Study Title	A Prospective, Randomized, Double-Blind, Dose-Comparison Concurrent Control Study to Assess the Safety and Tolerability of GRF6019 Infusions in Subjects with Mild to Moderate Alzheimer's Disease
NCT Number	NCT03520998
Document Description	Statistical Analysis Plan (Final Version 2.1)
Document Date	09 June 2019

STATISTICAL ANALYSIS PLAN

PROTOCOL: ALK6019-201

A Prospective, Randomized, Double-Blind, Dose-Comparison Concurrent Control Study to Assess the Safety and Tolerability of GRF6019 Infusions in Subjects with Mild to Moderate Alzheimer's Disease

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DATE: June 09, 2019

STATUS: Final Version 2.1

Statistical Analysis Plan
Protocol：ALK6019-201
Final Version:2.1 Date: 09 June 2019

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AMENDMENT HISTORY

Not applicable

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADAS Cog/11	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change rating
ADL	Activities of Daily Living
AE	Adverse Event
ALS	Amylotrophic lateral sclerosis
ANCOVA	Analysis of Covariance
APOE	Apolipoprotein E
ASL	Arterial Spin Labeling
C-SSRS	Columbia-Suicide Severity Rating Scale
CDR	Clinical Dementia Rating Scale
CDR-SOB	Clinical Dementia Rating Scale – Sum of Boxes
CFT	Category Fluency Test
CS	Clinically significant
CSF	cerebrospinal fluid
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EVAL	Evaluable Population
fMRI	Functional Magnetic Resonance Imaging
GPT	Grooved Pegboard Test
ITT	Intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemia Scale
MMSE	Mini-Mental State Examination
NCS	Not clinically significant
NPI-Q	Neuropsychiatric Inventory Questionnaire
PPROT	Per protocol
SAE	serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	standard deviation
SOB	Sum of Boxes
TEAE	Treatment-emergent AE
TFLs	Tables, Figures, and Listings

vMRI	Volumetric Magnetic Resonance Imaging
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled "A Prospective, Randomized, Double-Blind, Dose-Comparison Concurrent Control Study to Assess the Safety and Tolerability of GRF6019 Infusions in Subjects with Mild to Moderate Alzheimer's Disease" (V6.0 12OCT2018, V7.0 02NOV2018). Analysis related to exploratory objectives (assessment of changes in composition and distribution of blood-based and CSF (in consenting subjects) biomarkers, as well as changes in imaging results as measured by vMRI, fMRI, and ASL) will be described in a separate plan. Mock shells for the CSR Appendix 14 are also produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the finalized SAP. The SAP is to be interpreted in conjunction with the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

1.1 Study Objectives

Primary Objective
To assess the safety, tolerability and feasibility of GRF6019, a [redacted] human plasma protein fraction administered by IV infusion in subjects with mild to moderate Alzheimer's Disease (AD).

Secondary Objective
To assess the effects of the study agent on subjects' cognitive function.

Exploratory Objectives
- To identify specific biomarkers associated with cognitive functional changes and/or indicators of AD progression
- To assess the potential therapeutic effects of GRF6019 on AD biomarkers of neuronal death, synaptic function, inflammation, and growth factors utilizing the CSF collected in the optional CSF biomarker research.
- To identify potential indicators of AD progression and potential therapeutic effect based on brain imaging performed at the start and end of study for comparison.

1.2 Study Design

This is a prospective, randomized, double-blind, dose-comparison concurrent control study to assess the safety, tolerability, and feasibility of GRF6019, a [redacted] human plasma protein fraction, administered by intravenous (IV) infusion to subjects with mild to moderate AD, and will be conducted at up to 10 sites in the United States.

The overall duration of the study is approximately 15 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 12 months. The subject participation period is approximately 7 months from screening through end of study, unless prematurely discontinued.

The study consists of approximately 40 subjects randomized to one of the following two dose levels: 20 subjects at 100 mL and 20 subjects at 250 mL. All subjects will receive one infusion per day at the randomized dose for 5 consecutive days during weeks 1 and 13.

All subjects will undergo a screening visit, baseline visit, treatment visits, follow-up visits and an end of study/early termination visit. During the two 5-day dosing periods, subjects will reside in inpatient study observation units to facilitate safety evaluation. Subjects will be discharged from the inpatient facility the day after the 5th day of dosing. Subjects who are eligible and consent to participate in the optional cerebrospinal fluid (CSF) biomarker research at participating sites will undergo two lumbar punctures for CSF collection, the first occurring prior to initial dosing, and the second occurring following final dosing.

Safety and tolerability assessments will occur at every visit. Neurocognitive and psychomotor assessments will be performed at baseline and at periodic interim assessments following dosing. In the event of early termination of a subject, the end of study procedures will be performed unless the subject has withdrawn consent. A comprehensive efficacy and safety assessment of all data *in toto* will be conducted at the end of the study.

[redacted]

1.3 Sample Size Estimation

A total of approximately 40 subjects (20 in the 100 mL and 20 in the 250 mL groups) will be randomized in the study with the intent of obtaining ~30 evaluable subjects who have received at least 5 doses and completed through Visit 8. Subjects who discontinue prior to Visit 8 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced.

The primary endpoint of this study is safety and tolerability. Using the statistical approximation described by Hanley (aka the “Rule of Threes”), the upper bound of the 95% confidence interval for the rate of an unreported AE is at most 7.5% (3/number of subjects receiving active drug). In addition, the proposed sample size may be sufficient to identify trends in the effects of plasma-derived factors and in the relationship between dose and cognitive effects.

1.4 Randomization and Blinding

The study will be randomized with a mixed block size of 2 and 4 and stratified by sex. The randomization will be web-based and centralized. The randomization codes will be generated by a statistician who has no involvement in the study other than generation and maintenance of the randomization codes.

All study outcome measures will be assessed by blinded Outcomes Assessors. The Outcomes Assessors will observe the subject during the infusion of the study agent and collect and/or manage/report adverse events (AEs) and serious adverse events (SAEs). To ensure that Outcomes Assessors, subjects, and trial partners are unaware of the dose being administered, appropriate measures will be taken to mask the infusion pump and glass vials containing the study agent such that they will only be visible as necessary to the unblinded Infusion Nurse for appropriate dosing. In addition, a curtain, drape, or equivalent will be used to shield the infusion administration setup from view of all but the unblinded Infusion Nurse. Communication between the Outcomes Assessor and the Infusion Nurse will be restricted to only that required to ensure immediate patient safety.

Finally, to avoid potential unblinding based on patient albumin levels, serum albumin lab results will remain blinded until the conclusion of the study.

1.5 Study Data

The study data being analyzed per this Statistical Analysis Plan includes all clinical data captured by eCRF as well as safety lab data. The eCRF database will be locked for the final analyses and the final data transfers from the central lab will be utilized. Savonix Neurocognitive Assessments, Imaging data, and biomarker data, are not included in the eCRF database.

2 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. No imputation will be performed for missing data unless stated otherwise. Listings for CSR Appendix 16.2 will include all the subject data points being collected or derived for analyses, and will be sorted by treatment group, site, and subject number.

2.1 Treatment Groups

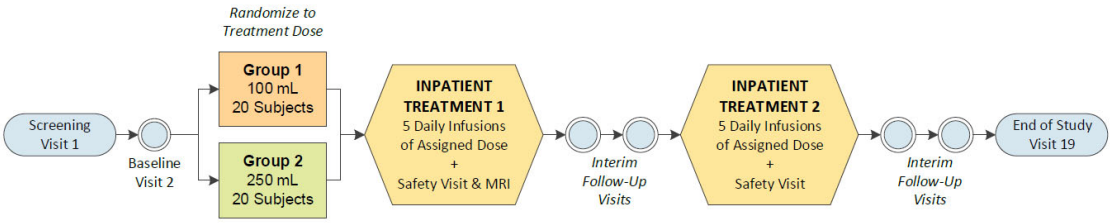
The [redacted] treatment groups will be labelled as 100 mL, 250mL, [redacted] within the statistical output. [redacted]

2.2 Statistical Hypothesis Tests

Inasmuch as the study design is focused on safety and tolerability, the statistical approach taken with the secondary endpoints will be primarily descriptive with only modest amounts of hypothesis testing; within-subject changes from baseline for each dosing group and between-group differences will be evaluated for the purpose of designing future studies. Inferential statistics for any within-group and between-group comparisons will be described for each specific endpoint as applicable. For all statistical tests, the nominal two-sided p values will be reported.

2.3 Study Phase, Visit, and Day

Phase	Screening/ Baseline	Treatment: Period 1	Follow-up: Period 1			Treatment: Period 2	Follow-up: Period 2			
Visit	1 to 2	3 to 7	8	9	10	11 to 15	16	17	18	19/Exit
Day	-28 to -1	1 to 5	6	28±7	56±7	85-89	90	112±7	140±7	168±7



The study is set up as shown above, along with assigned study period, visit, and day. In general, the baseline is defined as the last assessment before the first intake of the study medication unless otherwise specified. All scheduled assessments after first administration of study drug will be used. Repeat/unscheduled assessments will not be used in descriptive statistics or any per-time point analyses but will be shown in listings as applicable. Pre-dose unscheduled assessments will be taken into account for baseline determination and post first dose unscheduled assessments will be taken into account for worst-case determination as applicable.

Reference date refers to the start date of the first study drug administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date. The relative day will be defined as: visit date – reference date + 1 for visits on or after the reference date and visit date – reference date for visits before the reference date. Consequently, there is no 'Day 0' defined.

2.4 Analysis Sets

- Screened set (SCRN): All subjects who were screened and entered into EDC.
- Screen Failure set (SCRF): All subjects who were entered as screen failures in the EDC.
- Intention-to-Treat Dataset (ITT): All subjects who were randomized.
- Safety set (SAF): All subjects who received at least one dose of the study agent.
- Evaluable set (EVAL):All subjects who received at least 5 of the 10 planned doses.
- Per Protocol set (PPROT): A subset of the Evaluable set comprised of subjects who do not have any of the deviations listed below or any other deviation affecting efficacy identified prior to database lock.

Deviation Type	Deviation	Additional Clarification
Eligibility Inclusion Criteria Not Met	Diagnosis of probable AD based upon the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria	Subjects with a clinical diagnosis of AD according to NIA-AA criteria who have a negative amyloid PET scan will also be excluded.
Eligibility Inclusion Criteria Not Met	MMSE Score 12-24 inclusive	
Eligibility Inclusion Criteria Not Met	Modified Hachinski Ischemia Scale (MHIS) score of <=4	
Eligibility Exclusion Criteria Met	Evidence of clinically relevant neurological disorder(s) other than AD	
Eligibility Exclusion Criteria Met	Initiation or change in the dosage of cholinesterase inhibitors (AChEI), memantine, Axona, vitamin E supplementation, or selegiline within 3 months prior to screening	Will be determined based upon actual date of change and proximity to screening. Will be determined prior to database lock
Eligibility Exclusion Criteria Met	Treatment with any human blood product, including transfusions and IV immunoglobulin, during the 6 months prior to screening	
Eligibility Exclusion Criteria Met	Concurrent daily treatment with benzodiazepines, long-acting opioids, or other medications that, in the investigator's opinion, interfere with cognition	
Eligibility Exclusion Criteria Met	Concurrent participation in another interventional clinical trial. Prior clinical trial subjects must have been off study agents for at least 30 days (or 5 half-lives, whichever is longer), 4 months for disease modifying therapies, and 1 year for vaccine or immunotherapy trials prior to screening.	

Deviation Type	Deviation	Additional Clarification
Eligibility Exclusion Criteria Met	A history of a major psychiatric disorder diagnosed before the onset of AD, including schizophrenia, major depression or bipolar disorder, and/or alcohol/substance dependency. Psychiatric symptoms that occur in the context of AD (e.g. psychosis, irritability, depression) are not exclusionary unless the PI believes they could interfere with study procedures	
Eligibility Exclusion Criteria Met	>2 lacunar strokes or other imaging abnormality on baseline MRI that would make the interpretation of subsequent MRI scans of the brain difficult.	Only if the MRI findings are indicative of another cause of dementia/cognitive impairment
Eligibility Exclusion Criteria Met	Any other condition and/or situation that the investigator believes may interfere with the safety of the subject, the intent and conduct of the study, or interpretation of study data	Only when interfering with the interpretation of study data
Compliance	Incorrect treatment dispensed and administered to subject	
Compliance	Received less than 5 doses	
Out of Window	Efficacy Procedures performed outside of the protocol window which are a consistent pattern or potential risk to study data outcomes	
Study Drug Temp Excursion	Study drug temperature excursions when determined to have impacted the quality of the study drug	
Concomitant meds	Use of prohibited concomitant medications as defined in the protocol that have an effect on cognition	

Decisions regarding which subjects are included in PPROT will be made before database lock.
A summary table of number (%) of patients in each analysis set and applicable treatment assignment will be provided (Table 14.1.1).

2.5 Definition of Subgroups

Subjects will be categorized into mild and moderate AD based on the baseline Mini-Mental State Examination (MMSE) with the recalculated total score >20 and <=20, respectively.

2.6 Descriptive Summaries

All tabulated summaries will include the two treatment groups [redacted] and overall (includes data from both treatment groups). For endpoints that are continuous in nature: number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive summary. For endpoints that are categorical in nature: frequency counts and percentages will be presented in the descriptive summary.

The number of decimal places to display for calculated data will be determined by the original scale of the data. Means, medians, and confidence intervals will be reported with one (1) additional decimal place. Standard deviation will be reported with two (2) additional decimal places. Minimum and maximum will be reported with the same number of significant digits as the method of capture.

For all efficacy and safety tables summarizing change from baseline, the baseline and post-baseline results at all planned timepoints will be included.

3 PLANNED INTERIM ANALYSIS

No interim analyses are planned.

4 SUBJECT INFORMATION

In general, all subject-level parameters will be summarized for the SAF set unless stated otherwise.

4.1 Disposition Information

Summaries will be provided for the following disposition information: Number of subjects screened, screening failures, randomized, completed study, discontinued study with the reasons of discontinuation from study, discontinued from study drug with the reasons of discontinuation from study drug, and discontinued from study but completed study drug dosing. The randomized treatment group will be shown for ITT set (Table 14.1.2).

4.2 Protocol Deviations

The number and percentage of subjects with protocol deviations will be tabulated per coded protocol deviation by severity (major vs minor) for the ITT set (Table 14.1.3.1).

The success of blinding will be assessed based on all occurrences (intentional or unintentional) of unblinding of blinded study subjects, their trial partners or study personnel (e.g. investigators, medical providers, cognitive testing raters, the Sponsor or their representatives) during infusions. Number of subjects with any occurrence of unblinding will be summarized on any day any period, any day each period, and each day within each period (Table 14.1.3.2).

4.3 Demographics and Baseline Characteristics

Descriptive statistics or frequency tabulation will be provided for the following parameters. The 'Declined to answer/don't know' will not be added for the denominator unless stated otherwise.

4.3.1 Demographic Parameters

Descriptive statistics or frequency tabulation will be provided for following parameters (Table 14.1.4.1):

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other Race, Multiple – derived if multiple races are checked)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Marital status (Single, Married, Widowed, Divorced/Separated)
- Family size
- Longest held career (Professional, Homemaker, Trade person, Arts/Entertainment)
- Annual household income ever reported (Less than $50,000, $50,000 to $99.999, $100,000 to $199,999, $200,000 or more).
- Weight at baseline (kg)
- Height at baseline (cm)
- Body Mass Index (BMI) at baseline = Weight at baseline (kg) / [Height at baseline (m)]^2 (rounded to 1 decimal. Although available in the raw data, BMI will be recalculated from last weight and height measurement before start of treatment)
- Duration of AD (years)
- Any Prior Treatments for AD (Yes/No)

4.3.2 Baseline Assessment of Modified Hachinski Ischemia Scale (MHIS)

No tabulation summary will be provided for MHIS data, which will be included in a subject data listing only.

4.3.3 Baseline Assessment of Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a simple series of questions for the assessment of suicidal ideation and behavior in clinical trials (Posner 2011). The C-SSRS (including Actual Attempts Lethality) in both Lifetime and Last 6 Months are evaluated at screening visit.

Descriptive statistics or frequency tabulation will be provided for following C-SSRS parameters (Table 14.1.4.2):

- Suicidal Ideation (Yes/No): Wish to be Dead, Non-Specific Active Suicidal Thoughts, Active Suicidal Ideation without Intent to Act, Active Ideation with Some Intent without Specific Plan, Active Ideation with Specific Plan and Intent

- Intensity of Ideation
  - Most Severe Suicidal Ideation (1-5)
  - Frequency of Suicidal Ideation (1-5)
  - Duration of Suicidal Ideation (1-5)
  - Deterrents of Suicidal Ideation (0-5)
  - Controllability of Suicidal Ideation (0-5)
  - Reason of Suicidal Ideation (0-5)
- Suicidal Behavior:
  - Actual Attempt (Yes/No)
  - Total Number of Attempts
  - Interrupted Attempt (Yes/No)
  - Total Number of Interrupted Attempts
  - Aborted Attempt (Yes/No)
  - Total Number of Aborted Attempts
  - Preparatory Acts or Behavior (Yes/No)
  - Suicidal Behavior (Yes/No)
- Lethality - Most recent attempt:
  - Actual Lethality/Medical Damage (0-5)
  - Potential Lethality (0-2)
- Lethality - Most lethal attempt:
  - Actual Lethality/Medical Damage (0-5)
  - Potential Lethality (0-2)
- Lethality - Initial/First attempt:
  - Actual Lethality/Medical Damage (0-5)
  - Potential Lethality (0-2)

4.3.4 APOE Genotype

Frequency tabulation will be provided for APOE Genotype (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4) (Table 14.1.4.3)

4.4 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject and the subject's trial partner during screening. The medical history should focus on duration of disease and recent history, with an emphasis on the history of cognitive symptoms related to probable AD. Additionally, the medical history should include:

- Current/past illnesses and conditions
- Current symptoms
- Surgeries and procedures
- Allergies
- Family history
- Social history (e.g. exercise, smoking, alcohol, illegal substances) and current living situation
- Cause of parental death (if not living)

- Prior radiologic imaging, CSF assessments, and/or PET Scan results (if available and within 12 months of screening)

4.4.1 Subject Medical History

All reported subject medical history findings will be summarized by MedDRA system organ class and preferred term, in order of descending overall frequency (Table 14.1.5.1).

4.4.2 Family Medical History

All reported family medical histories will be listed by type of family member (Father, Mother, Brother, Sister, Son, Daughter, Half-Brother, Half-Sister) for following parameters:

- Status (Living, Deceased)
- Age at time of death (Years)
- History of neurological disease (Any, Alzheimer's, Parkinson's, Lewy body dementia, Frontotemporal dementia, Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease, Vascular dementia, Other neurological Family Hx)

4.4.3 Social History

A frequency tabulation will be summarized for the following parameters (Table 14.1.5.2):

- Current Living Situation (In my home, In a relative or friend's home, In a care facility, Other, Declined to answer/don't know)
- Living conditions (Alone, With Family, With a Friend(s)/Roommate(s), With a Professional Caregiver, With One or More Pets, Declined to answer/don't know). Various living conditions will be arranged in order of descending overall frequency.

4.4.4 Exercise/Activity Level

Descriptive statistics or frequency tabulation will be provided for all evaluated parameters related to exercise/activity level (Table 14.1.5.3):

- Walk or bike at least 10 minutes (Yes, No)
- Days/week walking or biking>=10 minutes
- Hours/day walking or biking (derived by total minutes/60)
- Any other activity/sports (Yes, No)
- Days/week for other activity/sports
- Hours/day for other activity/sports (derived by total minutes/60)

4.4.5 Tobacco Use

Descriptive statistics or frequency tabulation will be provided for the following parameters related to tobacco use (Table 14.1.5.4):

- Smoking status (Never Smoked, Current Smoker, Ex-Smoker)
- Number of years smoked
- Average cigarettes/day
- Average pipes/day

- Average cigars/day
- Average cigarettes, pipes or cigars/day (derived by adding average cigarettes/day, average cigars/day, and average pipes/day)

4.4.6 Alcohol and Illicit Substance Use

Frequency tabulation will be provided for the following parameters related to alcohol use (Table 14.1.5.5):

- Had alcohol in past 6 months (Yes, No)
- Drinks on a typical day (One or two, Three to five, Six or more)
- Frequency of 6+ drinks (Less than monthly, Monthly, Weekly, Daily or almost daily)
- Problem with alcohol when young (Yes, No, Declined to answer)
- Any DUI (Yes, No, Declined to answer)
- Used illicit substances in the past (Yes, No)

4.5 Prior and Concomitant Medications

Subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject in the past 12 months (including previous treatments for AD) will be coded using the World Health Organization-Drug Dictionary and summarized separated for each of following two categories:

1) Prior medication: medication that ended before the first dose of study drug.
2) Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

A frequency tabulation of prior and concomitant medications will be shown by ATC class level 4 and preferred term (Table 14.1.6.1 and 14.1.6.2).

4.6 Extent of Exposure

The extent of exposure (days) per period is defined as date of last study drug intake – date of first study drug intake + 1 within each period. For subjects that have a "grace day" (i.e. they received 5 infusions over a period of 6 days instead of 5 infusions over 5 consecutive days), such dosing "grace day" is not considered an interruption. Extent of exposure as well as actual volume administered will be summarized descriptively per period and overall (two periods combined) (Table 14.1.7.1).

Descriptive statistics of actual infusion rate (mL/hour) will be summarized at each time point per infusion day (Table 14.1.7.2). The numbers of below, within and above the designated infusion rate reference will be tabulated at each time point per infusion day (Table 14.1.7.3). In addition, descriptive statistics or frequency tabulation will be provided for the following infusion parameters collected at each infusion day (Table 14.1.7.4):

- Required adjustment to flow rate (Yes, No)
- Entire assigned dose administered (Yes, No)

- Actual Volume Administered (mL)
- Maximum flow rate (mL/hour)
- Device used to administer infusion (Baxter Flo Gard, Other)

4.7 Treatment Completion

Treatment completion is calculated as the actual volume administered, as a percentage of the volume expected. The expected doses per treatment period will be calculated as [5 x total daily dose volume] for all subjects, regardless of study completion status. The expected doses overall will be calculated as [10 x total daily dose volume] for all subjects, regardless of study completion status. Treatment completion will be summarized descriptively and categorically (<75% and >=75%) per period and overall (Table 14.1.8.1).

In addition, number of subjects completing 1-4, 5, 6-9, and 10 infusions will be summarized (Table 14.1.8.2).

4.8 Tolerability

Number of subjects completing 8 weeks (i.e. through Visit 10) after receiving at least 5 infusions, and number of subjects completing 24 weeks (i.e. through End of Study) after receiving at least 10 infusions will be tabulated (Table 14.1.9.1 and 14.1.9.2).

4.9 Visit Compliance

Number of subjects with a visit at each scheduled analysis timepoint will be summarized (Table 14.1.10.1).

Kaplan-Meier curves of the time to completion or discontinuation of the trial will be produced. Note at the final analysis all subjects will have the event of completion or discontinuation and no subjects will be censored. Log-rank test p value may be reported (Figure 14.1.10.2).

5 EFFICACY

The study is not designed to detect significant changes in cognition over time. However, using available data from analysis of the secondary endpoints, including changes in cognition scores from baseline, descriptive summarization as well as appropriate 95% confidence limits will be developed. Of particular interest will be the within-subject changes from baseline and their distribution around a null value of zero and a comparison among groups to evaluate any trends in dose response. For each efficacy endpoint, paired t-test may be conducted to evaluate within-subject changes from baseline. Between-group differences may be assessed by Analysis of Covariance (ANCOVA) including baseline and sex as the covariates. Between-group difference may be assessed by analysis of Covariance (ANCOA) including baseline and sex as the covariates. Figures, including line graphs or bar graphs, may be generated to show treatment group differences on selected endpoints.

For analysis purposes, results at early termination visits will not be included in tabulated summaries.

Following efficacy endpoints will be analyzed based on both EVAL and PPROT sets.

5.1 Mini-Mental State Examination (MMSE)

The MMSE (Folstein 1975) consists of the following 5 components:

- Orientation to time and place (2 items)
- Registration of 3 words (1 item)
- Attention and calculation (1 item)
- Recall of 3 words (1 item)
- Language (6 items)

The scores from the 5 components are summed to obtain the overall MMSE total score. The MMSE total score can range from 0 to 30, with higher scores indicating better mental status.

Although available in the raw data, the MMSE total score will be recalculated. If a subject has 1 missing item, the following algorithm will be used to compute the total score: Total score = [(total score from completed items) / (maximum total score for completed items)] x (maximum total score [=30] for all items in the scale). The total score is then rounded to the next highest integer. If there is more than 1 missing item, the total score will be considered missing at that time point.

Changes from baseline for the recalculated MMSE total score will be summarized at each scheduled timepoint (Days 6, 90, and 168) (Table 14.2.1).

5.2 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS Cog/11)

The ADAS-Cog/11 (Rosen 1984) includes 11 items assessing cognitive function:

- Word Recall: the mean of the three trials is used, rounded to 2 decimal places
- Command
- Constructional Praxis
- Naming Objects and Fingers
- Ideational Praxis
- Orientation
- Word Recognition
- Remembering Test Instructions
- Comprehension
- Word Finding Difficulty
- Spoken Language Ability

Although available in the raw data, the ADAS-Cog/11 total score is derived as a linear sum of the scores recorded for the 11 individual domains. Higher scores reflect greater cognitive impairment.

Changes from baseline for the total score as well as 11 individual domain scores and will be summarized at each scheduled timepoint (Days 28, 112, and 168) (Table 14.2.2).

5.3 Grooved Pegboard Test (GPT)

The Grooved Pegboard Test is a manual dexterity test measuring visual-motor coordination (Lafayette 2002). The test consists of a pegboard with 25 holes with randomly positioned slots and pegs with a key along one side. The subject is to insert the pegs as quickly as possible into the slots in sequence, first with the dominant hand and then with the non-dominant hand. The score is the time it takes for the subject to complete the task with each hand. For subjects who fail to complete the test in 5 minutes the score is the number of total pegs inserted. In addition, to time to completion, the number of pegs dropped (for each hand) is recorded.

Changes from baseline for these GPT scores will be summarized for each hand (dominant and non-dominant) at each scheduled timepoint (Days 6, 28, 85, 90, 112, and 168) (Table 14.2.3).

5.4 Category Fluency Test (CFT)

Category fluency tasks are an important component of neuropsychological assessment, especially when evaluating for dementia syndromes. Subjects are asked to generate words from a specified semantic category (e.g., name as many different types of animals, vegetables, or fruits in a 60 second period) (Acevedo 2000). The number of correct, non-repeated responses constitutes the primary CFT raw score. In addition, the number of repetitions and other errors is recorded.

Changes from baseline for CFT scores will be summarized for each scheduled timepoint (Days 28, 112, and 168) (Table 14.2.4).

5.5 Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB)

The Clinical Dementia Rating Scale (CDR) is a global assessment instrument that yields Global and Sum of Boxes (SOB) scores, with the global score regularly used in clinical and research settings to stage dementia severity. The CDR is obtained via semi-structured interviews with patients and informants (e.g. trial partners) to characterize functioning in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care (Hughes 1982). Each domain is rated on a 5-point scale, and the CDR-SOB score is obtained by summing each of the domain box scores. The CDR-SOB is considered a more detailed quantitative general index than the Global score (O'Bryant 2008).

Changes from baseline for CDR global and CDR-SOB scores will be summarized at each scheduled timepoint (Days 28, 112, and 168) (Table 14.2.5).

5.6 Alzheimer's Disease Cooperative Study – Activities of Daily Living 23 (ADCS-ADL23)

The ADCS-ADL is an inventory of informant-based items used to assess activities of daily living and instrumental activities of daily living, (i.e., functional performance) for AD subjects (Galasko 1997). The interviewer asks the subject's caregiver a total of 23 questions regarding the subject's ability to maintain good hygiene, use a telephone, initiate conversations, etc. A score of up to 4 points may be assigned to each question. A higher score indicates less impairment; the maximum achievable score (indicating no ADL impairment) is 78. The sum of the responses for the 23 items of the inventory will be calculated for the total score and recorded into eCRF.

Changes from baseline for ADCS-ADL23 total score will be summarized for subject and trial partner separately, and at each scheduled timepoint (Days 28, 56, 112, 140, and 168) (Table 14.2.6.1 and 14.2.6.2).

5.7 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change rating (ADCS-CGIC)

The ADCS-CGIC is a process for obtaining an assessment of meaningful clinical change over time (Schneider 1997). It is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician. The ADCS-CGIC focuses on clinicians' observations of change in the subject's cognitive, functional and behavioral performance since the beginning of a trial. It relies on both direct examination of the subject and interview of informants. Unlike a targeted symptom scale, it takes into account a subject's overall functioning in the cognitive, behavioral and functional activity domains.

The ADCS-CGIC is a single value score based on a 7-point scale using the following values:

1 = Marked Improvement
2 = Moderate Improvement
3 = Minimal Improvement
4 = No Change
5 = Minimal Worsening
6 = Moderate Worsening
7 = Marked Worsening

Changes from baseline for ADCS-CGIC rating (1-7) will be summarized at each scheduled timepoint (Days 28, 112, and 168) (Table 14.2.7).

5.8 Neuropsychiatric Inventory Questionnaire (NPI-Q)

The NPI-Q evaluates the most frequent neuropsychiatric manifestations of dementia and determines their frequency and intensity (Kaufer 2000). It is designed to be a self-administered questionnaire completed by informants (e.g. trial partners) about subjects for whom they care. Generally, the NPI-Q is used to evaluate changes in subject behavior that have appeared during a given period. The NPI-Q comprises 12 domains: delusions, hallucinations, dysphoria, apathy, euphoria, disinhibition, aggressivity and restlessness, irritability, anxiety, aberrant

motor behavior, appetite and eating disorders, and nocturnal behavior. Initial responses to each domain question are "Yes" (present) or "No" (absent). If the response to the domain question is "No", the informant goes to the next question. If "Yes", the informant then rates both the severity of the symptoms present within the last month on a 3-point scale and the associated impact of the symptom manifestations on them (i.e., trial partner distress) using a 5-point scale. Thus, the NPI-Q evaluates response to therapy and provides symptom severity and distress ratings for each symptom reported, and total severity and distress scores reflecting the sum of individual domain scores.

Change from baseline for NPI-Q total severity score and total distress score will be summarized at each scheduled timepoint (Days 28, 56, 112, 140, and 168) (Table 14.2.8).

6 SAFETY

All safety analyses will be done on the Safety Set.

6.1 Adverse Events

6.1.1 Coding of AEs

The verbatim terms of AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Events are looked at on the level of their preferred term and system organ class.

6.1.2 Treatment-Emergent AE

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing. Treatment-emergent AEs (TEAE) are defined as AEs that were reported or worsened on or after the start of study drug dosing and up to and including the end of the follow-up.

6.1.3 Period Allocation of AE

Adverse events are allocated to a period based on their start date and time. If the start date and time of an event falls between (or on) the start and stop date and time of a period, the AE is attributed to that period (treatment-emergent principle).

Rule: period start datetime ≤ AE start datetime ≤ period stop datetime.

In case of partial AE start dates and or times, the events are allocated to the periods using the available partial information on start and end datetime; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods. In case of a completely missing AE start date, the event is allocated to the first period, except if the end date of the AE falls before the start of this period. In case of any other missing scenarios, the period allocation of AE will be determined by manual data review prior to database lock.

6.1.4 Variables Attributed to Adverse Events:

- AE term (verbatim and MedDRA preferred term and system organ class)
- Onset datetime, End datetime, and duration of AE
- Serious AE (Yes/No), if yes classification will be listed
- Severity (Mild, Moderate, Severe)
- Relation to study treatment (Unrelated, Possibly Related, Definitely Related)
- Frequency (Single Episode, Intermittent, Continuous)
- Action taken with study treatment (No Action Taken, Treatment Held, Treatment Discontinued)
- Other Action due to AE (Medication Therapy, Non-Drug Therapy, Other)
- Outcome of AE (Recovered/Resolved, Not Recovered/Not Resolved, Resolved/Resolved with Sequelae, Fatal, Unknown)
- AE leading to death (Yes/No)
-
- AE of special interest

6.1.5 Analysis Methods

There will be no formal statistical testing unless indicated otherwise.
A summary will be provided for the following TEAEs per period and overall (Table 14.3.1.1.1-14.3.1.1.3):

- Subjects with Any TEAE
- Subjects with Any Study Drug-Related1 TEAE
- Subjects with Any TEAE with an Outcome of Death
- Subjects with Any Serious TEAE
- Subjects with Any Study Drug-Related Serious TEAE
- Subjects with Any TEAE Leading to Discontinuation of Study Drug
- Subjects with Any Study Drug-Related TEAE Leading to Discontinuation of Study Drug
- Subjects with Any TEAE of Special Interest
- Subjects with Any Study Drug-Related TEAE of Special Interest

The adverse events will be shown by MedDRA system organ class and preferred term, in order of descending overall frequency. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized per period and overall. Incidence tabulations will be provided for overall summary (Table 14.3.1.2.1-14.3.1.2.3), summary by highest severity (Table 14.3.1.3.1-14.3.1.3.3), and summary by relatedness (Table 14.3.1.4.1-14.3.1.4.3).

Incidence of Serious TEAEs, TEAEs of Special Interest, TEAEs Leading to Subject Withdrawal and TEAEs Leading to Death will be tabulated by MedDRA System Organ Class and Preferred Term (Table 14.3.1.5.1-14.3.1.5.4), and listed as well (Listing 14.3.1.6.1-14.3.1.6.4).

Adverse events with preferred terms associated with blood pressure changes will also be presented by infusion period, SOC, PT, and treatment group. Infusion

period will be further categorized by whether the event start date occurred during the infusion period or after the infusion period. Examples of such events can be identified by the following preferred terms: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, blood pressure increased, increased blood pressure, blood pressure diastolic increased, blood pressure systolic increased, hypotension, hypertension, low blood pressure, high blood pressure. This is a non-exhaustive list and a review of AE MedDRA coding will be conducted prior to lock to identify all events associated with blood pressure changes. (Table 14.3.1.7.1-14.3.1.7.3).

6.2 Clinical Laboratory Evaluations

Numeric measurements of hematology, serum chemistry, urinalysis and urine chemistry will be investigated. Changes from baseline for all safety lab parameters will be summarized at each scheduled timepoint (Table 14.3.2.1.1-14.3.2.1.3). Frequency tables for categorical test results will be tabulated at each scheduled timepoint (Table 14.3.2.2). Shift tables from the baseline to each post-baseline scheduled timepoint will be presented (Table 14.3.2.3.1-14.3.2.3.3).

6.3 Vital Signs

Summary statistics will be presented for the actual values and change from baseline values (as appropriate) at each time point for all vital signs (Temperature, Pulse Rate, Systolic Blood Pressure (BP), Diastolic BP, Respiratory Rate) and weight. Changes from baseline for all vital sign parameters and weight will include pre-dose at Day 1 to pre-dose at subsequent days and at all timepoints during infusion (Table 14.3.3.1). In addition, changes from baseline for all vital sign parameters will include pre-dose at each infusion day to all post-dose timepoints within each infusion day (Table 14.3.3.2).

The incidence of the following categorized blood pressure values and changes from baseline will be summarized (Table 14.3.3.3):

- Systolic BP > 180
- Systolic BP > 200
- Systolic BP < 90
- Diastolic BP > 110
- Diastolic BP > 120
- Diastolic BP < 50
- An absolute change of >30% from Day 1 pre-dose (baseline) in systolic and/or diastolic BP. This change includes positive and negative percent changes.

6.4 Electrocardiogram

P-R interval, QT interval, QRS duration, Ventricular heart rate and QTc intervals using Bazett's correction formula and Fridericia's correction formula will be investigated. QTc values will be used as reported, they will not be recalculated. Changes from baseline for all Electrocardiogram (ECG) parameters will be summarized at each scheduled timepoint (Days 5, 85, and 89) (Table 14.3.4.1). In addition, frequency tabulation of the overall ECG results (Normal, Abnormal NCS, and Abnormal CS) will be summarized (Table 14.3.4.2).

6.5 Physical Examinations

For physical examination data, when calculating the percentage reporting each category, the "Not Done" category will not be included in the denominator.

Number (%) of subjects with abnormal physical examinations will be tabulated at screening and Day 168 (Tables 14.3.5.1). Normal/abnormal shift from screening to Day 168 will also be provided (Tables 14.3.5.2).

6.6 C-SSRS since Last Visit

The frequency of individual C-SSRS since last visit assessments (Yes/No) will be summarized at each scheduled timepoint (Days 6 and 90) (Tables 14.3.6).

6.7 MRI Testing, Echocardiogram, and PET Scan

All recorded MRI testing, Echocardiogram, and PET scan results captured in the CRF will be listed as part of CSR Appendix 16.2.

7 EXPLORATORY

All exploratory analyses will be described in a separate plan.

8 CHANGES FROM PROTOCOL

The Per Protocol dataset is defined in the protocol as: a subset of the Evaluable Dataset comprised of subjects who have no Major Protocol Deviations. All failed eligibility criteria are considered a Major Protocol Deviation, however, not all eligibility criteria failures should automatically remove a subject from the Per Protocol dataset. This SAP clarifies which protocol deviations will exclude a subject from the per protocol dataset and all protocol deviations will be reviewed by the study team prior to database lock to identify the final Per Protocol dataset definition.

Blood pressure values that constituted an AESI were at the discretion of the PI. As such, ranges for blood pressures of special interest (BPSI) were identified and will be analyzed according to section 6.3.

9 REFERENCES

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10 TABLES, LISTINGS, AND FIGURES FOR CSR APPENDIX 14

Following tables, listings, and figures are to be included in the post-text Appendix 14 of CSR and may be modified with Sponsor's approval.

Number	Title	Population
Table 14.1.1	Analysis Populations	SCRN
Table 14.1.2	Subject Disposition	ITT
Table 14.1.3.1	Protocol Deviations	ITT
Table 14.1.3.2	Assessment of Unblinding by Blinded Outcome Assessors	SAF
Table 14.1.4.1	Demographics	SAF
Table 14.1.4.2	Baseline Assessment of Columbia-Suicide Severity Rating Scale (C-SSRS)	SAF
Table 14.1.4.3	APOE Genotype	SAF
Table 14.1.5.1	Medical History	SAF
Table 14.1.5.2	Social History	SAF
Table 14.1.5.4	Exercise-Activity Level	SAF
Table 14.1.5.5	Tobacco Use	SAF
Table 14.1.5.6	Alcohol and Illicit Substance Use	SAF
Table 14.1.6.1	Prior Medication	SAF
Table 14.1.6.2	Concomitant Medication	SAF
Table 14.1.7.1	Exposure to Study Drug	SAF
Table 14.1.7.2	Actual infusion rate at each time point per infusion day	SAF
Table 14.1.7.3	Numbers of below, within and above the designated infusion rate reference	SAF
Table 14.1.7.4	Overall infusion parameters per infusion day	SAF
Table 14.1.8.1	Completion of Study Drug	SAF
Table 14.1.8.2	Number of subjects completing 5 and 10 infusions	SAF
Table 14.1.9.1	Number of subjects completing 8 weeks after receiving at least 5 infusions	SAF
Table 14.1.9.2	Number of subjects completing 24 weeks after receiving at least 10 infusions	SAF
Table 14.1.10.1	Visit Compliance	SAF
Figure 14.1.10.2	Kaplan-Meier curves of the time to completion or discontinuation of the trial	SAF
Table 14.2.1	Changes in scores on the Mini-Mental State Examination (MMSE)	EVAL, PPROT
Table 14.2.2	Changes in scores on the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog/11)	EVAL, PPROT
Table 14.2.3	Changes in scores on the Grooved Pegboard Test	EVAL, PPROT
Table 14.2.4	Changes in scores on the Category Fluency Test	EVAL,

Number	Title	Population
	(CFT)	PPROT
Table 14.2.5	Changes in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB)	EVAL, PPROT
Table 14.2.6.1	Changes in the Alzheimer's Disease Cooperative Study – Activities of Daily Living23 (ADCS-ADL23) for Subjects	EVAL, PPROT
Table 14.2.6.2	Changes in the Alzheimer's Disease Cooperative Study – Activities of Daily Living23 (ADCS-ADL23) for Partners	EVAL, PPROT
Table 14.2.7	Changes on the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)	EVAL, PPROT
Table 14.2.8	Change on the Neuropsychiatric Inventory Questionnaire (NPI-Q)	EVAL, PPROT
Table 14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events (TEAE)	SAF
Table 14.3.1.1.2	Overall Summary of Treatment-Emergent Adverse Events (TEAE) in Period 1	SAF
Table 14.3.1.1.3	Overall Summary of Treatment-Emergent Adverse Events (TEAE) in Period 2	SAF
Table 14.3.1.2.1.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.2.1.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term	SAF
Table 14.3.1.2.2.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term in Period 1	SAF
Table 14.3.1.2.2.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term in Period 1	SAF
Table 14.3.1.2.3.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term in Period 2	SAF
Table 14.3.1.2.3.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term in Period 2	SAF
Table 14.3.1.3.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity and MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.3.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity and MedDRA System Organ Class and Preferred Term in Period 1	SAF
Table 14.3.1.3.3	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity and MedDRA System Organ Class and Preferred Term in Period 2	SAF

Number	Title	Population
Table 14.3.1.4.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug and MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.4.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug and MedDRA System Organ Class and Preferred Term in Period 1	SAF
Table 14.3.1.4.3	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug and MedDRA System Organ Class and Preferred Term in Period 2	SAF
Table 14.3.1.5.1	Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.5.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.5.3	Incidence of Treatment-Emergent Adverse Events (TEAEs) Leading to Subject Withdrawal by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.5.4	Incidence of Treatment-Emergent Adverse Events (TEAEs) Leading to Death by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.6.1	Listing of Serious Treatment-Emergent Adverse Events (TEAEs)	SAF
Table 14.3.1.6.2	Listing of Treatment-Emergent Adverse Events (TEAEs) of Special Interest	SAF
Table 14.3.1.6.3	Listing of Treatment-Emergent Adverse Events (TEAEs) Leading to Subject Withdrawal	SAF
Table 14.3.1.6.4	Listing of Treatment-Emergent Adverse Events (TEAEs) Leading to Death	SAF
Table 14.3.1.7.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) for Preferred Terms Associated with Blood Pressure Changes by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.7.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) for Preferred Terms Associated with Blood Pressure Changes by MedDRA System Organ Class and Preferred Term in Period 1	SAF
Table 14.3.1.7.3	Incidence of Treatment-Emergent Adverse Events (TEAEs) for Preferred Terms Associated with Blood Pressure Changes by MedDRA System	SAF

Number	Title	Population
	Organ Class and Preferred Term in Period 2	
Table 14.3.2.1.1	Changes in hematology measurements	SAF
Table 14.3.2.1.2	Changes in serum chemistry measurements	SAF
Table 14.3.2.1.3	Changes in urinalysis measurements	SAF
Table 14.3.2.2	Frequency of categorical laboratory assessments	SAF
Table 14.3.2.3.1	Shift Table in hematology measurements	SAF
Table 14.3.2.3.2	Shift Table in serum chemistry measurements	SAF
Table 14.3.2.3.3	Shift Table in urinalysis measurements	SAF
Table 14.3.3.1	Changes from baseline in vital sign measurements and weight	SAF
Table 14.3.3.2	Changes from pre-dose in vital sign measurements within each infusion day	SAF
Table 14.3.3.3	Blood pressure measurements of special interest	SAF
Table 14.3.4.1	Changes from baseline in ECG measurements	SAF
Table 14.3.4.2	Frequency of overall ECG results	SAF
Table 14.3.5.1	Frequency of abnormal physical examination results	SAF
Table 14.3.5.2	Shift Table in physical examination results	SAF
Table 14.3.6	Frequency of Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit	SAF

11 LISTINGS FOR CSR APPENDIX 16.2

Number	Title	Population
Listing 16.2.1.1	Analysis Populations	SCRN
Listing 16.2.1.2	Screen Failures	SCRF
Listing 16.2.1.3	Subject Disposition	ITT
Listing 16.2.1.4	Protocol Deviations	ITT
Listing 16.2.1.5	Informed Consent	ITT
Listing 16.2.1.6	Study Visits	ITT
Listing 16.2.2.1	Inclusion Criterion Not Met or Exclusion Criteria Met	ITT
Listing 16.2.2.2	Assessment for AD using NIA-AA criteria	ITT
Listing 16.2.2.3	Drug Testing/Serology Screen	ITT
Listing 16.2.2.4	Randomization	ITT
Listing 16.2.3.1	Demographics	ITT
Listing 16.2.3.2	Baseline Characteristics	ITT
Listing 16.2.3.3	Baseline Assessment of Modified Hachinski Ischemia Scale (MHIS)	ITT
Listing 16.2.3.4.1	Columbia-Suicide Severity Rating Scale (C-SSRS) Lifetime	ITT
Listing 16.2.3.4.2	Columbia-Suicide Severity Rating Scale (C-SSRS) Last 6 Months	ITT
Listing 16.2.3.5	APOE Genotype	ITT
Listing 16.2.4.1.1	Medical History	SAF
Listing 16.2.4.1.2	Alzheimer's Disease History	SAF
Listing 16.2.4.2	Family Medical History	SAF
Listing 16.2.4.3	Social History	SAF
Listing 16.2.4.4	Exercise/Activity Level	SAF
Listing 16.2.4.5	Tobacco Use	SAF
Listing 16.2.4.6	Alcohol and Illicit Substance Use	SAF
Listing 16.2.4.7	PET Scan	SAF
Listing 16.2.4.8	Echocardiogram Results	SAF
Listing 16.2.5.1.1	Prior Medications	SAF
Listing 16.2.5.1.2	Previous Treatment for Alzheimer's Disease	SAF
Listing 16.2.5.2	Concomitant Medications	SAF
Listing 16.2.5.3	Extent of Exposure	SAF
Listing 16.2.5.4	Infusion Rate	SAF
Listing 16.2.5.5	Daily Summary of Infusion Administration	SAF
Listing 16.2.5.6	Treatment Completion	SAF
Listing 16.2.5.7	Tolerability	SAF
Listing 16.2.5.8	Assessment of Blinding	SAF
Listing 16.2.6.1	Mini-Mental State Examination (MMSE)	ITT
Listing 16.2.6.2	Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS Cog/11)	ITT

Number	Title	Population
Listing 16.2.6.3	Grooved Pegboard Test (GPT)	ITT
Listing 16.2.6.4	Category Fluency Test (CFT)	ITT
Listing 16.2.6.5	Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB)	ITT
Listing 16.2.6.6	Alzheimer's Disease Cooperative Study – Activities of Daily Living 23 (ADCS-ADL23)	ITT
Listing 16.2.6.7	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change rating (ADCS-CGIC)	ITT
Listing 16.2.6.8	Neuropsychiatric Inventory Questionnaire (NPI-Q)	ITT
Listing 16.2.7.1	Non Treatment Emergent Adverse Events	SAF
Listing 16.2.7.2	Treatment Emergent Adverse Events	SAF
Listing 16.2.8.1	Clinical Laboratory Results	SAF
Listing 16.2.8.2	ECG Results	SAF
Listing 16.2.8.3	MRI Testing	SAF
Listing 16.2.9	Vital Signs	SAF
Listing 16.2.10	Physical Examinations	SAF
Listing 16.2.11	Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Assessment	SAF

12 ATTACHMENTS

None