STATISTICAL ANALYSIS PLAN

PROTOCOL: ALK6019-202

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer's Disease

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DATE: December 11, 2019

STATUS: Final Version 1.1

Statistical Analysis Plan
Protocol: ALK6019-202
Final Version: 1.1 Date: 11-December-2019

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AMENDMENT HISTORY

Not applicable

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADCS-ADL-Severe	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory for Severe Alzheimer's Disease
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Caregiver Input
ADL	Activities of Daily Living
AE	Adverse Event
ApoE	Apolipoprotein E
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CRO	Contract Research Organization
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICH E6 R2	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemia Scale
MMSE	Mini-Mental State Examination
NIA-AA	National Institute on Aging – Alzheimer's Association
NODscid	Non-obese diabetic severe combined immunodeficiency
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory Nursing Home Version
NSG	NODscid Gamma
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIB	Severe Impairment Battery
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPCR	Urine Protein-to-Creatinine Ratio
US	United States

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled “A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer’s Disease” (V2.0 03DEC2018). A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unblinding of the study data. Analysis related to exploratory objectives (serial compositional analysis of plasma proteins to identify specific biomarkers associated with cognitive function and/or indicators of disease progression) 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 and tolerability of GRF6019, a [redacted] human plasma protein fraction administered by IV infusion in subjects with severe AD.

Secondary Objective
To assess the potential effects of GRF6019 on subjects’ cognition and function.

Exploratory Objectives
Blood and plasma will be collected and analyzed to identify specific biomarkers associated with cognitive functional changes and/or indicators of AD progression.

1.2 Study Design

This is a prospective, randomized, double-blind, placebo-controlled study conducted at up to four (4) sites in the United States.

The overall duration of the study is approximately 12 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 9 months. The subject participation period is approximately 9 weeks from Screening through End of Study, unless prematurely discontinued.

Subjects that meet eligibility for inclusion in the trial will be randomized in a 2:1 ratio to GRF6019 (Group1) or placebo (Group 2). Treatment groups will be stratified by sex. There will be one (1) dosing period during which subjects randomized to GRF6019 will receive GRF6019, while subjects randomized to placebo will receive placebo. The dosing period consists of 5 consecutive days (“pulsed dosing”) of IV infusions of 250 mL of either GRF6019 or placebo.

During the Screening Period, subjects will undergo all Screening assessments including an echocardiogram. During the Baseline Period, subjects and their caregivers will complete a series of cognitive and functional assessments.

During the 5-day dosing period, subjects who do not already reside in a long-term care/skilled nursing facility will be admitted to such a facility to facilitate safety evaluation.

Safety and tolerability assessments will occur at every visit. Cognitive and functional assessments will be performed at Baseline and periodically at subsequent visits through End of Study/Early Termination. In the event of early termination of a subject who has received at least one dose, the End of Study procedures will be performed unless the subject/subject's legally authorized representative has withdrawn consent. A comprehensive safety and efficacy assessment of all data *in toto* will be conducted at the end of the study.

1.3 Sample Size Estimation

Approximately 20 subjects will be randomized in a 2:1 ratio to active GRF6019 or placebo with the intent of obtaining ~16 evaluable subjects. Subjects who discontinue prior to completing Visit 8 may be replaced. Subjects who withdraw or are withdrawn during Screening will be replaced. [redacted]

The primary endpoints pertain to safety and tolerability of the GRF6019 dosing regimen in subjects with severe AD.

1.4 Randomization and Blinding

To minimize the potential bias at the time of randomization, the study will be double-blind and randomized with a 2:1 ratio to GRF6019 (Group 1) or placebo (Group 2). A stratified block randomization will be implemented by sex. 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 or other blinded raters. However, [redacted] GRF6019 or placebo will be dispensed by an unblinded pharmacist, or other qualified staff responsible for drug accountability, to an unblinded Infusion Nurse who will administer the infusion. To ensure that Outcomes Assessors, raters, and other study personnel as well as subjects and their caregivers are unaware of the allocation, appropriate measures will be taken to mask the study agent/placebo containers and IV setup such that they will only be visible as necessary to the unblinded Infusion Nurse. In addition, a curtain, drape, or equivalent may be used to shield the infusion administration setup from view of all but the unblinded Infusion Nurse, and the unblinded Infusion Nurse will be responsible for concealing and returning used containers of the study agent or placebo to the pharmacy at the end of the Infusion Period. The unblinded Infusion Nurse will

enter the infusion data and blinding assessment into the eCRF to avoid unblinding of the source data during data entry.

During the infusion, communication between the blinded Outcomes Assessor and the unblinded Infusion Nurse should be limited to only that required to ensure the immediate safety of subjects. The Outcomes Assessors will observe the subject during the infusion and collect and/or manage/report AEs and SAEs.

Except for the unblinded CRA(s) whose sole responsibility is to ensure the study agent/placebo is being dispensed, administered, and disposed of properly, the study Sponsor and their representatives will be blinded with respect to the infusion product.

1.5 Study Data

The study data includes all clinical data captured by eCRF and 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. Biomarker data is considered exploratory and will not be included in the eCRF database.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into three separate categories (although not limited to) the following: (1) investigator's study file, (2) subject blinded clinical source documents, and (3) subject unblinded clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF, IRB approval with correspondence, informed consents, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and study-specific manuals (e.g., lab manual).

Subject clinical source documents would be separated according to blinded source and unblinded source and include (although are not limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiologic imaging, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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 two treatment groups will be labelled as GRF6019 250 mL or placebo within the statistical output.

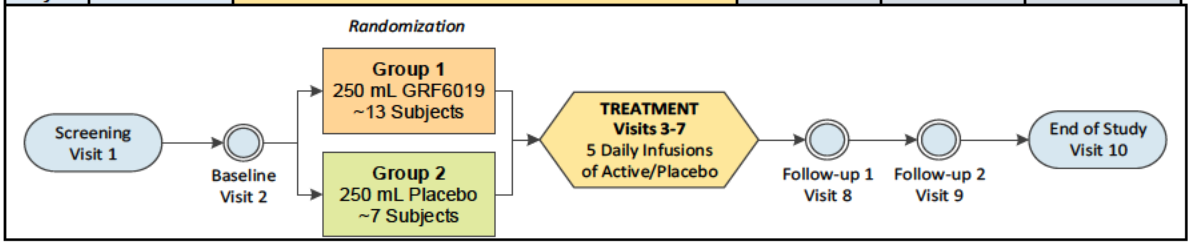
The treatment period includes a total of 5 infusions during Week 1. It is anticipated that sites will infuse subjects with 5 doses over 5 days. A “grace day” is allowed in the event of unanticipated safety or health concerns during the treatment period.

2.2 Statistical Hypothesis Tests

Because the primary objective of the study is safety and tolerability, it is not designed to detect statistically significant differences between active and placebo efficacy endpoints. The statistical approach toward secondary endpoints will be primarily descriptive; within-subject changes from baseline for each dosing group among-group differences will be evaluated.

2.3 Study Phase, Visit, and Day

Phase	Screening/ Baseline	Treatment	Follow-up		
Visit	1 to 2	3 to 7	8	9	10
Day	-28 to -1	1 to 5	6+3	12±3	33±7



The study is set up as shown above, along with study phase, 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 Datasets

- Screened Dataset (SCRN): All subjects who were screened and entered into EDC.
- Screen Failure Dataset (SCRF): All subjects who were entered as screen failures in the EDC.
- Intention-to-Treat Dataset (ITT): All randomized subjects.

- Safety Dataset (SAF): All subjects who received at least one dose of the study agent.
- Evaluable Dataset (EVAL): All subjects who receive at least 4 of the 5 planned doses.
- Per Protocol Dataset (PPROT): A subset of the Evaluable Dataset 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 AD based upon the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria	
Eligibility Inclusion Criteria Not Met	MMSE Score 0-10 inclusive	
Eligibility Inclusion Criteria Not Met	Modified Hachinski Ischemia Scale (MHIS) score of <=4	
Eligibility Inclusion Criteria Not Met	If on medications for cognition (e.g., rivastigmine, galantamine, donepezil, memantine), must be on stable dosage for at least 8 weeks prior to Baseline	Will be dependent upon timing of dose change
Eligibility Inclusion Criteria Not Met	If on daily antidepressant medications and/or benzodiazepines and/or typical or atypical antipsychotics, must be on stable dosage for 8 weeks prior to Baseline. If on prn dosing with atypical antipsychotics and/or benzodiazepines, these should not be given within 24 hours before each day of cognitive and other ratings (V1, V2, V8, V9, V10)	Will be dependent upon timing of dose change
Eligibility Exclusion Criteria Met	Evidence of clinically relevant neurological disorder(s) other than AD	
Eligibility Exclusion Criteria Met	Treatment with any human blood product, including transfusions and IV immunoglobulin, during the 6 months prior to screening	

Deviation Type	Deviation	Additional Clarification
Eligibility Exclusion Criteria Met	Concurrent participation in any other therapeutic treatment trial. If there was prior clinical trial participation, subject must have discontinued investigational agents for at least 30 days for small molecules, and 1 year for active or passive immunotherapies prior to Screening	
Eligibility Exclusion Criteria Met	Subjects who have a level of agitation that, in the opinion of the investigator, could interfere with study procedures	
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	
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 the PPROT will be made before database lock.

A summary table of number (%) of subjects in each analysis set and applicable treatment assignment will be provided (Table 14.1.1).

The presentation of baseline characteristics will be conducted on the ITT dataset. All safety analyses will be performed for the SAF dataset. Analyses of the secondary endpoints will focus on the EVAL and/or PPROT datasets.

2.5 Definition of Subgroups

Not applicable.

2.6 Descriptive Summaries

All tabulated summaries will include the two treatment groups and overall (includes data from both treatment groups). For endpoints that are continuous in nature: number of observations, mean, standard error of the mean (SEM),

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 of efficacy data are planned. Safety data will be assessed in an ongoing manner.

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, randomized not treated, completed study, discontinued from study drug with the reasons of discontinuation from study drug, and discontinued from study but completed study drug dosing with the reasons of discontinuation. The SCRN set will be used for the subject disposition table (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 caregivers 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 during treatment phase, each day during treatment phase within the study, and any day during the study (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) : calculated as the integer part of (Date of Informed Consent – Date of Birth + 1)/365.25
- Sex (Male, Female)
- Race (Caucasian, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Other Race, Multiple – derived if multiple races are checked, Not Done/Refused)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Education Level (No high school, Some High School, High school diploma/GED, Undergraduate, Masters, Doctoral, Unknown)
- Marital status (Single, Married, Widowed, Divorced/Separated)
- Family size
- Longest held career (Professional, Homemaker, Trade person, Arts/Entertainment, Declined to answer/Don't know, Other)
- Highest historical level of annual household income ever reported (Less than $50,000, $50,000 to $99,999, $100,000 to $199,999, $200,000 or more, Declined to answer/Don't know).
- 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 APOE Genotype

Frequency tabulation will be provided for APOE Genotype (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4) (Table 14.1.4.2)

4.3.4 Echocardiogram Baseline Assessment

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

4.4 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject and the subject's caregiver(s) during screening. The medical history should focus on 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 and any active medical condition
- Surgeries and procedures
- Allergies
- Family history in biological parents, siblings, and offspring of AD, other dementias, or neurological disorders, if known.
- Social history (e.g. smoking, alcohol, illegal substances), if known.
- Prior imaging, cerebrospinal fluid assessments, or other relevant diagnostic tests, including genetics, if available.

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)
- Cause of death
- 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 Tobacco Use

Descriptive statistics or frequency tabulation will be provided for the following parameters related to tobacco use (Table 14.1.5.3):

- 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)

4.4.5 Alcohol and Illicit Substance Use

Frequency tabulation will be provided for the following parameters related to alcohol and illicit substance use (Table 14.1.5.4):

- Consumed alcohol in past 6 months (Yes, No)
- Problem with alcohol when young (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) is defined as date of last study drug intake – date of first study drug intake + 1 within the dosing 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 overall (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)
- Volume of Saline Flush
- Device used to administer infusion (Baxter Flo Gard, Other)

Unscheduled changes in flow rate will be included in the subject data listing only

4.7 Treatment Completion

Treatment completion is calculated as the actual volume administered, as a percentage of the volume expected. The expected dose overall will be calculated

as [5 x total daily dose volume] for all subjects, regardless of study completion status. Treatment completion will be summarized descriptively and categorically (<75% and >=75%) overall (Table 14.1.8.1).

In addition, number of subjects completing 1, 2, 3, 4, and 5 infusions will be summarized (Table 14.1.8.2).

4.8 Tolerability

Number of subjects completing 4 weeks after receiving at least 5 infusions will be tabulated (Table 14.1.9).

4.9 Visit Compliance

Number of subjects with a visit at each scheduled analysis timepoint will be summarized (Table 14.1.10).

5 EFFICACY

The study is not powered to detect significant changes in cognition, function, ADLs, etc.; however, using available data from analysis of the secondary efficacy endpoints, including changes in scores from baseline, descriptive summaries 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 between groups to evaluate any trends in differences between subjects randomized to active and placebo agents.

For analysis purposes, results at early termination visits will not be included in tabulated summaries unless the number of early termination visits is > 5.

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 and 33) (Table 14.2.1).

5.2 Severe Impairment Battery (SIB)

The SIB is designed to assess cognitive abilities in patients with severe AD. The SIB is divided into scorable subscales that cover orientation to time and place, attention, language, praxis, visuospatial ability, construction, memory, orientation to name, and social interaction. Scoring gives credit to nonverbal and partially correct answers, thus decreasing the need for language output. There are 51 items, and it takes approximately 20 minutes to complete. The range of possible scores is 0-100 (Panisset 1994).

Although available in the raw data, the SIB scores will be recalculated. Changes from baseline for recalculated SIB subscale scores and the recalculated total score will be summarized at each scheduled timepoint (Days 6, 12, and 33) (Table 14.2.2).

5.3 Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL Severe)

The ADCS-ADL-Severe assesses the competence of patients with AD in performing basic activities of daily living. The ADCS-ADL-Severe contains 19 items covering physical and mental functioning and independence in self-care (e.g. dressing, grooming, bathing, eating, walking, and toileting). For each ADL, the informant (e.g., caregiver) is first asked if the patient attempted the activity during the past 4 weeks. If a patient did attempt the ADL, the informant is asked to choose the single most accurate definition of the patient's level of performance. The score ranges from 0 to 54, with higher scores indicating less functional impairment (Galasko 2005).

Although available in the raw data, the ADCS-ADL Severe total score will be recalculated. Changes from baseline for recalculated ADCS-ADL Severe total score will be summarized at the scheduled timepoint (Day 33) (Table 14.2.3).

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

The ADCS-CGIC 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 the trial. It relies on both direct examination of the subject and interview of informants (Ferris 1997, Schneider 1997). 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

ADCS-CGIC rating (1-7) will be summarized at each scheduled timepoint (Days 6, 12, and 33) (Table 14.2.4).

5.5 Neuropsychiatric Inventory Questionnaire (NPI or NPI-NH)

The NPI (Cummings 1994) comprises 10 behavioral areas and 2 neurovegetative areas (12 domains): delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite/eating changes. Information is gathered from caregivers familiar with the patient's behavior. To serve as an informant, the caregiver must have at least daily contact with the patient. Initial responses to each domain screening question are "Yes" (present) or "No" (absent). If the response to the domain question is "No," the interviewer goes to the next question. If "Yes," the interviewer proceeds to ask the informant a series of sub questions for that domain. For each behavioral domain, there are 4 scores: frequency, severity, domain total score (frequency x severity), and caregiver distress (NPI)/occupational disruptiveness (NPI-NH). Thus, the NPI evaluates response to therapy and provides symptom severity and distress ratings for each symptom reported, as well as total severity and distress scores reflecting the sum of individual domain scores.

The NPI-NH was derived from the NPI (Cummings 1994) to evaluate the neuropsychiatric manifestations and psychopathology of patients with AD and other dementias who reside in nursing homes, extended care facilities, or other long-term care settings. The NPI-NH is an interview-based scale designed to be administered to an informed professional nursing home caregiver (as opposed to a family or home-based caregiver in the standard NPI) involved in the daily care of the subject. Generally, the NPI-NH is used to evaluate changes in subject behavior that have appeared during a given period (Wood 2000).

Change from baseline for NPI or NPI-NH total severity score and total distress score will be calculated and summarized at each scheduled timepoint (Days 12 and 33) (Table 14.2.5).

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 Variables Attributed to Adverse Events:

- AE term (verbatim and MedDRA preferred term and system organ class)
- Onset datetime, End datetime, Study Day and duration of AE
- Serious AE (Yes/No), if yes classification will be listed (Death, Life-threatening Disability or Permanent Damage, Hospitalization – initial or prolonged, Congenital Anomaly/Birth Defects, Other Serious (Important Medical Events)).
- AE of special interest
- Frequency (Single Episode, Intermittent, Continuous)
- Severity (Mild, Moderate, Severe)
- Relation to study treatment (Unrelated, Possibly Related, Definitely
- Related)
- Action taken with study treatment (No Action Taken, Treatment Held, Treatment Discontinued)
- Other Action due to AE (No Action, Medication Therapy, Non-Drug Therapy, Other)
- Outcome of AE (Recovered/Resolved, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Fatal, Unknown)
- AE leading to death (Yes/No)

6.1.4 Analysis Methods

There will be no formal statistical testing unless indicated otherwise.
A summary will be provided for the following TEAEs overall (Table 14.3.1.1):

- Subjects with Any TEAE
- Subjects with Any Study Drug-Related 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. Incidence tabulations will be provided for overall summary (Table 14.3.1.2.1-14.3.1.2.2), summary by highest severity (Table 14.3.1.3), and summary by relatedness (Table 14.3.1.4).

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 14.3.1.5.5.).

6.2 Clinical Laboratory Evaluations

Numeric measurements of hematology, serum chemistry, and urinalysis 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). 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 (Oral Temperature, Pulse Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Respiration 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 as well as 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 blood pressure changes 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
- A 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 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 3, 6 and 33) (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 Days 1, 3, 5 and 33 (Tables 14.3.5.1). Normal/abnormal shift from pre-dose at Day 1 to pre-dose at subsequent days will also be provided (Tables 14.3.5.2).

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	SCRN
Table 14.1.3.1	Protocol Deviations	ITT
Table 14.1.3.2	Assessment of Unblinding	ITT
Table 14.1.4.1	Demographics	SAF
Table 14.1.4.2	APOE Genotype	SAF
Table 14.1.5.1	Medical History	SAF
Table 14.1.5.2	Social History	SAF
Table 14.1.5.3	Tobacco Use	SAF
Table 14.1.5.4	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 infusions	SAF
Table 14.1.9	Number of subjects completing 4 weeks after receiving at least 5 infusions	SAF
Table 14.1.10	Visit Compliance	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 Severe Impairment Battery Total score	EVAL, PPROT
Table 14.2.3	Changes in the Alzheimer's Disease Cooperative Study – Activities of Daily Living Severe (ADCS-ADL Severe)	EVAL, PPROT
Table 14.2.4	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)	EVAL, PPROT
Table 14.2.5	Change on the Neuropsychiatric Inventory Questionnaire (NPI or NPI-NH) total severity score and total distress score	EVAL, PPROT
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events (TEAE)	SAF

Number	Title	Population
Table 14.3.1.2.1	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.2.2	Incidence of Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term	SAF
Table 14.3.1.3	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity and MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.4	Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug and MedDRA System Organ Class and Preferred Term	SAF
Table 14.3.1.5.1	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 14.3.2.1.1	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 14.3.2.3.1	Shift Table in hematology measurements	SAF

Number	Title	Population
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 changes of special interest	
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

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	SCRN
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	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	APOE Genotype	ITT
Listing 16.2.3.5	Echocardiogram	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	Tobacco Use	SAF
Listing 16.2.4.5	Alcohol and Illicit Substance Use	SAF
Listing 16.2.4.6	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	Severe Impairment Battery	ITT
Listing 16.2.6.3	Alzheimer’s Disease Cooperative Study – Activities of Daily Living Inventory for Severe Alzheimer’s Disease (ADCS-ADL Severe)	ITT
Listing 16.2.6.4	Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change Caregiver Input rating (ADCS-CGIC)	ITT
Listing 16.2.6.5	Neuropsychiatric Inventory Questionnaire (NPI or NPI-NH)	ITT

Number	Title	Population
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 16.2.9	Vital Signs	SAF
Listing 16.2.10	Physical Examinations	SAF

12 ATTACHMENTS

None