Statistical Analysis Plan MP-101-01(b)

Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Patients with Dementia-Related Psychosis and/or Agitation and Aggression

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Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Patients with Dementia-Related Psychosis and/or Agitation and Aggression

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ABBREVIATIONS/DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
CRP	Clinical Research Physician
CSR	Clinical Study Report
C–SSRS	Columbia Classification Algorithm for Suicide Assessment
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
Interim Analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked
ITT	Intent-to-Treat
IWRS	Interactive Web-Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Exam
NPI	Neuropsychiatric Inventory
PK	Pharmacokinetics
PT	Preferred Term
QD	Once daily (quaque die)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TUG	Timed Up and Go
UPDRS Part III	Unified Parkinson's Disease Rating Scale, Part III
WHODD	World Health Organization Drug Dictionary
ZBI-22	Zarit Burden Interview - 22

1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

Study MP-101-01(b) is a Phase 2, multicenter, double-blind, 1:1 randomized, parallel, placebo-controlled, 10-week study of MP-101, consisting of screening, treatment, and follow-up periods, in patients with dementia-related psychosis and/or agitation and aggression.

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol MP-101-01(b), which was approved on 13 February 2017.

Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP.

The formats for the tables, listings, and figures described in this SAP are provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the clinical study report (CSR).

See the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

The time and events schedule for this study is provided in Section 9.

EMB Statistical Solutions will have responsibility for performing these analyses.

1.2. Study Objectives and Endpoints

Table 1 shows the objectives and endpoints of the study.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To test the hypothesis that oral administration of once daily (QD) MP-101 will improve psychotic symptoms and/or agitation and aggression in patients with dementia when compared to	Change from baseline to 10-week treatment endpoint in the Neuropsychiatric Inventory (NPI)-Psychosis subscale (combination of 2 items: hallucinations and delusions) and/or in the agitation/aggression domain.

Objectives	Endpoints
placebo.	
Secondary	
To assess whether MP-101 is superior to placebo in the following: neuropsychiatric disturbances, caregiver distress, and anxiety.	Change from baseline to 10-week treatment endpoint in the following: Clinical Global Impression of Improvement (CGI-I); NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress; NPI domain of anxiety.
To determine if MP-101 is safe and tolerable.	Treatment-emergent adverse events (TEAES); Unified Parkinson's Disease Rating Scale (UPDRS) Part III.
To assess the PK of MP-101 and its primary active metabolite, LY2812223.	Plasma PK concentrations.
Exploratory	
To assess whether MP-101 is superior to placebo in changes in patient behavior and care-giver burden.	Change from baseline to 10-week treatment endpoint in the following: NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; Mini-Mental State Examination (MMSE); Zarit Burden Interview-22 (ZBI-22).
To explore the effect of HTR2A and ApoE genotypes on response to treatment.	5-hydroxytryptamine serotonin 2A receptor (HTR2A) single nucleotide polymorphism (SNP) rs7330461 genotype data; HTR2A SNP rs6313 (102T/C) genotype data; ApoE genotype data.
To explore exposure-response relationships with efficacy and safety clinical endpoints, as needed.	Efficacy and safety clinical endpoints, as needed.

1.3. Definition of NPI Response and Core Total Response

NPI response will be defined using two NPI endpoints: 1) the psychosis domain score, calculated as the sum of the delusions and hallucinations domain scores, and 2) the aggression/agitation domain score. Each domain score is the product of the severity and frequency ratings.

A patient with a 30% improvement from baseline on a subscale will be considered a responder for that subscale. At baseline, patients will be given a diagnosis of psychosis and/or agitation/aggression. A patient with a psychosis diagnosis will be considered an overall responder with a response on the psychosis subscale, a patient with a diagnosis of aggression/agitation will be considered an overall responder with a response on the aggression/agitation subscale, and a patient with both diagnoses will be considered an overall responder with a response on either subscale.

The delusions, hallucinations, and aggression/agitation domain scores will be added together to form a Core Total score. A patient with a 30% improvement from baseline will be considered a responder on the Core Total score.

1.4. Sample Size Determination

Approximately 100 patients will be enrolled to enable approximately 80 evaluable patients to complete the study through at least Visit 5 (Week 4).

The primary analysis will use a one-sided Fisher's exact test with a 5% type 1 error rate.

If the NPI response rate in MP-101 treated patients is 30% greater than in placebo treated patients (65% vs 35%), with 40 evaluable patients per treatment group there is at least an 80% chance (i.e. Power) that MP-101 will demonstrate superiority to placebo.

The sample size was calculated assuming an expected 20% drop-out rate of patients in each arm prior to Week 4, so that 100 patients are planned to be enrolled to arrive at 40 patients/arm (N=80) in the Evaluable population.

2. GENERAL STATISTICAL METHODOLOGY AND CONVENTIONS

2.1. General Considerations

All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Before implementation of parametric methods of analysis, the distribution of analysis variables will be examined to determine if model assumptions are satisfied. Transformations or nonparametric methods of analysis may be used if warranted. However, in some cases, nonparametric analysis may be the initially proposed method due to the expected distribution of response. Whenever alternative methods of analysis are required, the description of the new method along with the rationale for its use will be documented in the Clinical Study Report (CSR).

Data listings will be sorted by treatment group, investigative site, and patient identification number, and patients will be identified in the listings by the investigator number concatenated with the patient number.

Some patients were enrolled under protocol MP-101-01(a). These patients completed the Cohen-Mansfield Agitation Inventory questionnaire, Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory, and Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change. These questionnaires were removed from MP-101-01(b). Data from these questionnaires will not be included in tables, listings, or figures but SDTM/AdAM datasets will be created. For the remaining instruments, assessments were discontinued at some visits. Data collected at these visits will be included in listings, but summary tables will only include the scheduled assessments under the current protocol.

2.2. Randomization and Unblinding Plan

Cenduit LLC will be responsible for the system that randomly assigns study treatments to patients. Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Randomization will be stratified by baseline MMSE score and eGFR value:

- MMSE < 16 or MMSE ≥ 16
- eGFR < 60 or eGFR ≥ 60

Members of the Assessment Committee and unblinded teams will gain access to unblinded data, prior to the final database lock, in order to perform the interim analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members (including Mediti Pharma, Inc. personnel) until the study and all data management activities have been completed at the end of the trial, unless there is information study sites need to know for the safety of their patients. Members of the Assessment Committee or unblinded teams will not disseminate any information derived from its privileged access to the data without the prior written approval of Mediti Pharma, Inc.

The investigator may determine that unblinding of a patient's treatment assignment during the trial is warranted for medical management of the patient. However, if it is decided that unblinding is warranted, every effort should be made to contact the Chorus clinical research physician (CRP) prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded for the investigator, Chorus must be notified immediately and the patient must be discontinued from the study, unless the investigator obtains specific approval from the Chorus CRP for the study participant to continue in the study. Emergency unblinding to the investigator for adverse events may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's ultimate well-being requires knowledge of the patient's treatment assignment.

Analyses will not include patient's data collected after the time of unblinding. Sensitivity analyses that include these data may be performed depending on how much of this data there is.

Cenduit LLC is responsible for making the randomization file available to the unblinded interim analysis team at EMB Statistical Solutions. After the last patient completes the study and all data management

data activities have been completed – data entered, coding completed, and all queries resolved – the Chorus Asset Manager or designee and Study Statistician will approve the unblinded interim analysis reporting team at EMB Statistical Solutions to release the randomization schedule.

A list of individuals who become unblinded prior to study completion will be maintained by the Assessment Committee chairperson, the Asset Manager, and/or the unblinded statistician at EMB Statistical Solutions and will be placed in the final Study Trial Master Files.

2.3. Analysis Populations

The analysis populations are described in Table 3.

Table 3. Analysis Populations

Population	Description
Randomized	All randomized patients who sign informed consent.
Safety	All randomized patients who take at least 1 dose of double-blind study treatment. In the event of a treatment error, patients will be analyzed according to the treatment they actually received.
Intent-to-Treat (ITT)	All randomized patients who take at least 1 dose of double-blind study treatment and have at least one post-baseline efficacy assessment. In the event of a treatment error, patients will be analyzed according to the treatment to which they were randomized.
Evaluable	All patients in the Intent-to-Treat population who complete at least Visit 5 (Week 4) with NPI efficacy scores. Specifically, patients with a diagnosis of psychosis must have at least one psychosis sub-scale score at Visit 5 or later and patients with a diagnosis of agitation/aggression must have at least one agitation/aggression sub-scale score at Visit 5 or later.

2.4. Treatment Groups

The primary analyses will be performed with patients grouped by treatment arm (i.e. MP-101 or placebo) regardless of their final dose level.

Patients will be randomized to the MP-101 or placebo arm at Visit 2 (Week 0). Patients in the MP-101 arm will begin dosing at 20 mg once daily (QD) of study drug. If in the opinion of the investigator the patient cannot tolerate the initial 20-mg QD dose of study drug (administered for the first week of dosing and assessed at or before Visit 3 [Week 1]), the patient will be discontinued from the study. Study drug intolerance will be determined by the investigator and includes treatment-emergent adverse events (TEAEs) of special interest identified from prior studies, e.g. dizziness, nausea, and vomiting.

At Visit 3 (Week 1), the dose of MP-101 (or equivalent placebo) will be increased to 40 mg. If intolerance is reported at a dose of 40 mg between Visit 3 (Week 1) and Visit 4 (Week 2), the patient will be discontinued from the study.

At Visit 4 (Week 2), the dose of MP-101 (or equivalent placebo) will be increased to 60 mg. If intolerance is reported at a dose of 60 mg between Visits 4 (Week 2) and Visit 5 (Week 4), the patient will be asked to return for an unscheduled visit for down-titration to 40 mg. Patients down-titrated to 40 mg prior to Visit 5 (Week 4) will remain at this dose for the remainder of the study.

At Visit 5 (Week 4), the dose of MP-101 (or equivalent placebo) will be maintained at 60 mg. If intolerance is reported at a dose of 60 mg at Visit 5 (Week 4), the patient will be down-titrated to 40 mg and will remain at this dose for the remainder of the study. If intolerance is reported at a dose of either 40 mg or 60 mg beyond Visit 5 (Week 4) the patient will be discontinued from the study.

2.5. Definition of Baseline Assessments

Day 0 (Week 0) is defined in this study as the day of Visit 2. The last assessment made before the first dose of study drug will be defined as the Baseline assessment. This should include all assessments made on or before Day 0. Adverse events that occurred on Day 0 will be assumed to be treatment-emergent, unless the eCRF records that the event started prior to the first dose of study drug.

2.6. Definition of Study Visit

Patient data will be analyzed according to the nominal visit collected in the eCRF. Unscheduled visits at which safety data is collected (e.g. labs and ECGs) may result in clinically significant findings or withdrawal, which will be included in adverse event and/or disposition summaries.

2.7. Handling of Dropouts and Missing Data

Dates

Imputation of missing or partial dates is not expected, but if a complete date is required for calculations, the following algorithms will be applied:

- For the start date:
  - If year, month, and day are missing then use the minimum of the patient's first visit date or the consent date.
  - If either only month or month and day are missing then use January 1.
  - If only day is missing, impute the first day of the month.
- For the end date:
  - If year, month, and day are missing then use the patient's last visit date.
  - If either only month or month and day are missing then use December 31.
  - If only day is missing then use the last day of the month.
  - Do not expand the record past the patient's last visit.

The original missing or partial date, the imputed complete date, and the indicator variable that indicates which dates were imputed will be retained in the database.

NPI Response

Patients whose response to treatment cannot be determined due to missing data (including early withdrawal) will be considered non-responders.

2.8. Adjustment for Multiplicity

There are no planned adjustments for multiple efficacy endpoints or analyses.

2.9. Adjustment for Multiple Centers

Differences between study centers will be not be incorporated into the statistical analyses for this study. There are no plans to analyze data within centers.

2.10. Adjustment for Covariates

Where possible, analyses will adjust for the baseline value of the endpoint and by the four baseline randomization strata, i.e.:

- MMSE < 16, eGFR < 60
- MMSE < 16, eGFR ≥ 60
- MMSE ≥ 16, eGFR < 60
- MMSE ≥ 16, eGFR ≥ 60

2.11. Subgroup Analyses

Subgroup analyses based on diagnosis (i.e. Psychosis and Agitation/aggression) at baseline will be performed for the NPI response rate. Other subgroup analyses may be performed. For purposes of analysis, a patient's baseline NPI scores will be used for diagnosis.

Specifically, a patient will be included in the Psychosis subgroup if at least ONE of the following is true at baseline:

- NPI score of ≥ 4 on either delusions or hallucinations individual items
- NPI score of ≥ 6 on the Psychosis Subscale (combined delusions and hallucinations)

A patient will be included in the Agitation/aggression subgroup if the following is true at baseline:

- NPI score of ≥ 4 on agitation/aggression domain

A patient can be in both subgroups.

2.12. Coding of Concomitant Medications and Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The versions of the dictionaries used for reporting will be provided in the CSR.

2.13. Computation of Questionnaire Scores

Neuropsychiatric Inventory (Cummings et al. 1994)

Ten behavioral and 2 neurovegetative areas (i.e. domains) are included in the NPI: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders and appetite and eating disorders. An initial question assesses the 10 items and 2 neurovegetative evaluations of the scale. If the answer to the initial question is 'no', no further questions are pursued. If the answer is 'yes', sub questions are asked; ratings of the frequency and severity of the behavior(s) are determined by the caregiver according to the criteria provided with each behavior. Distress induced in the caregiver by each behavior is also rated. Therefore, a total of 3 scores are recorded for each behavior type: frequency, severity, and caregiver distress. A domain score will be computed as the product of the frequency and severity scores. A domain score will only be computed if the frequency and severity scores are non-missing.

The psychosis domain score will be calculated as the sum of the delusions and hallucinations domain scores. If either domain score is missing, the psychosis domain score will be set to missing.

The 10-item Total score will be calculated as the sum of all individual NPI domain scores, except for the sleep and appetite domains. If any individual domain score is missing, the Total score will be set to missing.

Clinical Global Impression of Improvement (Guy, 1976)

The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to baseline (Visit 2). The scale ranges from 1=very much improved to 7=very much worse.

Mini-Mental State Examination (Folstein et al., 1975)

The MMSE is a simple, 30-question, pen-and-paper test that evaluates attention, orientation, memory, registration, recall, calculation, language, and the ability to draw a complex polygon. The range for the total MMSE score (i.e. the total number of correctly answered items) is 0 to 30, with lower scores indicating greater impairment. If any individual item is missing, the MMSE score will be set to missing.

Unified Parkinson's Disease Rating Scale Part III (Fahn, 1987)

Part III of the UPDRS is an investigator-scored scale used to assess the motor symptoms of patients with Parkinson's disease. The investigator rates the patient on 14 items based on observation or the performance of a task the patient performs (even in the context of any comorbidities) on a 5-point scale.

The scores range from 0 to 4, with higher scores indicate greater impairment. The total UPDRS score will be calculated as the sum of all items. If any individual item is missing, the UPDRS score will be set to missing.

Note that patients who enrolled under protocol MP-101-01(a) were to complete the UPDRS at baseline, at Weeks 2 and 10, the follow-up visit, and (possibly) at the early termination visit. For protocol MP-101-01(b), the Week 2 visit was moved to Week 4. For purposes of analysis, the Week 2 and Week 4 data will be summarized together as "Week 2/4".

Zarit Burden Interview-22 (Zarit et al., 1980)

Changes in caregiver burden will be assessed using the Zarit Burden Interview-22 (ZBI-22). The ZBI-22 is a 22-point scale used to assess caregiver burden in the dementia patient population. Each of the 22 items is rated on a scale of 0 to 4, where 0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = nearly always. The total score of the ZBI-22 is the sum of these 22 items.

Columbia Suicide Severity Rating Scale

Any occurrence of suicide-related thoughts and behaviors will be assessed using the C-SSRS, a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The first time the scale is administered in this study, the C-SSRS "Lifetime/Recent-Clinical" version will be used, and the findings will constitute the baseline assessment. The "Since Last Visit-Clinical" version will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, the additional information will be collected to allow for a more complete assessment of these behaviors.

Only listings will be created from the individual C-SSRS items.

3. INTERIM ANALYSES

An interim analysis of safety and PK data will be performed after approximately 20 patients have completed Visit 5 (Week 4). In order to minimize the operational and statistical bias that result from performing an interim analysis, the interim analysis for this study will be conducted under the auspices of an Assessment Committee (AC). The purpose of the AC is to advise the Sponsor regarding the continuing safety of study participants and the ongoing scientific validity and integrity of the trial.

No statistical tests will be performed on the data from the interim safety/PK analysis, and no adjustments will be made to the final analysis because of the interim safety/PK analysis.

Displays used the in the interim safety/PK analysis will be a subset of those used in the final analysis (except for one PK figure), so that the description of the display will be included in this SAP.

A second interim analysis may be performed to evaluate the futility of finding differences in the NPI response rates between treatment groups.

All interim analysis details, including unblinding plans and stopping rules for the futility analysis, will be documented in the AC Charter.

4. PATIENT CHARACTERISTICS

4.1. Patient Disposition

The disposition of all randomized patients will be presented. The number of patients will be presented by population, by randomization strata, and by last scheduled visit previous to withdrawal. In addition, the reason for study discontinuation will be tabulated for the overall population and by treatment group using the list of reasons provided in the eCRF.

4.2. Protocol Violations

A list of protocol violations that could potentially impact the analysis of the study will be determined during the conduct of the study by study team members who are blinded to study treatment being received. These will be presented in a listing.

4.3. Demographics and Baseline Assessments

Patient's baseline age, gender, race, height, body weight, body mass index, MMSE score, other baseline efficacy measures, initial disease history and pre-existing conditions, and eGFR values will be summarized using descriptive statistics by treatment arm and overall. These summaries will be based on the Safety population. Patients who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.

A summary will be made by age categorized as 50-64, 65-84, and 85 or older.

Results of examinations of Hepatitis B surface antigen, Hepatitis C antibody, and HIV results, and substance use will be included in listings.

Patient height and weight will be collected prior to randomization. Both variables will be reported in metric units (height in cm and weight in kg) and will be summarized as continuous variables along with Body Mass Index (in kg/m^2).

No statistical testing will be performed for comparisons of baseline characteristics.

4.4. Concomitant Medications

Concomitant medications will be defined as medications taken on or after the date of the first dose of study treatment. This includes all medications initially taken prior to the date of first dose of study treatment but with a stop date that is either missing or after the date of first dose of study treatment. Those medications where the stop date is documented as prior to the date of first dose of study treatment will be classified as prior medications. The prior medications will not be included in any summary reports.

The percent of patients who receive each concomitant medication, based on the WHODD preferred drug name, will be tabulated. By-patient listings of all concomitant medications that includes WHODD preferred drug names will be prepared.

5. EFFICACY ANALYSES

5.1. Primary Analysis

The primary analysis of the NPI response rate will use a one-sided Fisher's exact test with a 5% type 1 error rate. The lower 95% confidence limit of the difference in NPI response rates (MP-101 minus Placebo) will be calculated using an exact unconditional confidence interval.

Supporting Analyses

A supporting analysis of the NPI response endpoint will be performed using a Cochran-Mantel-Haenszel test, stratifying by the randomization strata.

5.2. Secondary Analyses

Summary statistics of all domains of the NPI will be computed for the observed and change from baseline values in the Evaluable and ITT populations. Summaries of other secondary endpoints will be computed for the observed and change from baseline values in the Evaluable population.

Supporting analyses of the secondary endpoints may be performed stratifying by randomization strata if there are sufficient numbers of patients within each strata.

Quantitative Endpoints

The quantitative secondary efficacy endpoints will be assessed by analyzing the change from baseline to the 10-week time point in the Evaluable population using PROC MIXED to model the difference in the Week 10 change from baseline score between treatment groups and to handle missing assessments. The change from baseline to each scheduled post-baseline visit will be estimated using repeated measures mixed models assuming data are missing at random, with covariates for baseline and visit. The lower 95% confidence limit of the difference in mean scores at Week 10 (MP-101 minus Placebo) will be estimated from the mixed model. The effects of baseline domain scores and treatment will be allowed to vary across visits. The following SAS code will be used, for assessments at Weeks 2, 4, 6, and 10. For patients who withdraw prior to Week 10, NPI data from the early termination visit will be used as the next visit's assessment; for example, if a patient's last scheduled assessment is at Week 4, the early termination data will be included in the analysis as Week 6.

```
proc mixed;
  class visit treatment patient;
  model psychosis=visit*baseline visit*treatment / s;
  repeated visit / type=vc subject=patient;
  random patient;
  estimate 'Trt Effect, week 10' visit*treatment 0 0 0 0 0 0 1 -1/cl alpha=.10;
run;
```

In addition, plots of each least squares mean domain score (± standard error) for the psychosis, delusions, hallucinations, agitation/aggression, and total scores by scheduled visit will be created.

Ordinal Endpoints

The Core Total Score response rate will be analyzed using a one-sided Fisher's Exact test. The lower 95% confidence limit of the difference in Core Total Score response rates (MP-101 minus Placebo) will be will be calculated using an exact unconditional confidence interval. The CGI-I will be analyzed using Cochran-Mantel-Haenszel tests using modified Ridit scores (i.e. van Elteren tests).

5.3. Exploratory Analyses

The exploratory efficacy objectives to determine whether MP-101 is superior to placebo in patient behavior and caregiver burden will be assessed using the same methods as the secondary endpoints.

The effect of HTR2A and ApoE genotypes on response to treatment, and the exposure-response relationships between efficacy and safety endpoints, may also be explored, as needed. If performed, these analyses will be described in the CSR.

6. SAFETY ANALYSES

All analyses of safety including the extent of exposure to study medication will be performed using the Safety population.

6.1. Study Medication Exposure and Treatment Compliance

Extent of Exposure

Patient exposure to study drug will be summarized by the duration of dose administration, the cumulative total dose while in the trial, and the maximum dose taken.

Study drug is administered on site at each visit the dose level is changed, except Visit 2. The last dose will be assumed to have been administered on the day before each drug accountability visit. Therefore, duration of dosing will be calculated as the numbers of days (inclusive) between the first day study drug was taken and the last day study drug was taken. Missing start or end dates will not be imputed.

MP-101 will be provided in a wallet design (blister pack) containing blister strips. Blister packs will be dispensed at Visits 2, 4, 5, and 6 (Weeks 0, 2, 4, and 6, respectively). Each wallet will contain 9 rows of 3 capsules each. For the 20mg active dose, each row contains 1 capsule of active drug and 2 placebo capsules. For the 40mg active dose, each row contains 2 capsules of active drug and 1 placebo capsule. For the 60mg active dose, each row contains 3 capsules of active drug. For patients in the placebo arm, all capsules contain placebo.

The number of capsules taken will be assumed to be 27 times the number of kits dispensed minus the number of capsules returned. For patients while on the 20mg and 40mg dose levels, it will not be possible to know how many active drug capsules were consumed if only partial doses were taken. Therefore, the cumulative total dose taken will be approximated as:

20*(1/3)*(number of capsules taken while at the 20mg dose level) +

40*(2/3)*(number of capsules taken while at the 40mg dose level) +

60*(number of capsules taken while at the 60mg dose level)

Treatment Compliance

Patient compliance with investigational product will be assessed at each visit by direct questioning and documentation of returned capsules. The number of days where a complete dose was not taken will be recorded and the total number of completed doses missed for each patients will be summarized along with extent of exposure.

Patients who are noncompliant should be discontinued from the study. The number of patients who were withdrawn from the trial for significant non-compliance will be included in the summary of patient status.

6.2. Adverse Events

Investigators will monitor the safety of patients and will be responsible for their medical care during the study. The investigator will interpret and document clinically significant signs and symptoms along with any change in conditions and will indicate whether each event is serious or otherwise medically important, considered related to the study medication, or if it caused the patient to discontinue the study medication before completing the study. The patient will be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained.

No statistical testing will be performed for comparisons of AEs.

Summaries of AEs will include the number of patients with at least one AE for each treatment group. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence in the MP-101 treatment group. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) include all adverse events that emerge or worsen after taking the first dose of study drug. TEAEs will be summarized for each treatment group by SOC and PT, and by PT in order of decreasing frequency of MP-101 preferred term.

Serious Adverse Events

Treatment-Emergent SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.

Treatment-Emergent Adverse Events Resulting in Death

If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of MP-101 preferred term.

Treatment-Emergent Adverse Events Leading to Study Discontinuation

TEAEs for which the action taken with medication is 'Drug Withdrawal' will be identified as TEAEs that lead to study discontinuation. The TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the Safety population. A by-patient listing of the TEAEs that lead to study drug discontinuation will also be provided.

Treatment-Related Treatment-Emergent Adverse Events

Every AE will be assessed by the investigator for its relationship to the randomly assigned study medication. The subset of TEAEs considered by the investigator as either possibly, probably, or definitely related to study treatment will be summarized as drug-related TEAEs by SOC and PT.

Treatment-Emergent Adverse Events by Maximal Severity

Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.

Treatment-Emergent (Not Including Serious) Adverse Events

The most common non-serious TEAEs will be summarized. All PT that occur in at least 5% of the Safety Population patients in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest – with preferred terms grouped in the categories of dizziness, nausea, and vomiting – will be identified prior to unblinding and summarized. This summary will also present the total number of TEAEs for each category and PT.

6.3. Clinical Laboratory Analyses

At each time point, the change from baseline will be derived for each numeric laboratory parameter. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group. A 95% confidence interval for the change from baseline will be computed for each treatment group using a large-sample T-statistic approximation; the Normality assumption will not be checked.

The number of patients discontinued due to abnormal liver laboratory assessments will be summarized.

6.4. Vital Signs and Weight

At each time point, the change from baseline will be derived for each numeric vital sign parameter. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group.

6.5. Electrocardiograms

At each time point, the change from baseline will be derived for each numeric ECG parameter. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group.

The number (percent) of patients who have an extreme QTcF value at any time while on treatment will be tabulated by treatment group. Extreme QTcF values will be determined using the following criteria:

- QTcF $\geq$ 500 msec
- QTcF $\geq$ 550 msec
- Change from baseline in QTcF $\geq$ 30 msec
- Change from baseline in QTcF $\geq$ 60 msec.

All on-treatment values, including unscheduled assessments, will be considered.

6.6. Other Safety Analyses

Gait and balance will be assessed with the Timed Up and Go (TUG) test. At each time point, the change from baseline will be derived for the time to perform the task. Descriptive statistics for the value at each time point and the change from baseline at each post-dose time point will be provided by treatment group.

The number of patients with any post-baseline clinically significant results of physical or neurological exams will be summarized. Any data captured by the C-SSRS will be included in by-patient listings.

7. PHARMACOKINETIC ANALYSES

At the visits specified in the Schedule of Activities (Section 9), venous blood samples will be collected from all patients, for a total of 5 scheduled samples per patient, to determine the plasma concentrations of MP-101 and its primary active metabolite LY2812223. The sparse sampling scheme in Table 2 will be used. The scheduled time for the 2 to 4 hour assessment was changed from Week 8 to Week 10 in Amendment b of the protocol. The concentration data will be summarized according to the time interval, ignoring differences in week or visit collected.

Table 2: Plasma Pharmacokinetic Sampling Scheme

Week	Visit	Sample Collection Time Intervals
2	4	4 to 8 hours post-dose
4	5	Pre-dose and 0 to 2 hours post-dose
6	6	8 to 12 hours post-dose
8/10	7/8	2 to 4 hours post-dose

The actual sample collection date and time (24-hour clock time) must be recorded, as well as the actual date and time of the 2 most recent doses. If a patient discontinues early, a sample should be taken at the early termination visit, if possible. Additional PK samples may be collected at additional time points during the study.

In the case of unscheduled PK samples or samples taken at the early termination visit, the actual time from the last dose to the PK sample will be calculated and the concentration assigned to the appropriate time interval.

The plasma concentrations of MP-101 and LY2812223 will be summarized using descriptive statistics: n, mean, standard deviation, coefficient of variation, minimum, median, maximum, geometric mean, and geometric coefficient of variation. In addition, the following figures will be created:

1) Plots of individual QTcF absolute values (y-axis) versus plasma drug concentrations (x-axis). Separate figures for MP-101 concentrations and LY2812223 concentrations.

   Different symbols will be used to denote the dose level the patients were on at the time of the PK assessment. The least-squares regression line of QTcF versus concentration will be added to the plot, by dose level if there are a sufficient number of patients at more than one dose level. All data points will be included in a single plot.

2) Plots of individual change from baseline QTcF values (y-axis) versus plasma drug concentrations (x-axis). Separate figures for MP-101 and LY2812223 concentrations. Different symbols will be used to denote the dose level the patients were on at the time of the PK assessment. A least-squares regression line of QTcF versus concentration will be added to the plot, by dose level if there are a sufficient number of patients at more than one dose level. All data points will be included in a single plot. This plot will be similar to the plot of absolute QTcF values versus concentration.

3) Plots of individual screening eGFR values (y-axis) versus individual average of dose normalized plasma drug concentrations (x-axis). Separate figures for MP-101 and LY2812223 concentrations. For each patient, all concentrations will be dose normalized and averaged; that is, the concentration will be divided by the dose the patient was on at the time of the assessment, and all the dose-normalized concentrations will be averaged. This resulting average concentration value will be plotted; all data points will be included in a single plot.

4) [For the safety interim analysis only.] Plot of individual plasma drug concentrations (y-axis) as a function of time from last dose (x-axis). Separate figures for MP-101 and LY2812223 concentrations. All dose groups overlaid and uniquely labelled.

a. For the interim analysis, there should be 3 assessments for each patient, which will be plotted at the following mid-points of the nominal time intervals: 0 = Visit 5/pre-dose values, 1 = Visit 5/0-2hr post-dose value, 6 = Visit 4/4-8hr post-dose value. All assessments from all patients will be included on the same figure, but the patients will not be differentiated. Different symbols will be used to denote the dose level the patients were on at the time of the PK assessment.

b. For the final analysis, the data will be evaluated using population PK/PD modeling techniques, by a vendor approved by the Sponsor. Data from this study may be combined with data from previous studies to develop the model.

8. REPORTING CONVENTIONS

The following conventions will be applied to all data presentations and analyses:

- Continuous variables will generally be summarized by the number of patients, mean, standard deviation, median, minimum, and maximum.
- Categorical variables will be summarized by the number and percentage of patients within each category.
- All mean and median values will be formatted to one more decimal place than the measured value.
- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percent of responses will be presented in the form XX (XX %), where the percentage is in parentheses. Percentages will be rounded to the nearest percent. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).
- All summary tables will include the analysis population sample size (i.e. number of patients) in each treatment group.
- Date variables will be formatted as ddMMMYY for presentation.

For PK data, the geometric coefficient of variation will be calculated assuming the data follow a log-Normal distribution. That is, let X = concentration.

If Y = log[X] has a Normal distribution with

$E[Y] = \mu$ and $Var[Y] = \sigma^2$,

then X has a log-Normal distribution with

$E[X] = \exp[\mu + .5*\sigma^2] = \exp[\mu]*\exp[.5*\sigma^2]$

and

$$Var[X] = \exp[2\mu + 2*\sigma^2] - \exp[2\mu + \sigma^2] = \exp[2\mu]*\exp[\sigma^2]*(\exp[\sigma^2] - 1)$$

so

$$SD[X] = \exp[\mu]*\exp[.5*\sigma^2]*\text{sqrt}(\exp[\sigma^2] - 1)$$

Therefore, $CV[X] = SD[X]/E[X] = \text{sqrt}(\exp[\sigma^2] - 1)$. The log-transformed concentration values will be computed and the coefficient of variation calculated using the sample variance.

9. SCHEDULE OF ASSESSMENTS

	Screen	Treatment Period (10 Weeks)							Follow-up	ET
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Week	**-1 to -5**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	
Days from Randomization (target)	**-1 to-35**	**0**	**7**	**14**	**28**	**42**	**56**	**70**	**77**	
Visit Window (± days from target)				**2**	**2**	**2**		**2**	**2**	
Study site visit	x	x		x	x	x		x	x	x
Informed Consent (before any procedures/tests)	x									
Clinical Assessments										
Demographics, height	x									
Weight	x	x		x	x	x		x	x	x
Vital signs (BP and pulse)	x	x		x	x	x		x	x	x
Medical history and physical exam	x									
Neurological exams	x	x						x		x
TUG (if applicable)	x	x		x	x	x		x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Inclusion/exclusion review	x	x								
Hepatitis B surface antigen, Hepatitis C antibody, HIV	x									
Randomization		x								
Investigational product dispensing		x		x	x	x				
Dose administration at site		x		x	x					
Investigational product accountability				x	x	x		x		x
Symptom directed physical exam		x		x	x	x		x	x	x
Habits (alcohol, caffeine, nicotine, tobacco)	x	x	x	x	x	x	x	x		x
Safety Measures										
Adverse event assessment	x	x	x	x	x	x	x	x	x	x
C–SSRS	x	x		x	x	x		x	x	x
Single 12-lead ECG	x	x		x	x			x	x	x
Efficacy and Outcome Measures										
NPI	x	x		x	x	x		x	x	x
CGI-S		x								

	Screen	Treatment Period (10 Weeks)							Follow-up	ET
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Week	**-1 to -5**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	
Days from Randomization (target)	**-1 to-35**	**0**	**7**	**14**	**28**	**42**	**56**	**70**	**77**	
Visit Window (± days from target)				**2**	**2**	**2**		**2**	**2**	
CGI-I					x			x	x	x
ZBI-22		x			x			x		
MMSE	x	x			x			x		x
UPDRS Part III		x			x			x	x	x
Laboratory Samples										
Clinical chemistry and hematology	x	x		x		x		x		x
Urinalysis	x	x						x		x
Plasma sample collection for PK analysis				x	x	x		x		x
Plasma and serum collection for biomarker research		x				x		x		x
Blood for epigenetic research		x				x		x		x
Blood for assessment of APOE and HTR2A SNPs		x								
Blood for pharmacogenetic research		x								

See protocol for footnotes.

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