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Study ID: ITI-007-201

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Subjects with Dementia, Including Alzheimer's Disease

Statistical Analysis Plan Date: 23 October 2018

STATISTICAL ANALYSIS PLAN

ITI-007-201

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY WITH AN OPEN-LABEL EXTENSION TO ASSESS THE EFFICACY AND SAFETY OF ITI-007 IN THE TREATMENT OF AGITATION IN SUBJECTS WITH DEMENTIA, INCLUDING ALZHEIMER'S DISEASE

AUTHOR: [redacted]

VERSION NUMBER AND DATE: FINALV1.0, 23OCT2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (Dated 23OCT2018) for Protocol ITI-007-201.

[redacted]

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

[redacted]

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Final 1.0	23OCT2018	[redacted]	Not Applicable First Version

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AR(1)	Autoregressive(1)
ARH(1)	Heterogeneous autoregressive(1)
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BLQ	Below limit of quantification
BMI	Body mass index
CMAI-C	Cohen-Mansfield Agitation Inventory – Community version
C-SSRS	Columbia – Suicide Severity Rating Scale
CGI-S	Clinical Global Impression Scale – Severity
CI	Confidence interval
CP	Conditional power
CPK	Creatine phosphokinase
CS	Compound symmetry
CSH	Heterogeneous compound symmetry
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	All Subjects Enrolled
FA0(q)	No Diagonal Factor Analytic
FAS	Full Analysis Set
FWER	Familywise error rate
GGT	Gamma-glutamyl transferase
HbA1c	Glycated Hemaglobin
HDL	High-density lipoprotein
HIS	Hachinski Ischemia Scale
HR	Heart rate
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITCI	Intra-Cellular Therapies, Inc. (Sponsor)
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LS	Least-squares
MAR	Missing at random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-Effects Model for Repeated Measures
MMSE	Mini Mental State Examination
MNAR	Missing not at random
MTP	Multiple testing procedure
NPI-C	Neuropsychiatric Inventory - Clinician

OLE	Open-label extension
OSA	Obstructive Sleep Apnea
PK	Pharmacokinetic(s)
PMM	Pattern mixture model
PP	Per protocol
PR	PR interval of the electrocardiogram; time duration between the P and R waves
PT	Preferred Term
QPM	Once daily in the evening
QRS	QRS interval of the electrocardiogram; duration of the QRS complex
QT	QT interval of ECG, duration between the Q and T waves
QTc	QT interval of ECG corrected for heart rate
QTcB	QT interval of ECG corrected for heart rate using Bazett's formula
QTcF	QT interval of ECG corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
RND	All Subjects Randomized
RR	Time duration between two consecutive R waves of the electrocardiogram
SAE	Serious Adverse Event
SAF	Safety Analysis
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SAS®	Statistical Analysis Software
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
TOEP	Toeplitz structure
TOEPH	Heterogeneous Toeplitz structure
TST	Total Sleep Time
ULQ	Upper limit of quantification
WASO	Wake After Sleep Onset
WHO	Worl Health Organisation

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, and pharmacokinetic (PK) data for Protocol ITI-007-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Protocol Amendment Version 5.2, dated 22Oct2018. It details the analyses for the double-blind portion of the study (Part A) and only references the open-label extension (OLE) where it pertains to the Part A analyses.

3. STUDY OBJECTIVES FOR PART A (DOUBLE-BLIND)

3.1. PRIMARY OBJECTIVE

The primary objective of Part A of this study is to compare the efficacy, measured as change from baseline to Day 29 in the Cohen-Mansfield Agitation Inventory Community version (CMAI-C) symptoms related to Aggressive Behavior, Non-Aggressive Agitated Behavior, and/or Verbally Agitated Behavior, for 9 mg ITI-007 administered orally once daily in the evening (QPM) to that of placebo in subjects with dementia.

3.2. SECONDARY OBJECTIVES

3.2.1. KEY SECONDARY EFFICACY OBJECTIVE

The key secondary objective of Part A of this study is to compare the efficacy of 9 mg ITI-007 administered orally QPM to that of placebo in relation to the difference in the change from baseline to Day 29 in the Clinical Global Impression Scale for Severity (CGI-S) of illness (e.g., CGI-S of Agitation and/or CGI-S of Aggression).

3.2.2. [redacted]

[redacted]

[redacted]

3.2.3. SAFETY OBJECTIVES

The safety objectives of Part A of this study are to determine the safety and tolerability of 9 mg ITI- 007 administered orally once daily for 4 weeks in subjects with dementia, compared to placebo. Safety and tolerability will be assessed in relation to:

- Incidence of adverse events (AEs);
- Mean change from screening in the Mini Mental State Examination (MMSE);
- Mean change from baseline in the Columbia Suicide Severity Rating Scale (C-SSRS);
- Mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS);
- Mean change from baseline in the Barnes Akathisia Rating Scale (BARS);
- Mean change from baseline in the Simpson Angus Scale (SAS);
- Changes from baseline in clinical laboratory evaluations;
- Changes from baseline in electrocardiograms (ECGs);
- Changes from baseline in vital sign measurements;
- Modified physical examination and neurological findings.

3.2.4. [redacted]

[redacted]

3.2.5. [redacted]

[redacted]

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

The study will be conducted in two parts, Part A [redacted] Part A is a randomized, double-blind, placebo-controlled, two stage adaptive design study comparing the efficacy and safety of 9 mg ITI-007 versus placebo administered once daily in subjects with dementia, including Alzheimer's disease. Eligible subjects are those with a MMSE score of 8 to 26 at screening, who have frequent clinically significant symptom(s) of agitation secondary to probable Alzheimer Disease, and warrant treatment with a pharmacological agent. Subjects who safely complete treatment in Part A [redacted]

Approximately 292 subjects (146 subjects/treatment group, if no sample size adjustment is made at the interim analysis during Part A) will be randomized in a 1:1 ratio to receive one of two study treatments in Part A, 9 mg ITI-007 or placebo, stratified by the MMSE score at screening. A sample size of 292 subjects will provide approximately 264 subjects ssuming an approximately 9% discontinuation rate before the first post baseline assessment of the primary efficacy outcome measure (CMAI-C). 132 subjects per treatment group will provide approximately 90% power, assuming an effect size of 0.4 tat a two-sided significance level of 5%.

Study participation in Part A will last up to approximately 8 weeks and will include the following periods: a Screening Period, lasting up to 2 weeks prior to Day 1; an On-Treatment Period of 4 weeks of daily administration of study medication; and a Safety Follow-Up Period, with a safety follow-up visit approximately 2 weeks after the last dose of study medication, [redacted] The timing and assessments during each study period are described in the Schedule of Assessments (Table 6-1 of the protocol and APPENDIX 1).

[redacted]

4.2. [redacted]

[redacted]

[redacted]

5. FINAL AND INTERIM ANALYSES

The following analyses will be performed for Part A of this study:

- Interim Analysis
- End of Part A Final Analysis

5.1. INTERIM ANALYSIS

In Part A, one interim analysis will be performed after approximately 53% of the 264 subjects (i.e. 140 subjects) have completed the 28-day On-Treatment Period or confirmed to have discontinued treatment or study after at least one post baseline CMAI-C assessment. An independent external DMC will review the efficacy data available at the time of the planned interim analysis in an unblinded manner, and recommendations will be made based on an assessment of efficacy of 9mg ITI-007 compared to placebo as follows:

Stopping for Efficacy: Terminate the study due to superior efficacy if 9 mg ITI-007 is statistically significant effective compared to placebo for ***any*** *of the three CMAI-C components,* Aggressive Behavior, Non-Aggressive Agitated Behavior, or Verbally Agitated Behavior.

Stopping for Futility: Terminate the study due to futility if 9 mg ITI-007 is futile for ***all*** *three CMAI-C components,* Aggressive Behavior, Non-Aggressive Agitated Behavior, or Verbally Agitated Behavior.

Sample Size Adjustment: Increase the number of subjects in each treatment group based on the ***best*** *CMAI-C component,* Aggressive Behavior, Non-Aggressive Agitated Behavior, or Verbally Agitated Behavior (i.e., the CMAI-C component corresponding to the largest effect size).

Continue the study as planned without modifications.

Details of the interim analysis decision rules and impact on study design are described in APPENDIX 4.

Derivation of the primary efficacy variables and analysis methodologyof the interim data will be based on those required for the final Part A analysis described in this analysis plan, unless otherwise stated within this SAP.

The IQVIA study team, including those responsible for creating the programs to produce the outputs for the Interim Analysis, will remain blinded. Once the programs have been produced by the IQVIA study team, these programs will be sent to an independent IQVIA statistician, who will utilize the randomization codes to provide the DMC with a set of unblinded outputs.

5.2. FINAL ANALYSIS

The final analyses for Part A detailed in this SAP will be performed by IQVIA Biostatistics following ITCI authorization of the SAP, ITCI authorization of Analysis Sets, final Database Lock and Unblinding of Treatment.

6. ANALYSIS SETS

For Part A, analysis of efficacy and safety endpoints will be performed based on the analysis sets defined in this section and as specified for each endpoint throughout this SAP. Inclusion/exclusion of subjects from each analysis set will be determined prior to the interim and final analyses (and approved by ITCI) based on blinded data review.

Note: Analysis sets defined in the sections below are defined for Part A of the study.

6.1. ALL SUBJECTS ENROLLED [ENR] SET

The All Subjects Enrolled (ENR) Set will contain all subjects who signed informed consent for this study.

6.2. ALL SUBJECTS RANDOMIZED [RND] SET

The All Subjects Randomized (RND) Set will contain all subjects who signed informed consent and were randomized to study medication.

For analyses and displays based on RND, subjects will be classified according to randomized treatment.

6.3. INTENT-TO-TREAT [ITT] SET

The Intent-To-Treat (ITT) Set will contain all randomized subjects who received at least one dose of the study medication and who had a valid baseline (pre-dose) measurement and at least one valid post baseline measurement of CMAI-C. All analyses using the ITT Set will classify subjects according to the randomized treatment, regardless of the treatment received during the course of the study. Note that the clinical study protocol refers to this population as the Full Analysis Set (FAS).

6.4. [redacted]

[redacted]

6.5. SAFETY ANALYSIS [SAF] SET

The Safety Analysis (SAF) Set will contain all randomized subjects who received at least one dose of study medication. For all analyses using the SAF set, subjects will be classified according to treatment actually received.

6.6. [redacted]

[redacted]

7. GENERAL CONSIDERATIONS

Relative Study Day will be calculated from the date of Day 1, which is the day of first treatment with study medication in Part A (Study Day 1), and will be used to show the start and/or stop days of treatments, study procedures and assessments, prior, concomitant and post-treatment medications, and adverse events.

- If the date of the treatment, procedure, or event is on or after Study Day 1 date then:

  Relative Study Day = (date of variable of interest Day 1 date) + 1.

- If the date of the treatment, procedure, or event is prior to the Day 1 date then:

  Relative Study Day = (date of variable of interest Day 1 date).

In the situation where the date is partial or missing, Relative Study Day, and any corresponding durations will appear missing in the listings and will not be included in the calculations of data summaries.

Analyses presented by visit or study day will be based on the scheduled visits as planned in the protocol. Visit windows for unscheduled visits or early discontinuation visits in Part A are defined in Table A, which provides the mapping of relative day ranges to the scheduled target days and the study periods. If more than one assessment is available in the same 'Range of Relative Study Days' (window), the assessment closest to the Scheduled Target Day will be selected and assigned to the Scheduled Target Day. If two or more assessments are available in the same window and are equidistant from the Scheduled Target Day, the latest assessment will be selected [redacted]

Listings will include scheduled, unscheduled, retest and early discontinuation data.

Table A: Part A - Mapping of Relative Day Ranges to Schedule Target Day

Study Phase	Study Period	Range of Relative Study Days	Scheduled Target Day
Pre-Treatment	Screening	Up to 14 days before baseline (Day 1) date	14
Pre-Treatment	Baseline	Baseline assessments on Day 1 prior to first treatment with study medication in the evening of Day 1	Day 1
Study Treatment	On-Treatment	1 to 4 days relative to Day 1 date	Day 1
Study Treatment		5 to 11 days relative to Day 1 date	Day 8
Study Treatment		12 to 18 days relative to Day 1 date	Day 15
Study Treatment		19 to 25 days relative to Day 1 date	Day 22
Study Treatment		≥ 26 days relative to Day 1 date and after the last dose of treatment and before the start of the Safety Follow-up Period (one day after actual Day 29 visit) or before enrolling in Part B (for subjects who rolling over into Part B).	Day 29
Post-treatment*	Safety Follow-up	> 29 days relative to Study Day 1 date for treatment completers (28 day on-treatment) and after Day 29 post-treatment assessments.	Day 43

* Only for subjects not rolling over into Part B of the study upon completing treatment in Part A.

First treatment with study medication and baseline assessments are scheduled for Visit 2 on Relative Study Day 1. Unless otherwise specified, baseline is defined as the last non-missing pre-treatment measurement.

Assessments will be considered baseline if the measurement date is before the date of the first treatment or if the measurement was done on Study Day 1 and, according to the Study Schedule of Events, was supposed to be performed on Day 1, prior to treatment (including unscheduled measurements).

For parameters planned to be collected multiple times at the same time point (ECG, blood pressure and pulse rate), the average of the measurements collected at Visit 2 on Day 1, prior to treatment, will be considered as baseline.

[redacted]

Unless otherwise specified, the following calculations will be used for change from baseline and percent change from baseline:

Change from baseline visit will be calculated as:

- Value at Visit X Baseline Value

Percent change from baseline will be calculated as:

- $\frac{\text{Value at Visit X} - \text{Baseline Value}}{\text{Baseline Value}} \times 100$

The baseline value for parameters collected from physical and neurological examination, Hachinski

Ischemia Scale (HIS), MMSE and NPI-C will be from assessments made at the Screening visit.

All investigative sites with fewer than 6 ITT subjects will be pooled as follows: The largest site with fewer than 6 ITT subjects will be pooled with the smallest site with fewer than 6 ITT subjects. If this results in a pooled site still having fewer than 6 ITT subjects, this site will be pooled together with the next smallest investigative site, if one exists; otherwise, no further pooling is needed. Sites with the same number of ITT subjects will be ordered in ascending order of their numerical site identification number. This will serve as a tie-breaker rule in case multiple sites have the same number of ITT subjects. If the primary efficacy analysis model, described in section 15.1.3 presents convergence issues due to the too small number of subjects per site, the same site pooling algorithm will be applied again, but this time pooling sites with fewer than 12 ITT subjects. Should the primary efficacy analysis model still present convergence issues, after testing the sequence of correlation structures listed in section 15.1.3, then the site effect will be reconsidered and may be dropped from the model. These pooled investigative sites, as determined based on the primary efficacy response variable, will be used for any analysis that has investigative site as a fixed effect in the model. The actual investigative site numbers will be included in the listings.

The default significant level for statistical tests will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. All analyses will be conducted using SAS® version 9.4 or higher.

7.1. MISSING DATA

The total and subscale scores of any assessment with more than one item will be derived from the individual items. Any individual missing item in any scale will not be imputed. If one or more items are missing at a visit, then the associated total score or subscale score will be set to missing. This will apply to CMAI-C, CGI-S, NPI-C, MMSE, HIS, C-SSRS, AIMS, BARS and SAS.

The main objective of the analyses in Part A of this study is to evaluate treatment effect of 9 mg ITI-007 compared to placebo if the treatment is administered for the planned treatment duration. In order to evaluate this estimand in the presence of subjects that may discontinue treatment prematurely, the primary efficacy analyses will be performed based on the assumption of data being missing at random (MAR). This implies that subjects discontinuing from treatment early are considered to have unobserved values similar to the observed ones in their respective treatment group for subjects who have similar history, i.e., the distribution of the unobserved future values for subjects who had discontinued treatment is the same as the distribution of the observed values for those subjects who completed treatment, conditional on the available data prior to discontinuation.

The MMRM method will be used for the analysis of the primary and key secondary efficacy endpoints in Part A. The MMRM approach does not impute missing data but is based on all subjects included in the analysis set using all available longitudinal data (either complete or partial). This approach is based on the MAR assumption as described above.

[redacted]

[redacted]

7.2. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8. OUTPUT PRESENTATIONS

The Tables, Listings and Figures (TLFs) shells provided with this SAP describe the presentations for the double-blind phase of this study (Part A) and therefore the format and content of the summary TLFs to be provided by IQVIA Biostatistics.

Continuous variables will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum, unless otherwise stated). The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database.

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the calculation of percentage will be based on the number of subjects in the analysis set of interest.

P-values will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to two more decimal places than the raw data.

Source data for summary tables and statistical analyses will be presented as subject data listings.

9. DISPOSITION AND WITHDRAWALS

Subject disposition and withdrawals will be presented by treatment group, when applicable, and overall for the ENR Set. The number and percentage of subjects who were screened, screen failed, randomized, completed or discontinued the 28-day On-Treatment Period and completed or discontinued Part A of the study, and reasons for treatment discontinuation and study discontinuation will be presented. The reasons for study withdrawal and treatment discontinuation are listed in Table B.

The reasons for treatment discontinuation will also be presented by treatment group and by time to treatment discontinuation, categorized based on the planned visits (Day 1 - ≤ Day 8, > Day 8 - ≤ Day 15, > Day 15 - ≤ Day 22, > Day 22 - ≤ Day 29) for all subjects in the Safety Set. [redacted]

A subject is defined to have completed the Part A treatment period if the subject completed the 28-day On-Treatment period and Day 29 post-treatment assessments, recorded as completed treatment on eCRF End of Treatment form.

A subject is defined to have completed Part A of the study:

[redacted]

- if the subject has completed the 28-day On-Treatment Period and the Part A safety follow-up assessments at Visit 7

Table B: Part A - Reasons for Study Withdrawal and Study Medication Discontinuation Terminology

Case Report Form Terminology	Study	Study Medication
Screen failure	X	
Adverse event	X	X
Adverse event associated with worsening of agitation *	X	X
Adverse event not associated with worsening of agitation *	X	X
Death	X	X
Lack of efficacy	X	X
Lost to Follow-up	X	
Laboratory safety assessments	X	
Symptoms or an intercurrent illness	X	
Protocol violation	X	X
Physician decision	X	X
Study terminated by sponsor	X	X
Subject withdrew consent:	X	X
Personal or family reasons;	X	X
Refused to provide a reason or refused all end-of-study procedures;	X	X
Self-reported adverse event;	X	X
Self-reported lack of efficacy	X	X
Other	X	X

* Adverse event associated with worsening of agitation will be identified by a Medical Monitor review prior to database lock.

The number and percentage of randomized subjects who discontinued due to an adverse event associated with worsening of agitation will be summarized. The number and percentage of randomized subjects discontinued due to an adverse event not associated with worsening of agitation will also be presented.

The time to treatment discontinuation due to all reasons, adverse events (all, associated with worsening of agitation or not), lack of efficacy, subject withrew consent or due to any other reason of special interest will be evaluated separately using the Kaplan-Meier method. Time to treatment discontinuation of subjects in the Safety Set will be defined as the date of discontinuation minus date of first dose of study medication plus 1. Subjects who complete the Part A Treatment Period or who discontinue for a reason other than the one being evaluated will be censored. The Log-rank test will be used to compare the time to discontinuation between the 9 mg ITI-007 treatment group and placebo group. The same analysis will be repeated for time to treatment discontinuation for any reason, where only subjects who complete the 28-day On-Treatment Period will be censored.

The number and percentage of subjects randomized will also be summarized by site for the RND Set. The number of subjects who discontinued treatment will be summarized by site for the Safety Set. The number and percentage of subjects who withdrew from the study will be summarized separately by visit and by site, in each case presented by treatment group and overall for all subjects in the RND Set. The number of subjects remaining on treatment over time will be presented in a figure.

10. [redacted]

[redacted]

[redacted]

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT, PP and SAF Sets.

No formal statistical testing will be carried out for comparing demographic or other baseline characteristics between the two treatment groups.

The following demographic and other baseline characteristics will be reported for Part A of the study:

Demographics

- Age (years) calculated as (Date of Informed Consent Date of Birth)/365.25
- Gender
- Child bearing potential (Female only)
- Race
- Ethnicity

Other Baseline Characteristics

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2) calculated as weight (kg) / height (m)^2

Stratification Factor - Mini Mental State Examination (MMSE) as per IVRS

- MMSE Total Score
- MMSE strata:
    - 1 = 8-10 (MMSE 1)
    - 2 = 11-14 (MMSE 2)
    - 3 = 15-18 (MMSE 3)
    - 4 = 19-22 (MMSE 4)
    - 5 = 23-26 (MMSE 5)
- MMSE severity
    - Mild (19-26)
    - Moderate (11-18)

- Severe (8-10)

Consumption Habits

- Alcohol
- Caffeine
- Tobacco

Efficacy parameters at baseline (for ITT and PP Sets)

- Cohen-Mansfield Agitation Inventory (CMAI-C)
  - CMAI-C symptoms related to Aggressive Behavior Score
  - CMAI-C symptoms related to Non-Aggressive Agitated Behavior Score
  - CMAI-C symptoms related to Verbally Agitated Behavior Score
  - CMAI-C Total Score
  - CMAI-C Factor Composite Score
- Clinical Global Impression - Severity (CGI-S)
  - CGI-S Agitation Score
  - CGI-S Aggression Score
- [redacted]
- [redacted]
- [redacted]

[redacted]

Safety parameters at baseline (ITT and SAF Sets)

- Baseline safety parameters, including Columbia Suicide Severity Rating Scale (C-SSRS) assessment of suicidal behavior/ideation, Abnormal Involuntary Movement Scale (AIMS) Score, Barnes Akathisia Rating Scale (BARS) Total Score and global assessment of akathisia, Simpson-Angus Scale (SAS) Score, Hachinski Ischaemia Score (HIS) at screening
- STOP-Bang Questionnaire: Obstructive Sleep Apnea (OSA)
    - OSA - Low Risk : Yes to 0 - 2 questions
    - OSA - Intermediate Risk : Yes to 3 - 4 questions
    - OSA - High Risk : Yes to 5 - 8 questions or Yes to 2 or more of 4 STOP questions + male gender or Yes to 2 or more of 4 STOP questions + BMI > 35kg/m^2 or Yes to 2 or more of 4 STOP questions + neck circumference 17 inches / 43 cm in male or 16 inches / 41 cm in female.

The following caregiver information, collected a screening, will be listed, but not summarized

- Demographic characteristics of Caregiver
    - Race
    - Ethnicity
    - Relationship to subject (Spouse/Partner; Son/Daughter/Son-in-Law/Daughter-in-Law; Other Relative; Friend/Neighbor; Paid Caregiver; Other)
- Providing care for the subject
    - Number of caregivers are involved in the care of the subject
    - How long a caregiver has been providing care for the subject
    - Frequency of care per week (daily, 3 to 6 times per week, 1 to 2 times per week, less than once per week)
    - Number of hours per day and part of the day (morning, afternoon, evening, night)
    - Help with activities (washing and/or dressing/undressing, showering, taking medication, eating meals, walking/standing; household tasks, cooking/food preparation, transport/driving, shopping, administration, external activities, odd jobs, coping with fears/anger/confusion, other)

12. MEDICAL HISTORY

Medical history information will be presented for the SAF Set and will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher.

The number and percentage of subjects with at least one medical history condition as well as the number of subjects with each medical history condition will be summarized by system organ class

(SOC), preferred term (PT), and treatment group. Within each subject, multiple reports of medical history conditions that map to a common PT and SOC will be condensed into a single medical history for incidence counts.

13. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be presented for the SAF Set and coded to preferred names using the WHO Drug Dictionary.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, prior concomitant, concomitant, or post-treatment, the medication will be classified by the worst case, i.e. concomitant.

For Part A, a medication is considered to have started prior to the first dose of study medication if indicated to have started prior to the first dose of study medication on the eCRF. If the medication started prior to the first dose of study medication, it is considered to have ended prior to the first dose of study medication if indicated to have ended prior to the first dose of study medication on the eCRF.

A medication is considered to have started after the last dose of study medication if indicated as such on the eCRF, assuming it started after completion of all study procedures and assessment related to the last dose of study medication.

- Part A 'Prior' medications are medications which started and stopped prior to date of first dose of study medication.
- Part A 'Prior concomitant' medications are medications which started prior to and stopped after the date of first dose of study medication.
- Part A 'Concomitant' medications are medications which:
    - started after the date of first dose of study medication and started prior to the date of last dose of study medication,
    - AND stopped after the date of first dose of study medication or were ongoing at the completion of Day 29 post-dose assessments on Day 29 (or last treatment day for subjects who discontinue treatment), or after the last dose of study medication (if planned assessments are not performed).
- Part A 'Post-treatment' medications are medications which started after completion of Day 29 post-dose assessments (or on or after last treatment day for subjects who discontinue treatment) which are planned to be conducted after the Part A last dose of study medication [redacted]

Prior, prior concomitant, concomitant, and post-treatment medication use will be summarized by preferred term using frequencies and percentages by treatment group. Medications will be sorted alphabetically by preferred term in summaries. Subjects with multiple occurrences of a medication in the same preferred term will only be counted once within the preferred term for each summary.

During Part A, subjects are required not to use any short-acting anxiolytic except lorazepam, according to the instructions outlined in Protocol Table 5-7, which specifies the doses allowed by study day. In addition, during Part A, a subject may be treated with benztropine for treatment of extrapyramidal

side effects and propranolol may be given for treatment of akathisia. The number and percent of subjects in the ITT set receiving lorazepam, the total dose, and the total number of days on lorazepam will be summarized by treatment group for the screening period and for each week on study treatment (Days 1-8, Days 9-15, Days 16-22, Days 23-29, inclusive).

Other medications will be summarized by treatment group and study period if deemed necessary.

14. STUDY MEDICATION EXPOSURE AND TREATMENT COMPLIANCE

Exposure to study medication and treatment compliance in Part A will be presented for the ITT and SAF Sets.

The date of first and last study medication administration will be taken from the eCRF 'First Dose Administration' and 'End of Treatment' forms, respectively. If a discontinued subject is missing the end of treatment date from the 'End of Treatment' form, the last known dispense date will be used as the date of last study medication administration.

Duration of exposure will be summarized by treatment group as a continuous variable, using mean, SD, median, minimum and maximum. In addition, the number and percentage of subjects within each planned study visit (Day 1 - < Day 8, ≥ Day 8 - < Day 15, ≥ Day 15 - < Day 22, ≥ Day 22 - < Day 29 and ≥ 29 days), will be presented.

For each subject, compliance with study medication (%) will be calculated as 100 x (Number of compliant days) / (Number of days in the On-Treatment Period), where a compliant day is defined as any day during the On-Treatment Period on which the subject took 2 capsules, and 'Number of days in the On-Treatment Period' is equivalent to 'Duration of Exposure' as defined above.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLES AND DERIVATION

For the double-blind portion of the study (Part A), the primary efficacy variables are defined as change from baseline to Day 29 in the Cohen-Mansfield Agitation Inventory Community version (CMAI-C) items related to three categories: Aggressive Behavior, Non-Aggressive Agitated Behavior, and Verbally

Agitated Behavior.

The CMAI-C is a 37-item scale for identifying and quantifying agitated behaviors in elderly persons in a community setting. Each CMAI-C item is rated from 1='Never' to 7='Several Times Per Hour' based on a semi-structured caregiver interview. Each category, Aggressive Behavior, Non-Aggressive Agitated Behavior, and Verbally Agitated Behavior, contains a pre-specified subset of the CMAI-C items, and serves as a primary outcome measure. The score of each category is the sum of the CMAI-C items included in that category):

- Aggressive Behavior Sum of 9 CMAI-C items and ranges from 9 to 63;
- Non-Aggressive Agitated Behavior Sum of 6 CMAI-C items and ranges from 6 to 42;
- Verbally Agitated Behavior Sum of 4 CMAI-C items and ranges from 4 to 28.

Details related to score computation are described in APPENDIX 3. If a subject has the score of one or more items is missing at a visit, the category score for that subject will be set to missing for that visit.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY ENDPOINT

The primary analysis method for evaluating the primary efficacy endpoints is the likelihood-based MMRM method described in detail in Section 15.1.3. The use of MMRM inherently implies that the treatment effect on the change from baseline in a CMAI-C category score will be similar for the subjects who withdraw and for those who complete the treatment in their respective treatment groups, conditional on the outcomes observed prior to withdrawal (MAR assumption). To evaluate the robustness of the MMRM method under the MAR assumption, sensitivity analyses of the primary efficacy endpoints under different assumption about missing mechanism will be performed, as detailed in Section 15.1.4.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLES

The primary objective of Part A of this study is to compare the efficacy, measured as change from baseline to Day 29 in the Cohen-Mansfield Agitation Inventory Community version (CMAI-C) symptoms related to Aggressive Behavior, Non-Aggressive Agitated Behavior and Verbally Agitated Behavior, for 9 mg ITI-007 administered orally once daily in the evening (QPM) to that of placebo.

The treatment effect of 9 mg ITI-007 compared to placebo will be estimated at the planned interim and final analyses. At each stage the treatment effect on each primary efficacy endpoint will be evaluated using an MMRM approach. The model will include the change from baseline at each pre-specified time point as the response variable and study visit, baseline value of the CMAI-C endpoint score, MMSE stratification factor, treatment (9 mg ITI-007 or placebo), site (or pooled site), baseline value-by-study visit interaction and treatment-by-study visit interaction as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the correlation among repeated measurements within subject. [redacted]

[redacted]. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. The

treatment and treatment-by-time interaction terms allow for comparisons of the treatment groups at the time point of interest (Day 29). Treatment differences will be evaluated via contrasts for the time-by-treatment factor.

The primary efficacy analysis will be performed for the ITT and PP Sets.

[redacted]

For each primary efficacy endpoint, summary statistics of change from baseline , as well as least squares mean (LSM) estimate for change from baseline, standard error and 95% CI for LSM, will be presented by treatment group at day 29. Contrast estimate (LSM) for between-group comparison, the corresponding 95% CI, effect size, and p-value will be presented.

Effect size will be calculated for 9 mg ITI-007 as: $\frac{\text{LS Mean Difference}}{\text{Pooled estimate of within patient error standard deviation}}$

[redacted]

15.1.4. [redacted]

[redacted]

[redacted]

15.2. KEY SECONDARY EFFICACY

The key secondary efficacy analyses will be performed for the ITT and PP Sets.

For Part A, the key secondary efficacy endpoints are the change from baseline to Day 29 in the Clinical Global Impression scale for Severity (CGI-S) of illness: CGI-S of Agitation and CGI-S of Aggression. The CGI-S is a single value assessment of illness severity and ranges from 1='Normal, not at all ill' to 7='Among the most extremely ill'. A higher score is associated with greater illness severity, and a screening and baseline scores of at least 4 are required to be eligible to participate in the study.

Change from baseline in the CGI-S score will be evaluated using an MMRM method similar to the one specified for the primary efficacy endpoints, where the change from baseline to each pre-specified time point in CGI-S score is the response variable and study visit, baseline value of the CGI-S, MMSE stratification factor, treatment (9 mg ITI-007 or placebo), site (or pooled site), baseline value-by-study visit interaction, and treatment-by-study visit interaction as fixed effects and subject as a random effect. See Section 15.1.3, the primary analysis of primary efficacy endpoints, for more details.

[redacted]

15.3. [redacted]

[redacted]

15.3.1. [redacted]

[redacted]

[redacted]

15.3.2. [redacted]

[redacted]

[redacted]

15.3.3. [redacted]

[redacted]

15.3.4. [redacted]

[redacted]

15.3.5. [redacted]

[redacted]

15.3.6. [redacted]

[redacted]

15.3.7. [redacted]

[redacted]

[redacted]

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF Set.

For Part A, certain safety measures including, but limited to, vital signs and clinical laboratory tests, will be evaluated for whether there is a difference in ITI-007 versus placebo. These selected safety endpoints will be compared between each of the treatment groups and placebo using the ANCOVA with LOCF imputation method. Comparisons are considered exploratory.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary currently in effect at the time of interim analysis or final Part A database lock.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and, before or one day after the last date of study medication in Part A.

All AEs with an onset date after the last dose of study medication plus one day, [redacted] will be listed in the AE data listing and labelled as 'Follow-up Adverse Event'.

See Appendix 2 for handling of partial or completely missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as the worst case, i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-sections 16.1.1 and 16.1.2 below will be provided as specified in the TLF shells.

Listings will include all AEs, TEAEs and Non-TEAEs.

16.1.1. AEs AND TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

The number and percentage of subjects with at least one TEAE and total number of subjects having events for each PT and SOC will be summarized. A summary of TEAEs will be provided with only PTs and a separate summary for only SOCs. Additional summaries of TEAEs and TEAEs related to study medications ('possibly related', 'probably related', or 'definitely related') will be provided for PTs occurring in at least 5% of subjects in any treatment group (9 mg ITI-007 or placebo). Within each subject, multiple reports of events that map to a common MedDRA PT and/or SOC will be condensed into a single AE for incidence counts. Summaries will present SOCs in alphabetical order and PTs by

descending (total) frequency within SOCs, by treatment group.

TEAEs will also be categorized according to the onset date of the TEAEs. The total number of subjects having events for each PT and SOC will be summarized by first onset categories, based on planned study visits (Day 1 - ≤ Day 8, > Day 8 - ≤ Day 15, > Day 15 - ≤ Day 22, > Day 22 - ≤ Day 29).

Relative risk of at least one TEAE and for each PT and SOC will also be presented along with 95% CIs and p-values obtained by the Chi-square test for association.

AE severity is classed as "mild", "moderate", "severe", "life-threatening" by the investigator. AEs and TEAEs with a missing severity will be classified as "not specified". If a subject reports a TEAE more than once within the same PT and SOC, the event with the worst case severity will be used in the corresponding severity summaries.

Relationship to study medication, as indicated by the Investigator, is classed as "unrelated", "unlikely to be related", "possibly related", "probably related", "definitely related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE "possibly related", "probably related" or "definitely related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "not specified". If a subject reports the same AE more than once within the same PT and SOC, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. A summary of related TEAEs by SOC and PT will be presented.

AEs leading to study discontinuation will be identified by using the Completion/Withdrawal from Study page of the eCRF, where 'Primary Reason' indicates "AE". TEAE leading to disontinuation of study medication will be identified by using the End-of-Treatment page of the eCRF, where 'Primary Reason' indicates "AE". For AEs leading to early study withdrawal or discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.2. SERIOUS ADVERSE EVENTS AND DEATH

Serious adverse events are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of SAEs by SOC and PT will be prepared. A listing of all SAEs will be presented.

AEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. Deaths may also be recorded on the End of Treatment page and the Completion/Withdrawal from Study page of eCRF. A listing all deaths will be prepared based on these sources.

16.1.3. FALLS TEAES

Treatment-emergent adverse events of falls will be defined by the Standard MedDRA Query (SMQ) labeled as Accidents and Injuries. The number and percentage of subjects with at least one AE PT mapped to a falls term contained in the SMQ will be presented. In addition, the falls terms will be summarized. Separate tables will be presented for the narrow and broad interpretation of the SMQ.

16.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for hematology,

clinical chemistry and screening serology. A list of laboratory assessments to be included in the outputs is included in the protocol, Section 6.5. Summary statistics will be presented in standard international (SI) and US conventional units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantitation (BLQ), or "> X", i.e. above the upper limit of quantitation (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Blood samples for laboratory evaluations will be collected after an overnight fast (≥10 hours) during screening and on Days 29 and 43 [redacted] or at early terminations. All laboratory parameters collected non-fasting will be excluded from descriptive statistics but will appear in the data listings.

Change from baseline to last on-treatment value in total cholesterol, HDL, LDL, glucose, insulin, triglycerides, and prolactin will be presented by treatment group.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit, and for last on-treatment assessment where applicable (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- Shift from baseline according to markedly abnormal criteria defined in Section 16.2.1 (for quantitative measurements and categorical measurements)
- Number and percentage of subjects with markedly abnormal criteria
- Listing of subjects meeting markedly abnormal criteria.
- Incidence of liver function related values meeting pre-defined criteria, as defined in Section 16.2.2, during the treatment period and the entire Part A of the study

16.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and US Conventional units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be identified in accordance with the predefined markedly abnormal criteria as presented in Table D.

Table D: Markedly Abnormal Values for Laboratory Evaluations

Hematology Parameter	Markedly Abnormal Range
Hemoglobin	Male: ≤ 11.5 g/dL
	Female: ≤ 9.5 g/dL
Hematocrit	Male: ≤ 37%
	Female: ≤ 32%
White Blood Cell (WBC) Count	≤ 2.8 x 10^3 cells/µL
	≥ 16 x 10^3 cells/µL
Neutrophils (percent)	≤ 15%
Eosinophils (percent)	≥ 10%
Platelet Count	≤ 75 x 10^3 cells/µL
	≥ 700 x 10^3 cells/µL
Chemistry Parameter	**Markedly Abnormal Range**
Alkaline Phosphatase	≥ 2 x ULN
Gamma-glutamyl transferase (GGT)	≥ 3 x ULN
Alanine aminotransferase (ALT)	≥ 3 x ULN
Aspartate aminotransferase (AST)	≥ 3 x ULN
Total Bilirubin	≥ 2 x ULN
Albumin	< 2.5 g/dL
Glucose	< 45 mg/dL
	> 160 mg/dL
Sodium	< 130 mEq/L
	> 150 mEq/L
Potassium	< 3 mEq/L
	> 5.5 mEq/L L
Chloride	< 90 mEq/L
	> 115 mEq/L

Calcium	< 7 mg/dL
	> 12 mg/dL
Blood Urea Nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Creatine Phosphokinase (CPK)	≥ 5 x ULN
HbA1c	≥ 7.5%
Prolactin	≥ 5 x ULN
Total Cholesterol (fasting)	≥ 300 mg/dL
LDL Cholesterol (fasting)	≥ 200 mg/dL
Triglycerides (fasting)	≥ 300 mg/dL

16.2.2. LIVER FUNCTION RELATED CRITERIA

Liver function-related laboratory tests will be summarized in accordance to the criteria in Table E.

Table E: Liver Function Pre-defined Criteria

Liver Function Parameter	Criteria
ALT	≥ 3 x ULN
	≥ 5 x ULN
AST	≥ 3 x ULN
	≥ 5 x ULN
GGT	≥ 3 x ULN
	≥ 5 x ULN
Total Bilirubin (in combination with ALT or AST criteria)	> 1.5 x ULN
	> 2 x ULN
CPK	≥ 5 x ULN
Hy's Law	
ALT or AST	> 3 x ULN

Total Bilirubin	> 2 x ULN
Alkaline phosphatase	< 2 x ULN

16.3. ECG EVALUATIONS

During Part A, ECG will be performed during screening, at baseline and on Day 29 and Day 43 or Early Termination Visit [redacted]. ECGs will be collected in triplicate and will be analyzed as an average of the non-missing measurements at each time point. In all cases, ECGs are conducted before other assessments scheduled in the same time window. Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

For Part A, the following ECG parameters will be reported:

- HR (bpm)
- QRS Interval (msec)
- PR Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived by central ECG]
- QTcB Interval (msec) [derived by central ECG]
- RR Interval (msec)
- Overall assessment of ECG

For the overall ECG assessment, there are five possible results for each triplicate: 'Abnormal, Significant', 'Abnormal Insignificant', 'Incomplete Analysis', 'Normal', and 'Uninterpretable'. Overall assessments with a result of 'Incomplete Analysis' or 'Uninterpretable' will be considered missing. Triplicates will be analyzed according to the worst assessment and categorized in the following order, 'Abnormal Significant', 'Abnormal, Insignificant' and 'Normal'.

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit, and for last on-treatment assessment where applicable (for quantitative measurements, except unadjusted QT)
- Incidence of abnormal and normal ECGs by visit
- Shift from baseline to each visit according to markedly abnormal criteria (for quantitative measurements and categorical measurements)
- Incidence of markedly abnormal results defined in Section 16.3.1
- Listing of subjects meeting markedly abnormal criteria

16.3.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT, QTcB and QTcF intervals will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT, QTcB and QTcF intervals will be classified as:
  - > 30 msec increase from baseline
  - > 60 msec increase from baseline

16.4. VITAL SIGNS

The following vital signs measurements will be reported for Part A of this study:

- 10-minute supine/ 1-minute sitting / immediately after standing/ supine/ 3 minutes after standing systolic blood pressure (mmHg)
- 10-minute supine/ 1-minute sitting / immediately after standing/ supine/ 3 minutes after standing diastolic blood pressure (mmHg)
- 10-minute supine/ 1-minute sitting / immediately after standing/ supine/ 3 minutes after standing pulse rate (bpm)
- Respiratory rate (breaths/min)
- Oral temperature (^{o}C)
- Height (cm) at screening
- Weight (kg)
- BMI (kg/m^2) [calculated as weight (kg) / height (m)^2]

Vital signs, including 3-positional blood pressure (systolic blood pressure, diastolic blood pressure) and pulse rate, respiratory rate and oral temperature will be measured during screening, at baseline and on Day 15, Day 29 and Day 43 or Early Termination Visit [redacted] The 3-positional blood pressure and pulse rate will be measured after 10 minutes in the supine position, 1-minute sitting, immediately after standing, and 3 minutes after standing. Pulse will be measured by counting pulse over 60 seconds. Height will be measured only at screening. Body weight will be measured at screening, at baseline and on Days 15, 29 and 43 (or Early Termination Visit).

BMI measurements classify a subject's weight status as underweight, normal, overweight, or obese using Table G. Shifts from Baseline to Day 43 will be produced by treatment group for the SAF Set to show the percentage of subjects who fall into each BMI category combination.

Table F: BMI Weight Status Categories

BMI (kg/m^2)	Weight Status
< 18.5	Underweight
18.5 ≤ BMI < 25.0	Normal
25.0 ≤ BMI < 30	Overweight
30.0 ≤ BMI	Obese

The following summaries will be provided for vital sign data:

- Actual and change from baseline by visit, and for last on-treatment assessment where applicable
- Incidence of markedly abnormal values
- Listing of subjects meeting markedly abnormal criteria
- Shifts from baseline by visit and time point according to markedly abnormal criteria.
- Incidence of patients meeting the criteria of orthostatic hypotention at each visit, where orthostatic hypotention is defined as a reduction in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg when a subject assumes a standing position.

The analysis of change from baseline in all vital sign measurements to Day 29 will be performed using ANCOVA with LOCF, with effects for baseline value, stratification variable (MMSE score at screening), site (or pooled site) and treatment. LSMs for each treatment group, the LSM difference between treatment groups, the associated standard errors and two-sided 95% CIs for the differences between the 9 mg ITI-007 treatment group and placebo, and p-values for between-treatment tests of differences will be presented.

16.4.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria in the table below.

Table G: Markedly Abnormal Criteria for Vital Signs

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND decrease from baseline ≥ 20 mmHg	≥ 180 mmHg AND increase from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND decrease from baseline ≥ 15 mmHg	≥ 105 mmHg AND increase from baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND decrease from baseline ≥ 15 bpm	≥ 120 bpm AND increase from baseline ≥ 15 bpm
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

16.5. MODIFIED PHYSICAL AND NEUROLOGICAL EXAMINATION

For Part A, the following summaries will be provided for physical examination data:

- Incidence of abnormalities at screening (baseline)
- Incidence of abnormalities post baseline

A modified physical examination, including neurological and excluding genital/rectal examinations, will be performed during screening and on Day 29 and Day 43 or Early Termination Visit [redacted] the OLE. The examination should include evaluation of general appearance; eyes, ears, nose, and throat; skin; head and neck; lungs and chest; heart; abdomen; and extremities. Neurological examinations include an assessment of motor function, sensory function, reflexes, and gait. All physical and neurological examination findings are recorded in the eCRF.

16.6. OTHER SAFETY ASSESSMENTS

Handling of missing data for the following assessments is presented in Section 7.1.

16.6.1. MINI-MENTAL STATE EXAMINATION (MMSE)

The MMSE is a brief cognitive test assessing general cognitive function. The MMSE consists of 5 components: 1) orientation to time and place, 2) registration of 3 words, 3) attention and calculation, 4) recall of 3 words, and 5) language. The scores from each of the five components are summed to obtain the overall MMSE score. The score can range from 0 to 30, with lower scores indicating greater impairment in function. This will be used to assess severity at screening and at the end of the study on-treatment period (Day 29) as per eCRF MMSE page.

The observed and change from screening in MMSE total scores to Day 29 will be summarized by treatment.

16.6.2. HACHINSKI ISCHEMIA SCALE

The Hachinski Ischemia Scale (HIS) as a 8-item brief clinical tool helpful in the differentiation of the most common dementia types, dementia of Alzheimer's type and vascular dementia and will be performed during screening and on Days 29 and Day 43 or Early Termination Visit [redacted] the OLE. The range of total score is 0 to 12.

The observed and change from screening in HIS total scores will be summarized by treatment and visit.

16.6.3. BARNES AKATHISIA RATING SCALE (BARS)

The BARS is a rating scale, measuring the observable, restless movements that characterize akathisia. It consists of 4 items: objective restlessness, awareness of restlessness, distress related to restlessness and global clinical assessment of akathisia. Each item is on a 4-point scale (0 to 3), except for the global clinical assessment which is on a 6-point scale (0 to 5), both using low values to represent absence of akathisia and high representing severe akathisia. The BARS total score is the sum of items 1 through 3 and ranges from 0 to 9. Higher values of the BARS total score indicate akathisia is higher in severity. If one or more items at a visit are missing the total will not be calculated.

The observed and change from baseline in BARS total scores to Day 29 will be summarized by treatment.

16.6.4. ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

The AIMS is a clinician rated assessment of abnormal movements. It contains items related to: facial and oral movements; extremity movements; trunk movements; global judgments and dental status. Seven items of the AIMS range from 0= "None" to 4= "Severe". A score of "mild" (2) in two or more categories or a score of "moderate" or "severe" in any one category results in a positive AIMS score (i.e. the scores are not averaged). The global severity score is the response to "Severity of abnormal movements" found within the global judgments section. Additionally, overall severity is scored on the basis of severity of abnormal movements and incapacitation due to abnormal movements.

The (non-global) AIMS total score is the sum of items 1 through 7. The possible range for the AIMS total score is 0 to 28. Higher values of the total AIMS score indicate increased severity in abnormal movement. If one or more of the AIMS total score items are missing at a visit, the score will be set to missing.

The observed and change from baseline in AIMS total scores to Day 29 will be summarized by treatment.

16.6.5. SIMPSON-ANGUS RATING SCALE (SAS)

The SAS is a measure of extrapyramidal side effects consisting of 10 items: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, , head rotation, glabella tap, tremor, salivation and

akathisia. Items are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS total score is defined as the sum of all 10 items and ranges between 0 and 40. Lower values of the SAS total score indicate milder symptoms. If one or more items are missing at a visit the SAS total score will be set to missing.

The observed and change from baseline in SAS total scores to Day 29 will be summarized by treatment.

16.6.6. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is an instrument designed to systematically assess and track suicidal behavior and suicidal ideation throughout the study. The C-SSRS includes the following four sections: Suicidal Ideation, Ideation Intensity, Suicidal Behavior and Actual Suicide Attempts. The strength of this suicide classification system is in its ability to accurately and comprehensively assess suicidality, while limiting the over-identification of suicidal behavior. The C-SSRS will be administered by a trained rater at the site.

Suicidal Ideation is assessed by 5 questions, the responses to which equate to a 6-point scale from 0="No ideation present" to 5="Active ideation with plan and intent". A score of 4 or 5 on this scale indicates serious suicidal ideation. Any score greater than 0 will be counted as having suicidal ideation.

The Ideation Intensity total score is the sum of five items from the Ideation Intensity scale: frequency, duration, controllability, deterrents, and reasons for ideation. If a subject did not endorse any suicidal ideation, a score of 0 for the intensity total score will be given. The possible range for the Intensity total score is 0 to 25.

The number and percentage of subjects with each type of suicidal ideation or any suicidal ideation during each study period will be summarized. The most severe ideation, the ideation intensity items (frequency, duration, controllability, deterrents, and reasons for ideation), and the ideation intensity total score will also be summarized descriptively.

Suicidal Behavior is collected as actual attempt, non-suicidal self-injurious behaviour, interrupted attempt, aborted attempt, preparatory acts or behavior, suicidal behavior, and suicide. The number and percentage of subjects with each type of suicidal attempt (actual attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior) will be summarized for each scheduled visit and overall by study period. The number and percentage of subjects with any suicidal behavior and those completing suicide will also be summarized for each scheduled visit and overall by study period.

The number and percentage of subjects with suicidality as measured by the C-SSRS will be summarized, where suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior. The suicidality indicator will be set to 1 if the subject exhibits suicidality for each visit, 0 if the subject does not exhibit suicidality, and missing otherwise. This data will be summarized at each scheduled visit and overall by study period (treatment and post-treatment).

Data collected on actual suicide attempts (lethality of actual attempts and potential lethality of attempts) will be presented in a data listing.

An overall summary of C-SSRS data (post-Baseline data across all scheduled visits) will include the frequency and percentage of the following:

- At least one suicidal ideation post-Baseline

- Emergence of suicidal ideation (no suicidal ideation at Baseline, and any type of suicidal ideation post-Baseline)
- Emergence of serious suicidal ideation (no suicidal ideation at Baseline, and any serious suicidal ideation [ideation score of 4 or 5] post-Baseline)
- Most severe type of ideation post-Baseline
- Worsening of suicidal ideation (most severe suicidal ideation post-Baseline was more severe than it was at Baseline)
- At least one suicidal behavior post-Baseline
- Emergence of suicidal behavior (no suicidal behavior at Baseline, and any type of suicidal behavior post-Baseline)
- At least one actual attempt post-Baseline
- At least one interrupted attempt post-Baseline
- At least one aborted attempt post-Baseline
- At least one preparatory acts or behaviors post-Baseline
- At least one instance of suicidality [any ideation or behavior] post-Baseline
- Emergence of suicidality (no suicidality at Baseline, and any suicidality post-Baseline)
- Any completed suicides post-Baseline

17. [redacted]

[redacted]

18. [redacted]

[redacted]

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APPENDIX 1. PART A - SCHEDULE OF ASSESSMENTS

Study Period	Screening	Baseline	Double-Blind On-Treatment Period				Follow-up
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7 or ET[1]**
Study Week	**- 2**	**0**	**1**	**2**	**3**	**4**	**6**
Study Day	**Up to – 14**	**1**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**
	Clinic Visit	Clinic Visit	Phone contact	Clinic Visit	Phone contact	Clinic Visit	Clinic Visit
Informed Consent	Before Any Study-Specific Procedures are Conducted						
Review Subject / Caregiver Information Sheet	X						
Medical History including Demography and STOP-bang Questionnaire	X						
Modified Physical & Neurological Examination incl Calculation of BMI (he ght and Mod f ed Hach snk schem a Sca e at screen ng on y)	X					X	X
12-lead ECG[2]	X	X				X	X
Vital Signs[3]	X	X		X		X	X
Hepatitis / HIV Testing	X						
Drug and Alcohol Screen	X	X					
Laboratory Assessments[4]	X					X	X
Dementia Diagnosis	X						
MMSE	X					X	
C-SSRS	X	X				X	X
CMAI-C[9]		X		X		X	
CGI-S of Agitation[9]	X	X		X		X	
CGI-S of Aggression[9]	X	X		X		X	
Caregiver Diary[5]	X	X		X		X	
Day / Night Actigraphy[6]	X	X		X		X	

Schedule of Assessments (continued)

Study Period	Screening	Baseline	Double-Blind On-Treatment Period				Follow-up
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7 or ET[1]**
Study Week	**- 2**	**0**	**1**	**2**	**3**	**4**	**6**
Study Day	**Up to – 14**	**1**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**
	Clinic Visit	Clinic Visit	Phone contact	Clinic Visit	Phone contact	Clinic Visit	Clinic Visit
Review Inclusion / Exclusion Criteria	X	X					
Eligibility Adjudication[7]	X						
NPI-C	X					X	
SAS & BARS & AIMS		X				X	
Blood Draw for Pharmacokinetic Assessments[8]		X				X	X
Blood Draw for Biomarker Assessments		X					
Randomization		X					
Medication Dispensed		X		X			
Unused Medication Returned				X		X	
Treatment Compliance Assessment				X		X	
AEs / SAEs	X	X	X	X	X	X	X
Prior / Concomitant Medications	X	X	X	X	X	X	X

An attempt should be made to collect as many Day 43 assessments as possible upon early discontinuation / early termination from study treatment.

[2] Each ECG assessment will comprise of triplicate 10 second epochs from 12-lead ECGs recorded 5 minutes apart. One triplicate ECG will be performed during screening, at baseline and on Days 29 and 43 (or Early Termination Visit). In all cases, ECGs are conducted before other assessments scheduled in the same time window; for example, when ECG, vital signs, and blood sample collection for PK measures are scheduled for the same time window, ECG measures should be conducted first, followed by vital signs and then blood sample collection.

[3] Vital sign assessments will include 3-positional blood pressure and pulse rate, respiratory rate, and oral temperature. The 3-positional blood pressure and pulse rate will be measured after 10 minutes in the supine position, 1 minute sitting, immediately after standing, and 3 minutes after standing. Pulse will be measured by counting pulse over 60 seconds. Height will be measured only at screening. Body weight will be measured during screening, at baseline and on Days 15 29 and 43 (or Early Termination Visit). Vital signs are always taken after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for labs or PK samples, scheduled in the same time window.

[4] Clinical laboratory samples are to be taken after an overnight fast of at least 10 hours, after any scheduled ECG or vital signs have been recorded. Screenig clinical laboratory may be fasting or non-fasting.

[5] Diaries will be dispensed at screening (Visit 1). Caregivers will be asked to fill out a daily diary during the screening/baseline period and throughout the study on-treatment period. Data collected during the screening period, up to 7 days prior to the baseline visit, will serve as baseline for the data collected in the diary and will serve to ascertain diary compliance before randomization. The diary will be reviewed by the investigator or approved clinical rater at the site to facilitate caregiver interviews and inform the clinical ratings.

[6] Actigraphy units will be provided at screening (Visit 1) to subjects and to caregivers who provide optional consent for the caregiver actigraphy data collection. Actigraphy units will be worn during the screening/baseline period and throughout the study on-treatment period; data will be downloaded from units at scheduled visits. The actigraphy data collected during the screening period, up to 7 days prior to the baseline visit (Visit 2), will serve as baseline for the data collected by actigraphy and will serve to ascertain actigraphy compliance before randomization.

[7] Screening adjudication process to confirm eligibility will take place between screening and baseline and will be administered by remote, independent expert raters and/or medical monitor(s) who are approved for this role by the sponsor and with the adjudication conducted in conjunction with the sponsor. This includes the Qualitative Assessment of Biopsychosocial Conditions (Qual-ABC) to confirm subject suitability and caregiver appropriateness for participation in the study.

[8] Blood sample collection for pharmacokinetic analysis will be collected pre-dose at baseline (Visit 2) and on Study Days 29 (Visit 6) and on Day 43 at the final safety follow-up visit (Visit 7 or Early Termination Visit if a subject does not complete the on-treatment period) for determination of ITI-007 (IC200056 parent) and its metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309) concentrations in plasma.

[9] CGI-S assessments should be completed by the same site rater on the same day after the NPI-C at screening and after the CMAI-C assessment at other visits.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date or start date>study med end date, then not TEAE If study med start date <=start date <= study med end date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If start date < study med start date or start date>study med end date, then not TEAE If study med start date <=start date <= study med end date, then TEAE
	Missing	If start date < study med start date or start date>study med end date, then not TEAE If study med start date <=start date <= study med end date, then TEAE
Partial, but known components show that it cannot be on or after study med start date or cannot be before study med end date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date but before study med end date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start date, assign as prior concomitant If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start date, assign as prior concomitant If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start date, assign as prior concomitant If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start date, assign as prior concomitant If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. **CMAI-C FACTOR COMPOSITE SCORE**

The CMAI-C is comprised of 35 specific symptom items (and two additional items to probe in an open-ended fashion for additional inappropriate behaviors not otherwise specified and the time of day that the behaviors occurred most often, not shown here). Factor analyses on the original 29-item (designed for nursing home use) demonstrated that many of the symptoms cluster together in Factors that largely represent agitation and aggression. Other symptom items failed to load on symptom factors reproducibly across studies, suggesting that these items may not accurately reflect agitation or aggression.

The CMAI-C Factor Composite designed specifically for use in the ITI-007-201 trial was based on factor analysis data from subject samples similar to the target subject population in the -201 trial. The CMAI-C Factor Composite includes those symptom items that reliably load onto Factors I (Aggressive Behavior), II (Physically Non-Aggressive Behavior or Non-aggressive Agitated Behavior), or III (Verbally Agitated Behavior) as described by Rabinowitz and colleagues (2005). The Factor Composite excludes symptom items, such as hoarding and hiding items, that are not related to the agitation and aggression Factors and are not included in the IPA consensus definition of clinically meaningful agitation in cognitive disorders as described by Cummings and colleagues (2015). The CMAI-C Factor Composite excludes symptom items that did not reliably load onto Factors, were excluded from the published factor analyses due to low occurrence, or were excluded from the published factor analyses because they are were items not represented in the original 29-item version of the CMAI.

Below, the 35 symptom items from the CMAI-C are listed and noted whether they were included in the Factor Composite, which Factor is represented by the item, how many studies replicated the finding, and whether the symptom item was also a designated example in the IPA consensus definition of clinically meaningful agitation. Likewise, symptom items that were excluded from the Factor Composite and reasons for exclusion are noted.

#1 [repeat sentences or questions] Factor III Verbally Agitated Behavior (3 studies)

#2 [verbal interruption, relevant] EXCLUDED, not included in 29-item Factor Analysis

#3 [verbal interruption, not relevant] EXCLUDED, not included in 29-item Factor Analysis

#4 [strange noises, laughter, moaning, crying] EXCLUDED, failed to load on Factors

#5 [scream, shout, howl] Factor I Aggressive Behavior (2 studies) IPA example

#6 [complain, whine] Factor III Verbally Agitated Behavior (6 studies)

#7 [requests for attention, nagging, pleading] Factor III Verbally Agitated Behavior (6 studies)

#8 [negative, uncooperative, bad attitude] Factor III Verbally Agitated Behavior (5 studies)

#9 [curse, verbally threatening, insulting] Factor I Aggressive Behavior (5 studies) IPA example

#10 [spit] EXCLUDED (Loads on Aggressive Behavior 1 study, failed to load 3)

#11 [verbally bossy or pushy] EXCLUDED, not included in 29-item Factor Analysis

#12 [verbal sexual advances] EXCLUDED, low occurrence

#13 [physical sexual advances] EXCLUDED, low occurrence

#14 [restless, fidgety] Factor II Non-Aggressive Agitated Behavior (6 studies) IPA example

#15 [pace, wander] Factor II Non-Aggressive Agitated Behavior (6 studies) IPA example

#16 [try to get out, sneak out] Factor II Non-Aggressive Agitated Behavior (5 studies)

#17 [dress or undress in appropriately] Factor II Non-Aggressive Agitated Behavior (5 studies)

#18 [repetitious mannerisms] Factor II (Loads on 2 studies, failed to load 3) IPA example

#19 [handle things inappropriately/rummage] Factor II Non-Aggressive Agitated Behavior (4 studies)

20 [grab or snatch] EXCLUDED, not included in 29-item Factor Analysis IPA example

#21 [hoard objects] EXCLUDED (loads on Factor separate from agitation/aggression)

#22 [hide objects] EXCLUDED (loads on Factor separate from agitation/aggression)

#23 [temper outburst, nonverbal] EXCLUDED, not included in 29-item Factor Analysis

#24 [hit people, self or objects] Factor I Aggressive Behavior (6 studies) IPA example

#25 [kick people or objects] Factor I Aggressive Behavior (6 studies) IPA example

#26 [throw things] Factor I (Loads on 2 studies, low occurrence 3, failed to load 1) IPA example

#27 [tear or destroy property] Factor I Aggressive Behavior (3 studies)

#28 [grab onto to cling to people] Factor I Aggressive Behavior (4 studies)

#29 [push other persons] Factor I Aggressive Behavior (6 studies) IPA example

#30 [bite people or things] EXCLUDED (low occurrence 5 studies) IPA example

#31 [scratch people, self or things] Factor I Aggressive Behavior (5 studies) IPA example

#32 [hurt him/herself, cutting, burning, other] EXCLUDED, low occurrence

#33 [hurt others, cutting, burning, other] EXCLUDED, low occurrence

#34 [fall intentionally] EXCLUDED, low occurrence

#35 [eat or drink nonfood substance] EXCLUDED, low occurrence/failed to load

Table: CMAI-C Factor Composite: Individual Factors

Factor I Aggressive Behavior	Factor II Non-Aggressive Agitated Behavior	Factor III Verbally Agitated Behavior
#5 [scream, shout, howl] #9 [curse, verbally threatening, insulting] #24 [hit people, self or objects] #25 [kick people or objects] #26 [throw things] #27 [tear or destroy property] #28 [grab onto to cling to people] #29 [push other persons] #31 [scratch people, self or things]	#14 [restless, fidgety] #15 [pace, wander] #16 [try to get out, sneak out] #17 [dress or undress in appropriately] #18 [repetitious mannerisms] #19 [handle things inappropriately/rummage]	#1 [repeat sentences or questions] #6 [complain, whine] #7 [requests for attention, nagging, pleading] #8 [negative, uncooperative, bad attitude]

The CMAI-C Factor Composite includes 19 symptom items categorized into 3 symptom domains. The scoring algorithm for the CMAI-C Factor Composite will be based on the scoring of each item rated 1-7 for frequency consistent with the original CMAI-C:

1=Never

2=Less than once a week

3=Once or twice a week

4=Several times a week

5=Once or twice a day

6=Several times a day

7=Several times an hour

Each symptom domain or Factor scores will be a sum of the scores for each individual item within that Factor. The CMAI-C Factor Composite score will be a sum of the scores for each individual item within all three Factors. Possible scores will range from 19 to 133.

APPENDIX 4. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 5. [redacted]

[redacted]

[redacted]