global Impression – Improvement (CGI-I)
    - Patient Global Impression – Severity (PGI-S)
    - Patient Global Impression – Change (PGI-C)
  - For functional disability
    - Sheehan Disability Scale (SDS)
  - For quality of life
    - EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)
  - For sleep
    - Pittsburgh Sleep Quality Index (PSQI)
  - For sexual function
    - Arizona Sexual Experiences Questionnaire (ASEX)

2.2.3 Exploratory Endpoints

Exploratory endpoints for the study are:

- HAM-A response and remission at Weeks 1, 2, 4, 8 and End of Study
- Drug Effect Visual Analog Scale (VAS) assessed on Day 2
- Mystical Experience Questionnaire (MEQ30) assessed on Day 2
- 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) assessed on Day 2
- The Treatment Assignment/Blinding Question assessed on Day 2

3 INVESTIGATIONAL PLAN

3.1 Study Design

This Phase 2 study will enroll approximately 180 male and female subjects 18-<75 years of age who meet DSM-5 criteria for generalized anxiety disorder (GAD) and have a minimum HAM-A Total Score of 20. Potential subjects who have contraindicated medical or psychiatric conditions or who are taking concomitant medications, supplements or other therapeutics that are contraindicated that cannot be paused will be excluded from the study. Subjects on contraindicated concomitant medications, supplements or other therapeutics at screening will undergo a medication taper prior to advancing to Baseline. Potential study subjects who provide informed consent will have eligibility evaluated/confirmed at 3 visits: Screening, Baseline and Day 1/Randomization. Eligible subjects will be randomized in a 1:1:1:1:1 ratio to receive a single dose of either investigational drug at 4 dose levels (25, 50, 100 or 200 µg MM-120 freebase-equivalent) or placebo in a controlled clinical setting. After Day 1 subjects will have visits on Day 2, Week 1, Week 2, Week 4, Week 8 and Week 12.

3.2 Treatment

The study includes 4 dose levels of investigational product (IP): 25, 50, 100, or 200 µg MM-120 freebase-equivalent as well as a placebo arm. Subjects will receive one dose of study drug.

3.2.1 Randomization Scheme and Treatment Arm Assignment

Subjects will be randomized in a 1:1:1:1:1 ratio to one of the 4 dose levels of IP or placebo. Randomization will be centrally performed by a Randomization Trial Management System (RTMS). The 5 treatment groups are:

1. 25 µg (freebase-equivalent) of MM-120
2. 50 µg (freebase-equivalent) of MM-120
3. 100 µg (freebase-equivalent) of MM-120
4. 200 µg (freebase-equivalent) of MM-120
5. Placebo

3.2.2 Blinding

This double-blind trial will use a masking technique to blind subjects and study site personnel to

the treatment assignment. The subject, Investigator and Sponsor personnel who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments.

An unblinded statistician, who is not involved with the conduct of the trial, will perform randomization schema reviews and will be unblinded for the duration of the study.

At the end of the trial, and after medical/scientific review has been performed and data have been declared final and complete, the official final database will be locked and unblinded.

3.2.3 Dosing Schedule

Subjects will be administered a single dose of capsules to be taken orally on Day 1. Each capsule contains 25 µg MM-120 freebase-equivalent, or placebo. Each subject will receive a total of 8 capsules comprising of a combination of active and/or placebo as follows:

- The 25-µg arm consists of 1 active capsule + 7 placebo capsules
- The 50-µg arm consists of 2 active capsule + 6 placebo capsules
- The 100-µg arm consists of 4 active capsule + 4 placebo capsules
- The 200-µg arm consists of 8 active capsules
- The placebo arm consists of 8 placebo capsules

3.2.4 Subject Compliance

All subject dosing will occur at the site and be witnessed by the Investigator and/or Dosing Session Monitor(s) and the subject will be monitored at all times until release from the clinic.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Summary results will be provided by treatment group and where appropriate overall for all subjects. All tabulations will be based on pooled data across centers.

Subject data will be listed, sorted by treatment group, investigative center and subject number. When applicable, listings will be sorted by visit and assessment date/time as well.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Covington, KY) will perform all efficacy and safety statistical analyses.

4.1 Analysis Quality Control Procedures

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final

analysis.

All SAS programs used to create analysis data sets, tables, and listings will be double programmed. The SAS outputs will be compared and the programs will be updated until the outputs match.

4.2 Analysis Sets

The following populations will be defined for the purpose of analysis:

- Randomized Set (RAN) – all subjects who received a randomization number, regardless of receiving study drug. Subjects will be analyzed according to the treatment assigned.
- Safety Set (SAF) – all subjects who received the double-blind study drug. Subjects will be analyzed according to the actual treatment received.
- Full Analysis Set (FAS) – all randomized subjects with a valid baseline HAM-A assessment and at least one valid post-baseline HAM-A assessment. Subjects will be analyzed according to the treatment assigned.
- Per Protocol Set (PPS) - All subjects in the full analysis set who had no major protocol deviations deemed as impacting the primary endpoint. Subjects will be analyzed according to the actual treatment received.

An impact assessment will be performed prior to the unblinding of the study. The impact assessment will determine whether a major protocol deviation impacts the primary endpoint thereby leading to the removal of the respective subject(s) from the PPS.

4.3 Assessment Windows

Day 1 of the study will be defined as the date of first administration of study drug. Study Day will be measured relative to Day 1. Select efficacy endpoints will use analysis visit windows for the assigning of efficacy data to visits. Data from all scheduled and unscheduled visits will be included in these analyses. All other endpoints will be summarized/analyzed using the nominal study visit. Analysis visit windows are defined for the select efficacy endpoints in the tables below. The data point within an analysis visit window that is closest to the target visit day will be assigned to the respective analysis visit. In case of ties, the data point associated with the largest study day (i.e.; the latest data point) will be assigned to the respective analysis visit.

Table 1 Analysis Visit Windows for HAM-A, MADRS, SDS, EQ-5D-5L, and ASEX

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1-5 days prior to Day 1	<= Day 1
Week 1	Day 8	>= Day 2 and <= Day 11
Week 2	Day 15	>= Day 12 and <= Day 21
Week 4	Day 29	>= Day 22 and <= Day 43
Week 8	Day 57	>= Day 44 and <= Day 71
Week 12	Day 85	>= Day 72

Table 2 Analysis Visit Windows for CGI-S and PGI-S

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1-5 days prior to Day 1	<= Day 1
Day 2	Day 2	>= Day 2 and <= Day 4
Week 1	Day 8	>= Day 5 and <= Day 11
Week 2	Day 15	>= Day 12 and <= Day 21
Week 4	Day 29	>= Day 22 and <= Day 43
Week 8	Day 57	>= Day 44 and <= Day 71
Week 12	Day 85	>= Day 72

Table 3 Analysis Visit Windows for CGI-I and PGI-C

Analysis Visit	Target Study Day	Analysis Visit Window
Day 2	Day 2	>= Day 2 and <= Day 4
Week 1	Day 8	>= Day 5 and <= Day 11
Week 2	Day 15	>= Day 12 and <= Day 21
Week 4	Day 29	>= Day 22 and <= Day 43
Week 8	Day 57	>= Day 44 and <= Day 71
Week 12	Day 85	>= Day 72

Table 4 Analysis Visit Windows for PSQI

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1-5 days prior to Day 1	<= Day 1
Week 4	Day 29	>= Day 2 and <= Day 43
Week 8	Day 57	>= Day 44 and <= Day 71
Week 12	Day 85	>= Day 72

4.4 Unscheduled Visits

Unscheduled visits will be included in select efficacy analyses as noted above and will be presented in relevant subject listings. In certain circumstances laboratory test results from local labs, noted as 'unscheduled' will replace missing values from the central laboratory tests. In situations where a laboratory blood draw was performed according to the protocol schedule, but the central laboratory was unable to produce test results, another blood draw was performed, noted as

'unscheduled', and sent to the local laboratory. These local laboratory results will be reclassified as the visit in question and will be used for analysis.

4.5 Handling of Dropouts or Missing Data

Missing data on demographics, baseline information and safety measures will be treated as missing; no imputation is planned.

Missing or partial dates and times will be imputed for analysis purposes in a manner that imputes the most conservative date or time. Imputation methods for dates and times are described for each endpoint where applicable.

Details of missing data imputation will be specified in the analysis methods for the primary and key secondary efficacy endpoints. Subject-completed questionnaires will be considered missing if incomplete. Missing data will not be imputed for analysis of non-key secondary efficacy endpoints or safety endpoints.

4.6 Multiple Comparisons

The Multiple Comparison Procedure – Modeling (MCP-Mod) method will be used to assess the primary endpoint. Details of the method is provided in Section 6.1 below.

A hierarchical (i.e., simple fixed sequence testing) testing strategy will be used to protect the overall type I error rate when testing the primary efficacy endpoint with the key secondary efficacy endpoint.

No adjustment for multiplicity will be performed for testing the non-key secondary and exploratory endpoints.

4.7 Data Derivations and Transformations

The following derivations will be used in this study:

Study Day:

- Equal to (date of assessment - date of first dose + 1) for assessments done on or after date of first dose
- Equal to (date of assessment - date of first dose) for assessments before date of first dose

Baseline Observation: the last non-missing value prior to first study drug administration.

Duration: end date – start date +1; measured in days.

Change from Baseline: post-baseline value - baseline value

Percent Change from Baseline: (post-baseline value - baseline value) / baseline value x 100

5 STUDY PATIENTS

5.1 Disposition of Patients

A table of frequency counts of all subjects who are enrolled, randomized, treated, and in each analysis population will be provided. Frequency counts and percentages of subject disposition including study completion status and reasons for early termination will be tabulated. A subject

listing will be provided.

5.2 Protocol Deviations

Distribution of the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated by treatment group for the FAS. Protocol deviations will also be tabulated by severity (e.g., minor or major). A listing of all deviations will be provided.

5.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, sex at birth, self-identified gender, race, ethnicity, and baseline height, weight and BMI) by treatment group and overall, for the FAS and PPS populations. A listing of demographic characteristics will be provided.

5.4 Baseline Characteristics

Baseline values of HAM-A Total Score, MADRS Total Score, CGI-S, PGI-S, PSQI Global Score, SDS Total Score, and the proportion of subjects with sexual dysfunction according to the ASEX Total Score will be summarized for the FAS and PPS populations. The duration (in days) from the time of GAD diagnosis to study drug administration will be reported. A listing of baseline characteristics will be provided.

5.5 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT by treatment group and overall, for the FAS and PPS populations. A listing of subject medical history will be provided.

5.6 Psychiatric History

All psychiatric conditions will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The number and percent of subjects with each psychiatric condition will be presented for each SOC and PT by treatment group and overall, for the FAS and PPS populations. A listing of subject psychiatric history will be provided.

5.7 Prior and Concomitant Medications, Psychiatric Medications and Non-drug Treatments

Prior and concomitant medications and psychiatric medications taken for GAD will be coded using World Health Organization (WHO) drug classifications, version March 2022 B3. Non-drug treatments will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications are defined as medications that ended prior to the date of first dose of study drug administration (Day 1). Concomitant medications are defined as medications that started at any time but ended on or after the date of first dose (Day 1), including those that are ongoing at study completion. In the case of a missing or partial end date, in order to determine whether a medication is prior or concomitant, the following conservative imputation rule will be used: the unknown

portions of a medication end date will be imputed to the latest possible day or month. The imputed medication date will then be compared with the date of first dose to determine if the medication is prior or concomitant.

The number and percent of subjects using prior medications and concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) Level 2 and by preferred name. Prior medications will be summarized separately from concomitant medications and will be reported by treatment group and overall, for the FAS and PPS populations. A subject listing of all prior and concomitant medications will be provided.

Psychiatric medications taken for GAD will be summarized by ATC Level 2 and preferred name and presented by treatment group and overall. Prior psychiatric medications will be summarized separately from concomitant psychiatric medications for the FAS and PPS populations. A subject listing of all psychiatric medications taken for GAD will be provided.

Non-drug treatments will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall. Prior non-drug treatments will be summarized separately from concomitant non-drug treatments. A subject listing of all non-drug treatments will be provided.

5.8 Neuropsychiatric Examination

The Neuropsychiatric examination will be performed at Baseline, Day 1, and all subsequent visits including End of Study. The examination at Baseline will establish a standard comparison for possible acute and lasting effects of the study drug. A subject listing by visit will be provided.

5.9 Dosing Release Checklist

The Dosing Release Checklist will, at a minimum, be performed approximately 8 and 12 hours post-dose to ascertain if the subject meets DSM-5 criteria for Hallucinogen Intoxication. Subjects will be assessed hourly at 9, 10, and 11 hours post-dose until all release criteria are met. A summary of the number and percentage of subjects meeting release criteria at each hourly time point will be provided. A subject listing by time point will be provided.

6 EFFICACY ANALYSIS

All efficacy analyses, primary and secondary, will be carried out on the FAS population. Where noted, additional analyses on the PPS population may be included.

6.1 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is change from Baseline to Week 4 in HAM-A Total Score. The MCP-MOD method (Bretz 2005; Pinheiro 2014) will be used to assess the primary endpoint to investigate the dose-response relationship for the 4 doses levels of MM-120 versus placebo. The analysis of the primary endpoint using MCP-MOD will be performed on the FAS population. A sensitivity analysis will be performed on the PPS population.

The HAM-A consists of 14 items that encompass both psychological and somatic symptoms of anxiety. The HAM-A takes about 20 minutes to administer and will be completed by a central rater. The central rater will assess the extent to which the subject displays each given criterion and give a rating on a scale of 0-4, where 4 represents the most severe symptoms. The HAM-A Total Score will be calculated as the sum of the 14 items and will range from 0-56. Higher Total Scores

indicate increased severity of symptoms.

6.1.1 Handling of Missing Data and Potentially Biased Values

Missing data for the primary endpoint will be imputed using a multiple imputation approach assuming that the missingness mechanism can be retrieved from observed data. The imputation model will include the treatment group and the longitudinal sequence of HAM-A Total Score. Imputations will be performed 20 times using SAS PROC MI with the fully conditional specification (FCS) method.

For intercurrent events (IEs) the following methods will be used:

- The data recorded after the IE will be set to missing and imputed under a Missing Not at Random (MNAR) assumption by borrowing information from the placebo arm subjects (reference-based imputation) for the following:
    - Concomitant/prohibited medications that meet the threshold for impact = "Yes" during the impact assessment will be considered as the IE. Any observations after such an IE will be set to missing and will be imputed using the MNAR assumption.
- Available data will be used; missing data will be imputed under a Missing at Random (MAR) assumption, borrowing information from subjects in the same treatment arm for the following:
    - For IEs leading to study discontinuation due to other reasons
    - IEs related to the COVID-19 pandemic.

For missing data not due to IEs the imputation will be performed based on MAR assumption.

6.1.2 Analysis of Primary Endpoint

The following process will be followed to analyze the primary endpoint using the MCP-MOD method.

Step 1

A test statistic will be derived from the data using an analysis of covariance (ANCOVA) model with change from Baseline to Week 4 for the HAM-A Total Score as a response variable, treatment arm and Baseline value of HAM-A Total Score as covariates. Geographic region will be included as a covariate if clinical sites outside the US are used; otherwise, it will not be included in the model. Missing or potentially biased values occurring after IEs will be imputed as described in Section 6.1.1.

The ANCOVA model will be repeated for each imputed dataset, which results in a set of least squares (LS) mean estimates for all dose groups and the related covariance matrices. Rubin's rule will be used to combine the multiple sets of LS mean estimates and the related covariance matrices to a single set of LS mean estimates of change from Baseline to Week 4 for HAM-A Total Score for all dose groups and the related covariance matrix. The SAS procedure PROC MIANALYZE will be used to combine the results from imputed datasets and provide valid statistical inferences.

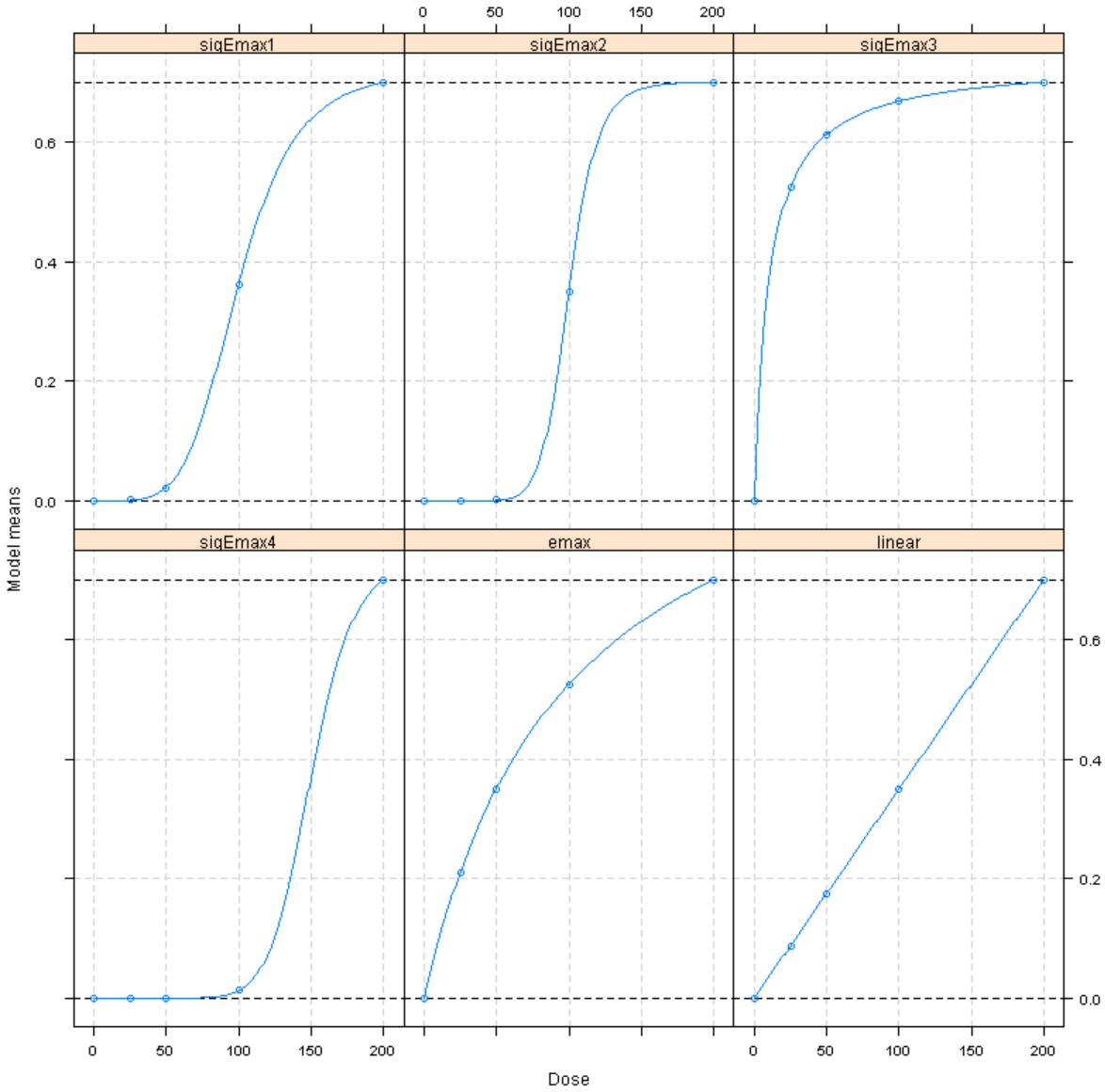
A range of possible dose-response relationships will be considered to take model uncertainty into account. The following six candidate dose-response curves, as depicted below in Figure 1, will be used to derive the optimal model contrasts for the multiple contrast tests:

- Sigmoid Emax (ED50, hill):
    - 10, 1
    - 100, 5
    - 100, 10
    - 150, 10
- Emax (D50 = 100)
- Linear

The optimal contrasts derived from the candidate model sets will be applied to the combined estimated dose means and covariance matrix to obtain the t-statistics for each candidate model and the common critical value $C_{0.05}$ derived from the reference multivariate t-distribution with the 6x6 correlation matrix induced by testing the candidate dose-range models with respect to comparing all MM-120 doses to the placebo group.

The null hypothesis will be rejected and the statistical significance of dose-response in change from Baseline to Week 4 for HAM-A Total Score will be established if the max (t_1, t_2, t_3, t_4, t_5, t_6) $\geq C_{0.05}$.

Figure 1 Candidate Dose-response Curves



Step 2

The response data in each imputed data set, including relevant covariates, will be used to fit the models in the candidate set. The estimated dose-response will be derived by using model averaging methods on a subset of candidate models, for which the associated contrast tests are statistically significant. The ≤ 3 models with the largest t-statistics $\geq C_{0.05}$ as calculated above will be selected as the basis for the model averaging.

Model averaging will be carried out for each imputed dataset, and the resulting mean efficacy estimates, and CIs will be derived using the combination variance that accounts for the uncertainty of the imputed data using Rubin's combination rules. Comparisons between MM-120 doses and placebo will be simultaneously derived for the model averaged estimates together with the CIs reflecting the imputation procedure applied. The model-averaging-based estimates of the mean changes from Baseline to Week 4 for HAM-A Total Score within each dose group, and the mean

differences between MM-120 and placebo and their CIs will then be displayed.

Target dose selection (e.g., minimum effective dose [MED], ED_p) will be based on the model change from Baseline to Week 4 for the HAM-A Total Score over the dose range studied. MED is defined as the lowest dose ensuring a clinically relevant and statistically significant improvement, $MED = \min\{d \in (d_1, d_5) : f(d) > f(d_1) + \Delta\}$, where Δ is the clinical relevance threshold. ED_p is defined as the lowest dose that gives a certain percentage p of maximum effect δ_{max}. $ED_p = \min\{d \in (d_1, d_5) : f(d) > f(d_1) + p\delta_{max}\}$. For this analysis, p will be set to 100%. The final choice of the target dose depends on the evaluation of the primary efficacy variable and other efficacy variables, as well as safety considerations.

The above will be repeated using only the model with the largest t-statistic $\geq C_{0.05}$.

6.2 Key Secondary Efficacy Endpoint and Analysis

6.2.1 Key Secondary Endpoint

The key secondary endpoint is change from Baseline to Week 8 in HAM-A Total Score. Analysis of this endpoint will follow the same process as the primary endpoint described in Section 6.1. The outcome for this endpoint will be considered confirmatory, if in agreement with the primary endpoint outcome and provided that the null hypothesis is rejected for the primary outcome. This gatekeeping function of the primary outcome allows for no adjustment of alpha level for multiplicity of testing.

6.3 Secondary Efficacy Endpoints and Analyses

All secondary efficacy endpoints will be analyzed on the FAS population. Additional analyses may be performed on the PPS population, where noted.

6.3.1 Change from Baseline in HAM-A Total Score

In addition to the primary and key secondary analysis for HAM-A, descriptive statistics will be presented for actual values and change from Baseline for scheduled visits. The change from Baseline will be analyzed using an analysis of covariance (ANCOVA) model including change from Baseline HAM-A Total Score as dependent variable, the baseline HAM-A Total Score as a covariate and treatment group as a fixed effect. The Least Square Means (LS Means) for each treatment group compared to placebo will be reported along with associated 95% CI and p-value. The ANCOVA comparisons will be performed for Week 1, Week 2, Week 4, Week 8 and the End of Study visit and will be presented for both the FAS and PPS populations.

A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.2 Change from Baseline in MADRS Total Score

The MADRS consists of 10 questions to assess depression severity and change due to treatment. The questionnaire will be administered by the central rater after completion of the HAM-A. Each question is scored with a range of 0-6 points, with 0 indicating item is not present or is normal, and 6 indicating severe or continuous presence of the symptom. The Total Score, ranging from 0 to 60, is calculated by summing the 10 individual scores. A higher score represents a more severe condition.

Descriptive statistics, including 95% CIs for the mean, will be presented for actual values, change

and percent change from Baseline for scheduled visits for the FAS. The change from Baseline difference in means between each dose of MM-120 and placebo, 95% CI for the difference and corresponding p value from a two-sample t-test will be presented for Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.3 Change from Baseline in CGI-S

The CGI-S assesses the subject's current severity of illness at the time of the assessment, as assessed by the clinician and in reference to the clinician's past experience with patients having the same diagnosis. The CGI-S consists of one investigator-completed rating ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients); a higher score indicates a more severe illness.

Descriptive statistics, including 95% CIs for the mean, will be presented for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo, 95% CI for the difference and corresponding p value from a two-sample t-test will be presented for Day 2, Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.4 Post-Baseline CGI-I Assessment

The CGI-I measures the clinician's assessment of how the subject's illness has improved or worsened relative to baseline. The CGI-I consists of one investigator-completed rating ranging from 1 (very much improved since the initiation of treatment) to 7 (very much worse since the initiation of treatment), where a lower score indicates improvement, and a higher score indicates worsening.

Descriptive statistics, including 95% CIs for the mean, will be presented for actual values for scheduled visits. The difference in means between each dose of MM-120 and placebo, 95% CI for the difference and corresponding p value from a two-sample t-test will be presented for Day 2, Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.5 Change from Baseline in PGI-S

The PGI-S measures disease severity as a patient reported outcome. The PGI-S consists of one subject-completed rating ranging from 1 (none) – 5 (very severe), where a higher score indicates a more severe illness.

Descriptive statistics, including 95% CIs for the mean, will be presented for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo, 95% CI for the difference and corresponding p-value from a two-sample t-test will be presented for Day 2, Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.6 Post-Baseline PGI-C Assessment

The PGI-C measures change in clinical status as a patient reported outcome. The PGI-C consists

of one subject-completed rating ranging from 1 (much better) – 5 (much worse), where a lower score indicates improvement in symptoms and a high score indicates worsening symptoms.

Descriptive statistics, including 95% CIs for the mean, will be presented for actual values for scheduled visits. The difference in means between each dose of MM-120 and placebo, 95% CI for the difference and corresponding p-value from a two-sample t-test will be presented for Day 2, Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided.

6.3.7 Change from Baseline in SDS Total Score

The SDS will assess the extent to which 3 major domains (work, social life/leisure activities, and family life/home responsibilities) are functionally impaired. The SDS is a self-reported assessment with 5 questions. The Total Score is derived as the sum of the response to the first 3 questions, each ranging from 0 (not at all) to 10 (extremely). The Total Score ranges from 0-30, where a higher score indicates increased functional impairment. The last 2 questions are not included in the SDS Total Score.

Descriptive statistics, including 95% CIs for the mean, for the SDS Total Score will be presented for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo and 95% CI for the difference will be presented for Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit will be provided for all SDS responses and the Total Score.

6.3.8 Change from Baseline in EQ-5D-5L Index Values and VAS

The EQ-5D-5L will assess health outcomes over 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and the EuroQol visual analog scale (EQ VAS). Each dimension has 5 levels of response scored as: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. The five dimensions are combined to create a 5-digit code to represent the subject's health state. An EQ-5D-5L index value will be calculated by applying a formula that attaches a weight to each level in each dimension, using the US standard value set. The index is calculated by deducting the appropriate weights from 1, the value of full health. The resulting index value is a number between 0 (equivalent to dead) and 1 (full health). Missing data will not be imputed for analysis.

The frequency and proportion of subjects reporting each level for each of the 5 dimensions will be presented by visit. Changes over time will be presented using figures to present the frequency and proportion of subjects reporting each level for each of the 5 dimensions at baseline and each post-baseline measurement.

The EQ-5D-5L index values will be summarized by descriptive statistics, including 95% CIs for the mean, for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo and 95% CI for the difference in means will be presented for Week 4, Week 8 and the End of Study visit.

The EQ VAS will be summarized by descriptive statistics, including 95% CIs for the mean, for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo and 95% CI for the difference in means will be presented for Week 1, Week 2, Week 4, Week 8 and the End of Study visit.

A by-subject listing of all EQ-5D-5L measures and the EQ VAS will be presented by visit.

6.3.9 Change from Baseline in PSQI Global Score

The PSQI will assess sleep quality and disturbances for the previous month through 19 self-rated questions and 5 questions rated by the bed partner or roommate. The self-rated questions consist of 7 components:

- Subjective sleep quality
  - Component 1 Score = Question 6 Score (0-3)
- Sleep latency
  - To calculate Component 2 Score
    1. Assign score to Question 2 as:
       ≤ 15 minutes = 0
       16-30 minutes = 1
       31-60 minutes = 2
       > 60 minutes = 3
    2. Add score from Question 2 to response from Question 5a
    3. Assign this sum as score of:
       0 = 0
       1-2 = 1
       3-4 = 2
       5-6 = 3
- Sleep duration
  - To calculate Component 3 Score, assign score as follows:
    > 7 hours = 0
    6-7 hours = 1
    5-6 hours = 2
    <5 hours = 3
- Habitual sleep efficiency
  - To calculate Component 4 Score
    1. Calculate the number of hours spent in bed (Question 3 minus Question 1)
    2. Calculate Habitual Sleep Efficiency (HSE) as:

$$HSE\ (\%) = \frac{number\ of\ hours\ slept\ \{Response\ to\ Question\ 4\}}{Number\ of\ hours\ spent\ in\ bed} \times 100$$

    3. Assign score as follows:
       >85% = 0
       75-84% = 1
       65-74% = 2
       < 65% = 3
- Sleep disturbance
  - To Calculate Component 5 Score:
    1. Add the scores from Questions 5b to 5j
    2. Assign score as follows:
       0 = 0
       1-9 = 1

10-18 = 2
19-27 = 3

- Use of sleeping medication
  - Component 6 Score = response to Question 7
- Daytime dysfunction
  - To calculate Component 7 Score
    1. Add responses to Question 8 and Question 9
    2. Assign Score as follows:

0 = 0
1-2 = 1
3-4 = 2
5-6 = 3

To Calculate the Global PSQI score, add the seven component scores.

Each self-rated component has a Component Score ranging from 0-3 points, which are summed to calculate the Global Score with a range of 0-21. A Global Score of 0 indicates no difficulty, and a score of 21 indicates severe difficulty in all areas.

Descriptive statistics, including 95% CIs for the mean, for the PSQI Global Score will be presented for actual values and change from Baseline for scheduled visits. The change from Baseline difference in means between each dose of MM-120 and placebo and 95% for the difference will be presented for Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including any unscheduled visits, will be provided for all PSQI responses and the PSQI Global Score.

6.3.10 Change from Baseline in ASEX Total Score

The ASEX questionnaire measures sexual experience, with categories of sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each of the 5 items will be scored from 1-6 and the Total Score will be calculated by summing each component. The total score will range from 5 to 30. Higher scores indicate the presence of sexual dysfunction. Sexual dysfunction is defined as having a total score ≥ 19, or a score of ≥ 5 on any item, or a score of ≥ 4 on three items.

The number and proportion of subjects with sexual dysfunction will be presented by sex at birth and treatment group for each visit. The observed difference in the rates of sexual dysfunction between each dose of MM-120 and placebo, along with the 95% CI for the difference, will be presented by sex at birth for Week 1, Week 2, Week 4, Week 8 and the End of Study visit.

Descriptive statistics, including 95% CIs for the mean, for the ASEX Total Score will be presented for actual values and change from Baseline for scheduled visits by sex at birth. The change from Baseline difference in means between each dose of MM-120 and placebo and 95% CI for the difference will be presented for Week 1, Week 2, Week 4, Week 8 and the End of Study visit. A by-subject listing of results by visit, including sex at birth, will be provided for all ASEX responses and the Total Score.

6.4 Exploratory Endpoints and Analyses

The endpoints of Drug Effect VAS, MEQ30 and 5D-ASC will be measured to explore the dose response on drug effects, altered perception and mystical experience. To assess the blind integrity and to examine whether guess rates are associated with outcomes such as AEs or mood/anxiety, a treatment assignment question will be administered.

6.4.1 HAM-A Response and Remission

HAM-A response is defined as a decrease from Baseline by ≥ 50% in HAM-A Total Score in response to treatment, and a Total Score of ≤ 7 indicates a remission of symptoms. The number and proportion of subjects with response and with remission will be presented by treatment group for Week 1, Week 2, Week 4, Week 8 and the End of Study visit. The observed difference in the rates of response and remission between each dose of MM-120 and placebo, along with the 95% CI for the difference, will be presented for each visit.

6.4.2 Drug Effect VAS

The Drug Effect VAS will be administered on Day 2 to retrospectively assess the subject's perception of drug effects experienced during the dosing session. A series of single-item 100 mm VAS questions will be used to measure the extent to which the subject experienced each of the following:

- 'any drug effect'
- 'good drug effect'
- 'bad drug effect'
- 'drug liking'
- 'fear'
- 'nausea'
- 'alteration of vision'
- 'alteration of sense of time'
- 'the boundaries between myself and my surroundings seem to blur'

Descriptive statistics for each VAS score will be presented for actual values at Day 2. A by-subject listing of results be provided.

6.4.3 MEQ30

The MEQ30 will be administered on Day 2 to retrospectively assess the subject's mystical experience during the dosing session. The MEQ30 includes 30 self-rated questions with 4 subscales: mystical, positively mood, transcendence of time and space, and ineffability. Each of the 30 questions will be scored from 0 to 5 as:

0 = none; not at all
1 = so slight cannot decide
2 = slight
3 = moderate
4 = strong (equivalent in degree to any other strong experience)
5 = extreme (more than any other time in my life and stronger than 4)

The 4 subscales will be calculated as follows:

- Transcendence (%) = sum of transcendence questions / 30

  - Transcendence questions are those marked with a 'T' on questionnaire: 1, 7, 11, 13, 19, and 22
- Positive Mood (%) = sum of positive mood questions / 30
  - Positive Mood questions are those marked with a 'P' on questionnaire: 2, 8, 12, 17, 27, and 30
- Ineffability (%) = sum of ineffability questions / 15
  - Ineffability questions are those marked with an 'I' on questionnaire: 3, 10, and 29
- Mystical (%) = sum of mystical questions / 75
  - Mystical questions are those unmarked on questionnaire: 4, 5, 6, 9, 14, 15, 16, 18, 20, 21, 23, 24, 25, 26, and 28

The MEQ30 Total Score (%) will be calculated by summing all 30 questions and dividing by 150. A subject is considered to have had a 'complete mystical experience' when ≥60% of the maximum possible score is achieved on all 4 factor subscales.

Descriptive statistics for each of the 4 subscales and for the MEQ30 Total Score will be presented for actual values on Day 2. The number and percentage of subjects defined as having 'a complete mystical experience' will be provided. A by-subject listing will be provided for all MEQ30 responses, the 4 subscales and the MEQ30 Total Score.

6.4.4 5D-ASC

The 5D-ASC will be administered on Day 2 to retrospectively assess the subject's peak alteration of consciousness during the dosing session as compared with their normal waking consciousness. The 5D-ASC consists of 94 self-rated 100 mm VAS questions with anchors of 0 = 'no not more than usually' to 100 = 'yes more than usually'. The 94 items are combined into 5 subscales.

1. Oceanic boundlessness – summation of questions 1, 3, 9, 12, 16, 18, 26, 34, 35, 36, 40, 41, 42, 45, 50, 52, 57, 62, 63, 69, 71, 73, 81, 86, 87, 91, and 94. Maximum value = 2700.
2. Anxious ego dissolution – summation of questions 6, 8, 21, 27, 32, 38, 43, 44, 46, 47, 53, 56, 60, 64, 67, 78, 79, 80, 85, 88, and 89. Maximum value = 2100.
3. Visionary destructuralization – summation of questions 7, 14, 20, 22, 23, 28, 31, 33, 39, 54, 58, 70, 72, 75, 77, 82, 83, and 90. Maximum value = 1800.
4. Auditory alterations – summation of questions 4, 5, 11, 13, 19, 25, 30, 48, 49, 55, 65, 66, 74, 76, 92 and 93. Maximum value = 1600.
5. Vigilance reduction – summation of questions 2, 10, 15, 17, 24, 29, 37, 51, 59, 61, 68, and 84. Maximum value = 1200.

The 5D-ASC Total Score will be calculated as the sum of all the questions. The maximum value for the Total Score is 9400.

Descriptive statistics for each subscale and the total score will be presented for each treatment arm. A figure showing the percent of maximum value for each subscale and total score by treatment arm will be provided. A listing of the 5D-ASC subscales and Total Score will be provided.

6.4.5 Treatment Assignment/Blinding Question

On Day 2, subjects will be asked to indicate which sentence they agree with most, using a 5-point Likert Scale:

1 = I am positive I received active drug

2 = I think I received active drug

3 = I cannot tell whether I received active drug or placebo

4 = I think I received placebo

5 = I am positive I received placebo

The number and percentage of subjects reporting each level will be presented. Also, the number and percentage of subjects correctly reporting (levels 1 and 2 for active drug or levels 4 and 5 for placebo) their treatment assignments will be reported. A listing will be provided.

6.5 Subgroup Analyses

Descriptive statistics, including 95% CIs for the HAM-A Total Score change from **b**aseline at Week 1, Week 2, Week 4, Week 8 and End of Study will be provided by the following subgroups:

- Baseline HAM-A Total Score: ≤ median baseline value, > median baseline value
- Age: ≤35 years, > 35 years
- Sex: male, female
- Race: white, non-white

7 SAFETY ANALYSIS

Safety assessments include adverse events, laboratory parameters, vital signs, electrocardiograms, physical exams and the Columbia Suicide Severity Rating Scale (C-SSRS). All safety summaries will be conducted using the safety (SAF) population and will be presented by treatment group. No formal hypothesis testing will be performed to compare differences between treatment groups.

7.1 Extent of Exposure

Subjects will be dosed 1 time during this study, consisting of 8 capsules. Descriptive statistics for the total number of capsules taken will be provided by treatment group.

In addition, the number and percent of subjects (or '0' if no subjects encounter such an event) with any of the following special situations for study drug administration will be provided:

- Medication error or incorrect drug administration
- Overdose
- Deliberate abuse
- Drug interaction
- Occupational exposure
- Breastfeeding with suspected infant exposure
- Drug accountability issue

A listing of all subject exposure data will be provided.

7.2 Adverse Events

Adverse events (AE) will be collected starting at the time of informed consent until the End of Study visit on Week 12. An AE is defined as any untoward medical occurrence in a clinical trial subject. AEs will be analyzed for subjects in the SAF population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.2.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs starting during or after administration of the first dose of study drug. A determination of treatment emergence for AEs with missing or partial AE start dates and times will use a conservative approach that assumes treatment emergence when the true start time or date is unknown.

7.2.2 Adverse Event Severity

Severity describes the intensity of a specific adverse event. The Investigator will determine the severity of each AE according to the NCI CTCAE v5.0. AEs will be characterized as 'mild', 'moderate', 'severe', 'life-threatening', or 'death'.

7.2.3 Adverse Event Relationship to Study Medication

The Investigator will assign a relationship to each AE based on his/her determination of whether there exists a reasonable possibility that the IP caused or contributed to the AE. The AE relationship will be characterized as 'not related', 'unlikely related', 'possibly related', and 'definitely related'. For analysis purposes, AEs will be summarized by 'Related' (including 'possibly related' and 'definitely related') and 'Not Related ('unlikely related' and 'not related'). AEs with missing relationship will be considered to be 'Related' events.

7.2.4 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that meets at least one of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in a disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

7.2.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as a subset of AEs that are suggestive of abuse potential and any special situations defined in Section 9.9 of the protocol that have an associated AE. The following MedDRA Preferred Terms will be used to classify AESIs related to abuse liability:

- Euphoria-related terms: Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate

affect.

- Terms indicative of impaired attention, cognition, and mood: Somnolence; Mood disorders and disturbances.
- Dissociative/psychotic terms: Psychosis; Aggression; Confusion and disorientation.
- Overdose- / Misuse-related terms not captured elsewhere: Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders.

7.2.6 Adverse Event Summaries

AEs (serious and non-serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

For treatment-emergent AEs (TEAEs) occurring during the entirety of the study, the following will be summarized and presented for the SAF set:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE by strongest relationship to study drug
   c. the number and percentage of subjects experiencing a TEAE by greatest severity
   d. the number and percentage of subjects experiencing a TEAE with NCI CTCAE grade 3 or higher
   e. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)
   f. the number and percentage of subjects experiencing a treatment emergent AESI
   g. the number and percentage of subjects experiencing a TEAE leading to study withdrawal
   h. the number and percentage of subjects experiencing a TEAE leading to death

ii. the number and percentage of subjects experiencing a TEAE by SOC and PT

iii. the number and percentage of subjects experiencing a TEAE by PT in overall descending order

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the highest severity

v. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to study drug

vi. the number and percentage of subjects experiencing a TESAE by SOC and PT

vii. the number and percentage of subjects experiencing a TESAE by PT in overall descending order

viii. the number and percentage of subjects experiencing a TESAE by strongest relationship to study drug

ix. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

x. the number and percentage of subjects experiencing a TEAE leading to study death by SOC and PT

xi. the number and percentage of subjects experiencing a treatment emergent AESI by SOC and PT

Additionally, two tables, the incidence by severity of TEAE by SOC and PT (ii), and the incidence by severity of TESAE by SOC and PT (vi), will also be presented separately for AEs starting on Study Day 1 (dosing day) and for those AEs starting post Study Day 1. For AEs starting on Day 1 (dosing day) the duration, in days, will be summarized by descriptive statistics.

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the Safety Analysis set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each subject, grouped by treatment group. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity, relationship to study medication, date and day of onset, date and day of resolution, action taken, the outcome, and whether the event was an SAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates. Additional listings of SAEs, AEs leading to Study Withdrawal, and Subject Deaths will be provided.

7.3 Clinical Laboratory Assessments

Clinical laboratory tests in chemistry, hematology and urinalysis will be performed throughout the study according to the schedule of assessments. The laboratory will also provide eGFR, calculated using the CKD-EPI formula. Descriptive statistics for actual values and change from Baseline values for laboratory tests will be presented for each scheduled measurement. The number and percentage of subjects with values beyond the laboratory normal ranges will be summarized by frequency tables and shift tables. A by-subject listing, including flags for abnormal or out-of-range values, will be provided. The laboratory tests to be performed are listed in Table 5.

Table 5 Clinical Laboratory Parameters with Standard Units

Serum Chemistry Panel	**Units**
Albumin	g/L
Total protein	g/L
Alkaline phosphatase	U/L
ALT	U/L
AST	U/L
Bicarbonate	mmol/L
Bilirubin, total	umol/L
Bilirubin, direct	umol/L
Blood urea nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	umol/L
Creatinine clearance	mL/s
FSH	U/L
GGT	U/L
Glucose	mmol/L
Lactate dehydrogenase	U/L
Cholesterol	mmol/L
HDL	mmol/L
LDL	mmol/L
Triglycerides	mmol/L
Phosphorus	mmol/L
Potassium	mmol/L
Sodium	mmol/L
TSH	mU/L
Free T4	mmol/L
eGFR	mL/min/1.73m^2

Hematology and Coagulation	**Units**
Hemoglobin	g/L
Hematocrit	%
Red blood cell count	x10^12/L
White blood cell count	x10^9/L
MCV	fL
MCH	pg
MCHC	g/L
RDW	%
Platelet count	x10^9/L
MPV	fL
Basophils	%
Eosinophils	%
Lymphocytes	%
Monocytes	%
Neutrophils	%

Urinalysis	**Units**
Protein	n/a
Glucose	n/a
Ketones	n/a
Bilirubin	n/a
pH	n/a
Nitrites	n/a
Specific gravity	n/a
Urobilinogen	n/a
Leukocyte Esterase	n/a

Microscopic Urine	**Units**
Bacteria	n/a
RBC	n/a
WBC	n/a
Epithelial cells	n/a
Casts	n/a
Crystals	n/a

7.4 Vital Signs

Descriptive statistics for actual values and change from Baseline values for vital signs will be presented for each scheduled measurement. Vital sign parameters include:

- height (cm, measured only at baseline)
- weight (kg)
- BMI (kg/m^2)
- systolic and diastolic blood pressure (mmHg)
- heart rate (beats per minute)
- temperature (°C)
- respiratory rate (breaths per minute)
- orthostatic blood pressure (mmHg)
- standing pulse (bmp)

Measurements from unscheduled visits will be excluded from the analyses but will be included in the data listings.

7.5 ECG

Electrocardiogram (ECG) measures will be collected at screening, Baseline and the Day 2 visit. The number and percent of ECG findings of normal; abnormal, not clinically significant; and abnormal, clinically significant will be presented for each scheduled measurement. The following ECG interval measurements will be summarized by presenting descriptive statistics of actual values and change from baseline values at each scheduled visit:

- PR Interval (ms)
- QRS Duration (ms)
- Ventricular Rate (bpm)
- QT Interval (ms)
- RR Interval (ms)
- QTcF Interval (ms)

Listings will include measurements at each scheduled visit as well as any unscheduled visits.

7.6 Physical Examination

The number and percentage of subjects with physical examination findings of normal and abnormal at each visit will be summarized and presented for each body system. A listing of physical examination findings will also be provided.

7.7 C-SSRS

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses a subject's suicidal ideation (severity and intensity) and behavior. The C-SSRS has 11 categories: 5 subtypes of suicidal

ideation, 5 subtypes of suicidal behavior and 1 subtype of self-injurious behavior without suicidal intent. All responses are binary (yes/no).

The number and percent of subjects answering 'Yes' to each of the 11 categories will be provided for each scheduled time point. No statistical comparisons between treatment groups will be performed. A by-subject data listing will be provided.

8 INTERIM ANALYSIS AND CHANGES FROM PROTOCOL

No formal interim analysis was planned for the study.

During the conduct of the study, a Sponsor decision was made to perform the analysis of the primary endpoint when all enrolled subjects reached their Week 4 visit. The approximately 180 subjects will provide adequate power to determine the dose-response relationship as defined in the primary objective of the study. No further subjects will be enrolled, and the study will continue to its normal conclusion.

This 'Top-Line' analysis will be the final analysis for the HAM-A primary endpoint at Week 4, HAM-A response and remission through Week 4, HAM-A change from baseline through Week 4, MADRS change from baseline through Week 4 and CGI-S through Week 4. Preliminary analysis of Subject Disposition, and Adverse Events will be provided as well. As this will be the final analysis for the select efficacy endpoints through Week 4, this is not considered an interim analysis and no adjustment to the overall alpha level of the trial is needed.

At the time of analysis, data for the select efficacy analyses through Week 4 will be cleaned and locked in the clinical trial database according to the Data Management Plan. Supporting data for the preliminary analyses will be cleaned and frozen, and a snapshot of the database taken.

A pre-defined unblinded statistician and programmer, not involved with the conduct of the study, will perform this analysis. The Study team will remain blinded through the completion of the study. The topline results for the primary endpoint will not be available to the Study Team or externally until the final subject has completed their last visit assessment.

The remaining secondary efficacy analyses and final safety analyses will be conducted at the completion of the trial.

9 SAMPLE SIZE AND POWER CALCULATIONS

A total sample of 180 subjects, 36 per arm, is required to ensure a mean power >87% for an MCP-Mod Analysis rejecting the hypothesis of a constant dose-response curve using the multiple comparisons procedure (MCP), assuming a null placebo response, a maximum standardized effect of 0.6 within the doses range, and a common standard deviation within the dose arms, if a study-wise one-sided type-1 error rate <0.05 is required.

The analysis assumes 4 doses of active medication (25, 50, 100 and 200 μg freebase-equivalent) and placebo. The required sample size for each arm is 36 subjects.

The R package Dose Finding (https://CRAN.R-project.org/package=DoseFinding) has been used to estimate the sample size and corresponding power. The power for each model is estimated as shown Table 6.

Table 6 Power by Model

Model	**Power (%)**
Sigmoid Emax (ED50, hill)	
10, 1	84.5
100, 5	90.7
100, 10	91.0
150, 10	89.9
Emax (D50 = 100)	83.2
Linear	85.0

10 REFERENCES

1. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

11 APPENDICES

11.1 Appendix A

Table 11-1 MMED008 Schedule of Activities

STUDY PERIOD	Optional Prescreen	SCREENING	BASELINE & DOSING			FOLLOW-UP					
Visit	**Prescreen**	**Screening[a]**	**Baseline**	**Day 1** Randomization (3A) & Dosing Session (3B)		**Day 2**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 (or Early WD)/EOS**
Visit Number	**N/A**	**1**	**2**	**3A**	**3B**	**4**	**5**	**6**	**7**	**8**	**9**
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Administrative Procedures											
Prescreen Informed Consent	X										
Informed consent		X									
Demographics	X	X									
Eligibility assessment		X	X	X							
Medical psychiatric and medication history[d]	X	*Medical/psychiatric and medication history will be collected via interview at Screening [Visit 1] if information about the medical/psychiatric and medication history is learned during the course of the study, this will also be recorded, even if first learned after Screening [Visit 1].*									
Medication taper (if applicable)		X									
Concomitant medication & non-medicinal therapy collection	X	*Medications/non-medicinal therapies used at Baseline [Visit 2] or any time after, including those taken between visits, regardless of whether the subject is on the medication/therapy at the time of the site visit, will be recorded in the designated CRF. Medications/therapies stopped prior to Baseline [Visit 2] are recorded in medication history.*									
Randomization				X							
Clinical Procedures/Assessments											
Physical examination		X				X					X
Neuropsychiatric examination			X			X	X	X	X	X	X
Vital signs[e] (BP, heart rate, respiration rate, temperature)		X	X	X[f]	X	X	X	X	X	X	X
Weight	X[g]	X									
Height	X[g]	X									
BMI	X	X									
12-lead safety ECG		X	X			X					
Adverse event collection		*AEs are evaluated from the time informed consent is given until completion of the study and captured at each visit. Events occurring between signing of the informed consent form and dosing with study drug will be recorded on the medical history page of the eCRF. Events occurring from the time study drug is administered through EOS will be recorded on the AE page of the eCRF.*									

STUDY PERIOD	**Optional Prescreen**	**SCREENING**	**BASELINE & DOSING**			**FOLLOW-UP**					
Visit	**Prescreen**	**Screening[a]**	**Baseline**	**Day 1** Randomization (3A) & Dosing Session (3B)		**Day 2**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 (or Early WD)/EOS**
Visit Number	**N/A**	**1**	**2**	**3A**	**3B**	**4**	**5**	**6**	**7**	**8**	**9**
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Laboratory Procedures/Assessment											
Blood sample collection for biobanking (DNA)				X *If the subject gives informed consent to provide a pharmacogenomic sample, collect a sample once during the study, preferably at Day 1/Randomization [Visit 3A].*							
Blood sample collection for safety laboratory assessments		X	X			X	Opt[h]	Opt[h]	X	X	X
[redacted]											
Urine pregnancy test (if applicable)		X		X			X	X	X	X	X
Serum pregnancy test (if applicable)			X								
Screening and Efficacy Questionnaires											
Placebo Script Review			X						X	X	
MINI	X	X									
C-SSRS Baseline/ Screening Version		X									
C-SSRS- SLV Version			X	X	X[k]	X	X	X	X	X	X
HAM-A (central rater)		X	X				X	X	X	X	X
MADRS (central rater)		X	X				X	X	X	X	X
CGI-S		X	X			X	X	X	X	X	X
CGI-I						X	X	X	X	X	X
PGI-S		X	X			X	X	X	X	X	X
PGI-C						X	X	X	X	X	X
SDS		X	X				X	X	X	X	X
EQ-5D-5L			X				X	X	X	X	X
PSQI			X						X	X	X
ASEX			X				X	X	X	X	X
Drug Effect VAS						X					
MEQ30						X					
5D-ASC						X					
Treatment assignment / blinding question						X					

STUDY PERIOD	Optional Prescreen	SCREENING	BASELINE & DOSING			FOLLOW-UP					
Visit	**Prescreen**	**Screening[a]**	**Baseline**	**Day 1** Randomization (3A) & Dosing Session (3B)		**Day 2**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 (or Early WD)/EOS**
Visit Number	**N/A**	**1**	**2**	**3A**	**3B**	**4**	**5**	**6**	**7**	**8**	**9**
Timing or Permitted Window	none	Up to 30 days prior to Baseline	1-5 days prior to Day 1[b, c]	Pre-dose	Dosing & post-dose	1 day after dosing	Day 8 ± 1 day	Day 15 ± 3 days	Day 29 ± 3 days	Day 57 ± 5 days	Day 85 ± 5 days
Dosing-Related Activities[l]											
Administration of study drug					X						
Subject education / follow-up session with both DSMs			X	X		X	X	X			
Subject under observation by both DSMs					X						
Subject dosing day release from clinic/ Dosing Release Checklist					X						

5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; AE: adverse event; ASEX: Arizona Sexual Experiences Questionnaire; AUDIT: Alcohol Use Disorders Identification Test; BP: blood pressure; BMI: body mass index; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; C-SSRS (– SLV): Columbia-Suicide Severity Rating Scale (– Since Last Visit); DUDIT: Drug Use Disorders Identification Test; ECG: electrocardiogram; eCRF: electronic case report form; EOS: End of Study; ICF: informed consent form; MADRS: Montgomery-Åsberg Depression Rating Scale ; MEQ30: Mystical Experience Questionnaire; MINI: Mini-International Neuropsychiatric Interview; PGI-C: Patient Global Impression – Change; PGI-S: Patient Global Impression – Severity; PSQI: Pittsburgh Sleep Quality Index; SDS: Sheehan Disability Scale; HAM-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; THC: tetrahydrocannabinol; VAS, visual analogue scale; WD: Withdrawal

[a] Screening (Visit 1) assessments may be performed over multiple days

[b] If Baseline labs are needed, a minimum of 48 hours is required prior to Day 1 to allow for all eligibility assessment results to be reviewed to confirm subject eligibility

[c] If the Baseline occurs within 14 days of Screening, Baseline labs are not required, and Dosing Session day (Visit 3B) may occur within 24 hours of the Baseline Visit

[d] Sites should make an effort to obtain, at minimum, pharmacy records for subjects, and medical and /or psychiatric records

[e] Vital signs should be performed prior to an ECG and/or a blood draw; Screening and Baseline vital signs require sitting, lying, and standing vital signs in order to capture orthostatic vitals.

[f] On Day 1 (Visit 3A), the pre-dose vital signs (blood pressure, heart rate, respiration rate, and temperature) should be measured within 1 hour (+/- 15 mins) prior to study drug dosing. Note: Only BP and Temperature at Visit 3A will be used to confirm final eligibility against inclusion/exclusion criteria

[g] Weight and height may be estimated during a remote Prescreen session but should be physically measured once the subject is on-site to determine eligibility

[h] Safety laboratory assessments are optional at Week 1 (Visit 5) and Week 2 (Visit 6) unless values at the prior visit were clinically significant and warrant follow up

[redacted]

[k] The Day 1/Dosing Session (Visit 3B) C-SSRS will be performed any time after 12 hours post dose and prior to the subject being released from the site

[l] Refer to section 8.6 and the Dosing Session Monitor Manual for full details of subject education and follow-up sessions with DSMs

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A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms

Protocol Number:	MMED008
Protocol Version:	6.0
Protocol Date:	26 July 2023

STATISTICAL ANALYSIS PLAN - ADDENDUM

Version 1.0

A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms

STATISTICAL ANALYSIS PLAN - ADDENDUM

Final Version 1.0

[redacted]

SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol version 6.0 (26Jul2023). The following table details the changes made to the SAP and/or addendum.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
1.0	All	Initial document	
Addendum	All	Initial Addendum document	Added safety and efficacy analysis after the Primary Efficacy Analysis was performed

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1 INTRODUCTION

This statistical analysis plan (SAP) addendum describes the planned statistical analysis to be performed for the study, MMED008 entitled "A Phase 2, Multi-center, Randomized, Double-Blind, Parallel-Group, Dose-Finding Study to Assess the Effect of Four Doses of MM-120 for the Treatment of Anxiety Symptoms." [redacted] has been engaged by Mind Medicine, Inc. (the 'sponsor') to develop the SAP and carry out the statistical analysis described in this SAP Addendum, including production of all tables, figures and listings.

This SAP addendum details statistical analyses that were added to the study after the unblinded review of the Primary Efficacy Endpoint. Thus, these analyses were not pre-planned in the protocol or SAP and are considered ad-hoc. This addendum contains no changes to the original pre-planned analyses contained in the final SAP, version 1.0 dated 01Aug2023.

2 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Summary results will be provided by treatment group and where appropriate overall for all subjects. All tabulations will be based on pooled data across centers.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

[redacted] will perform all efficacy and safety statistical analyses.

2.1 Analysis Quality Control Procedures

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to [redacted] for final analysis.

All SAS programs used to create analysis data sets, tables, and listings will be double programmed. The SAS outputs will be compared, and the programs will be updated until the outputs match.

2.2 Analysis Sets

The analysis sets defined in the Final SAP version 1.0, dated 01Aug2023 will be used for all analyses in this addendum.

2.3 Assessment Windows

The assessment windows defined in the Final SAP version 1.0, dated 01Aug2023 will be used for all analyses in this addendum.

2.4 Handling of Dropouts or Missing Data

Missing data will not be imputed for analysis of non-key secondary efficacy endpoints or safety endpoints.

2.5 Multiple Comparisons

No adjustment for multiplicity will be performed for testing the non-key secondary and exploratory endpoints.

2.6 Data Derivations and Transformations

Data derivations and transformations defined in the Final SAP version 1.0, dated 01Aug2023 will be used for all analyses in this addendum.

3 EFFICACY ANALYSIS

3.1 Change from Baseline in HAM-A Subscales – Somatic Anxiety and Psychic Anxiety

Two subscales will be defined from the HAM-A questionnaire.

Somatic Anxiety is defined as the sum of items 7 – 13 of the HAM-A questionnaire.

Psychic Anxiety is defined as the sum of items 1 - 6, and item 14 of the HAM-A questionnaire.

Descriptive statistics will be presented for actual values and change from Baseline for scheduled visits for the FAS and PPS analysis populations. The change from Baseline will be analyzed using an analysis of covariance (ANCOVA) model including change from Baseline HAM-A Somatic Anxiety, or Psychic Anxiety, score as dependent variable, the baseline HAM-A Somatic Anxiety, or Psychic Anxiety, score as a covariate and treatment group as a fixed effect. The Least Square Means (LS Means) for each treatment group compared to placebo will be reported along with associated 95% CI and p-value. The ANCOVA comparisons will be performed for Week 1, Week 2, Week 4, Week 8 and the End of Study visit and will be presented for both the FAS and PPS populations.

4 SAFETY ANALYSIS

All safety summaries will be conducted using the safety (SAF) population and will be presented by treatment group. No formal hypothesis testing will be performed to compare differences between treatment groups.

4.1 Adverse Events

Adverse events (AE) will be collected starting at the time of informed consent until the End of Study visit on Week 12. An AE is defined as any untoward medical occurrence in a clinical trial subject. AEs will be analyzed for subjects in the SAF population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

4.1.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs starting during or after administration of the first dose of study drug. A determination of treatment emergence for AEs

with missing or partial AE start dates and times will use a conservative approach that assumes treatment emergence when the true start time or date is unknown.

4.1.2 Adverse Event Summaries

AEs (serious and non-serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

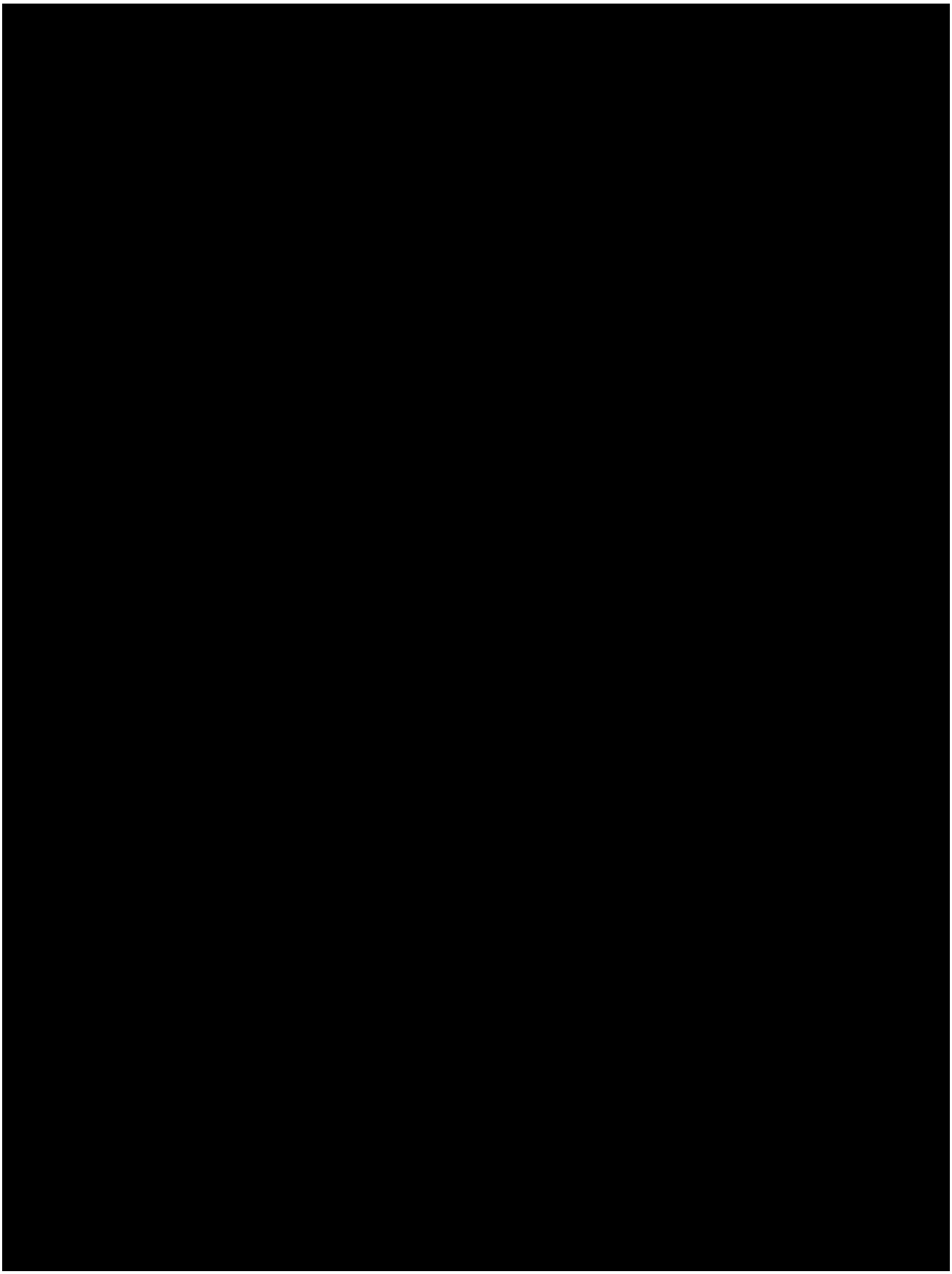
For treatment-emergent AEs (TEAEs) occurring during the entirety of the study, the following will be summarized and presented for the SAF set:

- The incidence of TEAEs occurring on dosing day by PT and severity
- The incidence of TEAEs occurring post dosing day by PT and severity
- The incidence of TEAEs occurring on dosing day by PT and relationship
- The incidence of TEAEs occurring post dosing day by PT and relationship
- The incidence of TEAEs occurring on dosing day and post dosing day by PT

The incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the Safety Analysis set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables for severity and relationship.

[redacted]

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