



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	Protocol (Version 7.0)
Document Date	02 November 2018



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

Protocol Number: ALK6019-201
Clinical Phase: 2
Sponsor: Alkahest, Inc.
125 Shoreway Road, Suite D
San Carlos, CA 94070
Investigational Drug: GRF6019
Indication: Alzheimer's Disease
Authorized Representative: [REDACTED]
125 Shoreway Road, Suite D
San Carlos, CA 94070
Telephone: 650-801-0469
Fax: 650-801-0480
Principal Investigator: [REDACTED]
Version Number: V7.0
Version Date: 02NOV2018
Replaces Version(s): V6.0, 12OCT2018

CONFIDENTIAL STATEMENT

The information contained in this document and all information provided as related to this clinical study are the confidential and proprietary information of the Sponsor and except as may be required by federal, state or local laws or regulations may not be disclosed to others without prior written permission of the Sponsor. The Principal Investigator may, however, disclose such information to supervised individuals working on the clinical study, provided such individuals agree to maintain the confidentiality of such information.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS..... 6

LIST OF DEFINITIONS 8

PROTOCOL APPROVAL PAGE 9

STATEMENT OF COMPLIANCE..... 10

PROTOCOL SUMMARY 11

SCHEMATIC OF STUDY DESIGN 13

1 KEY ROLES..... 13

 1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY 13

 1.2 STUDY ORGANIZATION..... 13

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE 13

 2.1 BACKGROUND INFORMATION..... 13

 2.2 RATIONALE..... 14

 2.3 POTENTIAL RISKS AND BENEFITS 16

 2.3.1 KNOWN POTENTIAL RISKS 16

 2.3.2 KNOWN POTENTIAL BENEFITS..... 17

3 OBJECTIVES AND PURPOSE 17

4 STUDY DESIGN AND ENDPOINTS 17

 4.1 DESCRIPTION OF THE STUDY DESIGN..... 17

 4.2 STUDY ENDPOINTS 18

 4.2.1 PRIMARY ENDPOINTS 18

 4.2.2 SECONDARY ENDPOINTS 18

 4.2.3 EXPLORATORY ENDPOINTS 19

5.1 INCLUSION CRITERIA..... 19

5.2 EXCLUSION CRITERIA..... 20

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION..... 21

5.4 SUBJECT WITHDRAWAL OR TERMINATION..... 22

 5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION..... 22

 5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION 22

5.5	PREMATURE TERMINATION OR SUSPENSION OF STUDY	23
6	STUDY AGENT	23
6.1	STUDY AGENT(S) AND CONTROL DESCRIPTION.....	23
6.1.1	ACQUISITION.....	23
6.1.2	FORMULATION, APPEARANCE, PACKAGING, AND LABELING	23
6.1.3	PRODUCT STORAGE AND STABILITY	24
6.1.4	PREPARATION	24
6.1.5	DOSING AND ADMINISTRATION	24
6.1.6	ROUTE OF ADMINISTRATION.....	24
6.1.7	DOSING SCHEDULE.....	25
6.1.8	DURATION OF THERAPY	25
6.2	STUDY AGENT ACCOUNTABILITY.....	25
7	STUDY PROCEDURES AND SCHEDULE	26
7.1	STUDY PROCEDURES/EVALUATIONS	26
7.1.1	STUDY SPECIFIC PROCEDURES	26
7.2	LABORATORY PROCEDURES/EVALUATIONS	33
7.2.1	CLINICAL LABORATORY EVALUATIONS.....	33
7.2.2	OTHER ASSAYS OR PROCEDURES.....	33
7.2.3	SPECIMEN PREPARATION, HANDLING, STORAGE, AND SHIPPING	35
7.3	STUDY SCHEDULE	35
7.3.1	SCREENING	35
7.3.2	BASELINE	36
7.3.3	RANDOMIZATION.....	36
7.3.4	TREATMENT	37
7.3.5	FOLLOW-UP.....	37
7.3.6	FINAL STUDY VISIT	39
7.3.7	EARLY TERMINATION.....	39
7.3.8	SCHEDULE OF EVENTS TABLE.....	39
7.4	CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES.....	39
7.5	PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES.....	40

8	ASSESSMENT OF SAFETY	40
8.1	SPECIFICATION OF SAFETY PARAMETERS.....	40
8.1.1	DEFINITION OF ADVERSE EVENTS (AE)	40
8.1.2	DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)	41
8.2	CLASSIFICATION OF AN ADVERSE EVENT	42
8.2.1	SEVERITY OF EVENT	42
8.2.2	RELATIONSHIP TO STUDY AGENT	42
8.2.3	EXPECTEDNESS	43
8.3	TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP.....	43
8.3.1	POST-STUDY AEs AND SAEs.....	44
8.4	REPORTING PROCEDURES	44
8.4.1	ADVERSE EVENT REPORTING.....	44
8.4.2	SERIOUS ADVERSE EVENT REPORTING	45
8.4.3	ADVERSE EVENTS OF SPECIAL INTEREST	46
8.4.4	REPORTING OF PREGNANCY.....	46
8.5	STUDY HALTING RULES	46
8.6	SAFETY OVERSIGHT	47
9	CLINICAL MONITORING	47
10	STATISTICAL CONSIDERATIONS.....	48
10.1	STATISTICAL AND ANALYTICAL PLANS	48
10.2	STATISTICAL HYPOTHESES.....	48
10.3	ANALYSIS DATASETS	48
10.4	DESCRIPTION OF STATISTICAL METHODS	48
10.4.1	GENERAL APPROACH.....	48
10.4.2	ANALYSIS OF THE PRIMARY ENDPOINT(S).....	49
10.4.3	ANALYSIS OF THE SECONDARY ENPOINT(S).....	49
10.4.4	SAFETY ANALYSES.....	49
10.4.5	ADHERENCE AND RETENTION ANALYSES.....	50
10.4.6	BASELINE DESCRIPTIVE STATISTICS.....	50
10.4.7	PLANNED INTERIM ANALYSES.....	50

10.4.8 ADDITIONAL SUB-GROUP ANALYSES 50

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY 50

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA 50

10.4.11 EXPLORATORY ANALYSES..... 50

10.5 SAMPLE SIZE 51

10.6 MEASURE TO MINIMIZE BIAS 51

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES 51

10.6.2 EVALUATION OF SUCCESS OF BLINDING 52

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE..... 52

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS 52

12 ETHICS/PROTECTION OF HUMAN SUBJECTS 52

12.1 ETHICAL STANDARD..... 52

12.2 INSTITUTIONAL REVIEW BOARD..... 53

12.3 INFORMED CONSENT PROCESS 53

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS 53

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION..... 53

12.4 PARTICIPANT AND DATA CONFIDENTIALITY 54

12.5 FUTURE USE OF STORED SPECIMENS 54

13 DATA HANDLING AND RECORD KEEPING..... 55

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES 55

13.1.1 INVESTIGATOR RESPONSIBILITIES 55

13.1.2 STUDY FILES..... 55

13.2 STUDY RECORDS RETENTION..... 56

13.3 PROTOCOL DEVIATIONS 56

13.4 PUBLICATION AND DATA SHARING POLICY 57

14 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY 57

15 LITERATURE REFERENCES 58

16 APPENDICES 61

17 SCHEDULE OF EVENTS 83

18 REVISION HISTORY 85

LIST OF ABBREVIATIONS

AD	Alzheimer’s Disease
ADAS-Cog/11	Alzheimer’s Disease Assessment Scale-Cognitive Subscale
ADCS-ADL ₂₃	Alzheimer’s Disease Cooperative Study – Activities of Daily Living ₂₃
ADCS-CGIC	Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change rating
AE	Adverse Event
ApoE	Apolipoprotein E
ARIA	Amyloid Related Imaging Abnormalities
ASL	Arterial Spin Labeling
BLA	Biologics License Application
CDR-SOB	Clinical Dementia Rating Scale – Sum of Boxes
CFR	Code of Federal Regulations
CFT	Category Fluency Test
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ICH E6 R2	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2
IEC	Independent Ethics Committee
IRB	Investigational Review Board
ITT	Intent-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemia Scale
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging-Alzheimer’s Association
NODscid	Non-obese diabetic severe combined immunodeficiency
NPI-Q	Neuropsychiatric Inventory Questionnaire
NSG	NODscid Gamma
PET	Positron-Emission Tomography
PT	Preferred Term
SAE	Serious Adverse Event

SOC	System Organ Class
SUSARS	Suspected Unexpected Serious Adverse Reactions
UPCR	Urine Protein-to-Creatinine Ratio
vMRI	Volumetric Magnetic Resonance Imaging
WHO	World Health Organization

LIST OF DEFINITIONS

<p>Infusion Nurse</p>	<p>The unblinded study personnel qualified by training and experience responsible for administering the infusion of the investigational product during the Infusion Period. The Infusion Nurse ensures that appropriate blinding techniques are used to prevent the inadvertent unblinding of study staff and study participants during and immediately following the Infusion Period.</p>
<p>Infusion Period</p>	<p>For 100 and 250 mL administrations, the Infusion Period is estimated to be between 2 hours to a maximum of 3 hours.</p>
<p>Outcomes Assessor</p>	<p>The blinded study personnel qualified by training and experience responsible for observing study subjects during the infusion of the investigational product and collecting and/or managing adverse events (AEs) that occur before, during, and after the Infusion Period.</p>

PROTOCOL APPROVAL PAGE

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

Protocol Number: ALK6019-201

Version/Date: V7.0_02NOV2018

**Sponsor Name and
Address:** Alkahest, Inc.
125 Shoreway Road, Suite D
San Carlos, CA 94070

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and applicable legal and regulatory requirements.

Approved by:



Sponsor Representative (print)



Signature

2 Nov 2018
Date

STATEMENT OF COMPLIANCE

Protocol 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

Protocol Number: ALK6019-201 Protocol Version 7.0_02NOV2018

By my signature, I:

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment and are thoroughly familiar with the appropriate use of the investigational drug described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Alkahest, Inc., or their designee
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with current relevant versions of the US Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of all source documents by Alkahest, Inc. or designee and to on-site inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, local governing regulatory bodies, and IRB/IEC inspectors.

Investigator's Signature

Date

Print Name

PROTOCOL SUMMARY

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 (AD)

Précis: 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.

Subjects will be randomized to one of two doses of active treatment in a double-blind manner: 20 subjects at 100 mL and 20 subjects at 250 mL. Dosing groups will be stratified by sex. All subjects will receive one infusion per day at the randomized dose for 5 consecutive days during weeks 1 and 13 and will have a total study duration of approximately 7 months.

The infusion duration for all subjects will be between 2 hours to a maximum of 3 hours to maintain blinding. Flow rates will be titrated according to dose-specific guidelines to ensure that the entire assigned dose is administered during this interval. The following measures will be taken to ensure adequate allocation concealment during infusions: blinding of subjects, trial partners, study coordinators, physicians, and cognitive test administrators to treatment dose; use of blinded Outcomes Assessors and unblinded Infusion Nurses; standard time for attachment to the IV infusion setup (up to 180 minutes); and measures to block view of vial(s) and infusion pump throughout the infusion.

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

Objectives: The primary objective of the study is to assess the safety, tolerability, and feasibility of 2 dose levels of GRF6019 in subjects with mild to moderate AD. As a secondary objective, the study will assess the potential effects on cognition of the 2 dose levels using various cognitive measures. The exploratory objectives include changes on MRI and analysis of blood and CSF for specific biomarkers associated with AD.

Endpoints: Primary endpoints will be assessed as follows:

- Incidence of treatment-emergent adverse events (AEs) identified by MedDRA preferred term (PT) and grouped by MedDRA System Organ Class.
- Feasibility and tolerability of each dose level.

Secondary efficacy endpoints will be assessed as follows:

- Changes in scores on the Mini-Mental State Examination (MMSE).
- Changes in scores on the 11-item Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog/11).
- Changes in scores on the Grooved Pegboard Test.
- Changes in scores on the Category Fluency Test (CFT).
- Changes in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB).
- Changes in the Alzheimer’s Disease Cooperative Study – Activities of Daily Living₂₃ (ADCS-ADL₂₃).
- Changes on the Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change rating (ADCS-CGIC).
- Changes on the Neuropsychiatric Inventory Questionnaire (NPI-Q).
- Changes in the Savonix Neurocognitive Assessments and Digit Span.

Secondary safety endpoints will be assessed as follows:

- Changes from baseline in clinical laboratory parameters.
- Changes from baseline in vital sign measurements.
- Changes from baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Changes on MRI scans designed to assess for Amyloid Related Imaging Abnormalities (ARIA).

Secondary feasibility endpoint will be assessed by:

- Subject compliance with the study visit schedule and study visit procedures
- Subject retention
- Success of blinding

Exploratory endpoints will be assessed as follows:

- Changes in imaging endpoints such as volumetric MRI (vMRI), functional MRI (fMRI), and Arterial Spin Labeling (ASL)
- Changes in blood-based biomarkers
- Changes in CSF biomarkers (in participating subjects)

Population: Approximately 40 subjects between 60 and 90 years of age with a diagnosis of probable mild to moderate AD. Assuming a drop-out rate of 25%, enrollment at this level will yield approximately 30 evaluable subjects.

Phase: 2

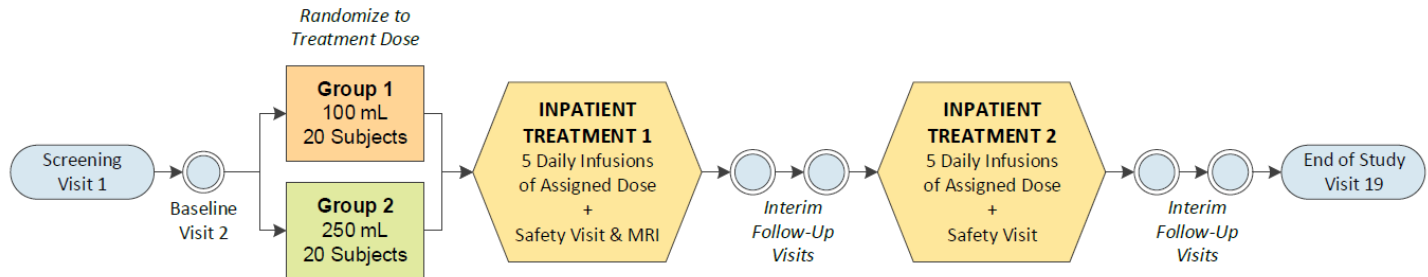
Number of Sites: Up to 10 sites in the United States

Description of Study Agent: GRF6019: A ██████ human plasma protein fraction for IV infusion

Study Duration: Approximately 15 months

Participant Duration: Approximately 7 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

[Redacted]

Alkahest, Inc.
 125 Shoreway Road, Suite D
 San Carlos, CA 94070
 Telephone: 650-801-0469

[Redacted]

1.2 STUDY ORGANIZATION

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), Sponsor’s medical expert and study monitor, Sponsor’s representative(s), laboratories, steering committees, and oversight committees [including independent ethics committees (IECs) and Institutional Review Boards (IRBs)], as applicable) will be maintained by the Sponsor and provided to the investigator.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Alzheimer’s Disease (AD) is a progressive pathophysiological disorder associated with cognitive decline. The initial symptoms typically include an inability to retain recently acquired information, whereas memory for remote events may be spared until late stage disease. As of 2018, approximately 5.7 million Americans have AD. This number includes an estimated 5.5 million people age 65 and older. By mid-century, that number is expected to grow to 14 million. By 2050 nearly 1 million new cases will be diagnosed per year ([Alzheimer’s Association 2018](#)).

During the course of the disease, synapses and ultimately neurons are lost within the cerebral cortex, hippocampus, and subcortical structures (including selective cell loss in the nucleus basalis of Meynert), locus coeruleus, and nucleus raphe dorsalis. Cerebral glucose use and perfusion is reduced in some areas of the brain (e.g., the parietal lobe and temporal cortices in early-stage disease, prefrontal cortex in late-stage disease). Neuritic or senile plaques (composed of neurites,

astrocytes, and glial cells around an amyloid core) and neurofibrillary tangles (composed of paired helical filaments) are likely to play a role in the pathogenesis of AD. The pathologic changes often precede symptoms of impaired cognition and memory ([Mayeux 2010](#)).

Effectiveness of existing approved therapies, including acetylcholinesterase inhibitors (e.g., donepezil) and N-Methyl-D-aspartic acid (NMDA) receptor agonists (e.g., memantine) varies across the population. These drugs neither provide relief from all symptoms of AD nor do they prevent the long-term progression of the disease. There are currently no disease modifying agents for use in AD ([Alzheimer's Association 2018](#)) and given the increasing prevalence and socioeconomic impact of the disease, identifying treatments for maintaining or improving cognitive function is an area of substantial unmet medical need.

In 2011, data in parabiotic animal models suggested that increased levels of systemic chemokines and increased immune signaling molecules may affect the aging brain, and that rejuvenating factors from young animals may ameliorate the effects of aging ([Villeda 2011](#)). Following their initial findings, the same team of investigators performed a study to explore the therapeutic effects of systemic exposure of aged mice to young plasma by direct injection ([Villeda 2014](#)). At the cognitive level, systemic administration of young plasma into aged mice improved age-related impairments. In addition, the data demonstrated that exposure of old mice to young plasma counteracts age-related impairment at the molecular and structural levels in the hippocampus ([Villeda 2014](#)). These studies lay the foundation for the hypothesis that soluble circulating factors from young plasma may have beneficial effects on human cognition.

Results from nonclinical studies conducted at Alkahest (see [Section 2.2, "Rationale"](#) below) suggest there is a beneficial effect of young human plasma and plasma protein fraction in age-related cognitive decline and histopathological endpoints in mouse models. These studies have raised the intriguing possibility that there are factors present in human plasma that may prove beneficial against brain aging and ameliorate some of the age-associated memory impairments in people, especially in those experiencing rapid cognitive decline from age-associated neurodegenerative diseases.

2.2 RATIONALE

Alkahest's study ALK6019-201 will evaluate 2 dose levels of GRF6019 administered via intravenous (IV) infusion. GRF6019 has been manufactured specifically for investigational purposes. It is a purified [REDACTED] plasma protein fraction made from pooled human plasma [REDACTED].

The rationale for using a plasma protein fraction was based on several factors. Although plasma is widely used and considered safe, there are inherent risks such as the potential transfer of unknown pathogens to recipients, histoincompatibility, and allergic reactions to proteins such as clotting factors and immunoglobulins. Therefore, the Blood Products Industry has developed safer products based on pooling plasma of highly selected donations, fractionating them into more defined products, and adding additional processing steps to reduce the potential for pathogen transmission. Leveraging this fractionation technology, GRF6019 is a [REDACTED]

Nonclinical studies conducted at Alkahest have demonstrated that both young whole plasma and [REDACTED] plasma protein fraction confer beneficial outcomes in age-related cognitive decline and histopathological endpoints in mouse models ([REDACTED]).

[REDACTED]). Mild to moderate AD patients will be selected for inclusion in this clinical study as they have identifiable deficits in cognitive function and suffer from a disease with limited treatment options, making them a population for whom the balance of risk to potential benefit of treatment with GRF6019 is reasonable.

Nonclinical studies were initiated at Alkahest to test whether the positive effects observed with young mouse plasma could be replicated using [REDACTED] human plasma. Treatment of aged NODscid (non-obese diabetic severe combined immunodeficiency) mice with [REDACTED] human plasma (100-150 μ L per injection, two injections per week for 3-5 weeks) resulted in improved cognitive and motor performance in standard behavioral tests. These cognitive changes were further supported by electrophysiological and histological correlates of enhanced memory. Together, these results provided support for the hypothesis that [REDACTED] plasma infusions may have functional benefits to man, potentially ameliorating or halting the progression of cognitive decline associated with AD [REDACTED].

Nonclinical studies conducted at Alkahest evaluated the effects of both young plasma and plasma protein fraction using various dosing paradigms in NODscid, NSG (NODscid Gamma) and C57BL/6J mice. Initially, mice were dosed with 150 μ L of [REDACTED] plasma, [REDACTED] plasma protein fraction or saline (control) via IV infusions 2 times per week for 5 weeks ([REDACTED]). A subsequent study examined the same dosing regimen for a period of 23 weeks, to assess the effects of treatment on age-dependent changes in behavioral and cognitive function over a period of approximately 6 months ([REDACTED]). Following these early studies, a novel dosing regimen of 150 μ L for 7 consecutive days (referred to as "pulsed dosing") was evaluated both alone and compared to other intermittent weekly dosing regimens ([REDACTED]). A final study examined pulsed dosing of 150 μ L for 5 consecutive days ([REDACTED]), which is the pulsed dosing regimen chosen for ALK6019-201.

Based on these nonclinical studies, significant improvements in cognitive performance and histological correlates were observed with a [REDACTED] plasma protein fraction. In addition, studies with [REDACTED] plasma demonstrated that the beneficial effect was observed long after initial dosing, indicating there is not a requirement for continuous repeat dosing. The effects were long-lived but did diminish over time such that 3 months after dosing benefits just reached significance.

Together, these studies indicate that 5 consecutive days of dosing ("pulsed dosing") of GRF6019, a batch of [REDACTED]

[REDACTED]. If safety and efficacy are demonstrated with GRF6019, pulsed dosing may be more convenient than weekly or monthly dosing for patients.

A prospective, randomized, double-blind, dose-comparison concurrent control study design has been selected to reduce or eliminate bias while facilitating the identification of a safe and feasible dosing paradigm, trends in changes of neurocognitive endpoints, and potential plasma derived factors that may affect these parameters. Within-patient and between-group cognitive changes associated with the 2 dose levels of GRF6019 will be evaluated.

Thus, while the primary objective of this study is safety and tolerability, and the study does not have the statistical power to test specific hypotheses regarding changes in cognitive function, the results are nevertheless expected to lay the foundation for larger trials designed and powered to characterize the potential benefits of GRF6019 in AD and other neurodegenerative disorders typified by cognitive dysfunction.

Human dose levels were selected based on known safety through clinical experience in man and scaling from efficacy in nonclinical studies. No safety concerns were observed in nonclinical studies using repeated doses of 150 μ L in mice. In determining potentially efficacious human doses, different methods can be used. Allometric scaling is primarily performed based on body surface area conversion in mg/m^2 . Using allometric scaling, a dose of 150 μ L yields an

equivalent human dose using body surface area scaling of 28.4 mL. Allometric scaling is used for small molecules whose elimination is dependent on hepatic metabolism. Alternative scaling methods include mg/kg (recommended for macromolecules >100 kDa) and volumetric scaling based on relative blood volumes. Because GRF6019 contains a complex mixture of proteins with a molecular weight predominantly <100kDa), and because the beneficial effects of these proteins on cognition are believed to occur in the circulation, the concentration of these proteins per blood volume may be the scaling method most likely to accurately estimate the human potential effective dose.

Using isometric scaling based on blood volume, the mouse dose of 150 µL is equivalent to a human dose of 413 mL, as outlined in **Table 1**. The top dose used in this study is 250 mL GRF6019, which is below the equivalent human dose of 413 mL.

[REDACTED]

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Collected human plasma may be used as a therapeutic product (known as “plasma” or “fresh frozen plasma”) or as source material for the production of pharmaceutical fractionated products (known as “plasma products” or “plasma derivatives”) ([Burnouf 2007](#)). GRF6019, a [REDACTED] human plasma protein fraction, [REDACTED] serves as a viable source of soluble, infusible plasma proteins from [REDACTED] healthy donors.

[REDACTED]

ABO antigen typing is not required prior to administration. Finally, the additional steps taken during production to remove viral pathogens provide an increased margin of pathogen safety in comparison to fresh frozen plasma.

[REDACTED] GRF6019 is not expected to significantly alter the urinalyses of recipients, their bleeding times, coagulation times, prothrombin times, prothrombin consumption, platelet counts or fibrinogen levels when given in quantities of up to 1000 mL. Hypotension may occur, particularly following rapid infusion or intraarterial administration to patients on cardiopulmonary bypass. The blood pressure may normalize spontaneously after the slowing or discontinuation of the infusion. [REDACTED]

[REDACTED]

GRF6019 is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that GRF6019 can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and including manufacturing steps with the capacity to inactivate and/or remove pathogens.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no known reported benefit of administering GRF6019 to patients with mild to moderate AD. However, if the findings in the nonclinical models are replicated in humans, there could be a substantial benefit to individual patients, including improvements in cognitive function, executive cognitive function, daily function, and/or neuropsychiatric symptoms.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is 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 AD. Secondly, this study aims to assess the effects of the study agent on subjects’ cognitive function. As an exploratory objective, blood and plasma will be collected and analyzed to identify specific biomarkers associated with cognitive functional changes and/or indicators of AD progression. In addition, subjects who are eligible and consent to participate in the optional CSF biomarker research at participating sites will undergo two lumbar punctures for CSF collection. The CSF will then be utilized to assess the potential therapeutic effects of GRF6019 on AD biomarkers of neuronal death, synaptic function, inflammation, and growth factors. Finally, changes in imaging results as measured by volumetric Magnetic Resonance Imaging (vMRI), functional MRI (fMRI), and Arterial Spin Labeling (ASL) may be evaluated to identify potential indicators of AD progression and potential therapeutic effect

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a prospective, randomized, double-blind, dose-comparison concurrent control study conducted at up to 10 sites in the United States.

Study subjects will be dosed for 5 consecutive days (“pulsed dosing”) with GRF6019 during two dosing periods over the approximately 6-month treatment period. Subjects will be randomized to one of two dose levels: 100 mL or 250 mL. Subjects will receive one infusion per day at the randomized dose for 5 consecutive days during Week 1 and again during Week 13.

During the 5-day dosing periods, subjects will reside in inpatient study observation units and will be discharged after the 5th day of dosing. Trial partners will have the option to stay with the subjects or may seek lodging nearby.

Subjects will be invited to participate in optional CSF biomarker research at participating sites. The CSF collection procedure, as well as the potential risks and benefits, will be explained to all study participants. Participation in the CSF

biomarker research is optional and not required for inclusion in the study. Subjects who are eligible and consent to participate 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 motor assessments will be performed at baseline and at periodic interim assessments following dosing. In the event of early termination of a subject who has received at least one dose of GRF6019, the end of study procedures will be performed unless the subject has withdrawn consent. Dosing groups will be stratified by sex. A comprehensive efficacy and safety assessment of all data *in toto* will be conducted at the end of the study.

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 8 months. The subject participation period is approximately 7 months from screening through end of study, unless prematurely discontinued.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

The primary endpoints in this study pertain to the safety, tolerability and feasibility of each dose level.

Safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (AEs) identified by MedDRA preferred term (PT) and grouped by MedDRA System Organ Class (SOC).

Tolerability endpoints are as follows:

- Number of subjects completing 8 weeks (i.e. through Visit 10) after receiving at least 5 infusions.
- Number of subjects completing 24 weeks (i.e. through End of Study) after receiving at least 10 infusions.

Feasibility endpoints are as follows:

- Number of subjects completing 5 and 10 infusions.

4.2.2 SECONDARY ENDPOINTS

This study is neither designed nor powered to detect statistically significant differences in cognitive or motor domains between the Baseline and End of Study values. However secondary cognitive endpoints will be summarized over the study period from Baseline values using descriptive statistics:

- Changes in scores on the Mini-Mental State Examination (MMSE) ([Folstein 1975](#)) ([Appendix 1](#)).
- Changes in scores on the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog/11) ([Rosen 1984](#)) ([Appendix 2](#)).
- Changes in scores on the Grooved Pegboard Test ([Lafayette 2002](#)).
- Changes in scores on the Category Fluency Test (CFT) ([Acevedo 2000](#)).
- Changes in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB) ([Hughes 1982](#)) ([Appendix 3](#)).
- Changes in the Alzheimer's Disease Cooperative Study – Activities of Daily Living₂₃ (ADCS-ADL₂₃) ([Galasko 1997](#)) ([Appendix 4](#)).
- Changes on the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) ([Ferris 1997](#)) ([Appendix 5](#)).

- Change on the Neuropsychiatric Inventory Questionnaire (NPI-Q) ([Kaufert 2000](#)) ([Appendix 6](#)).
- Change on the Savonix Neurocognitive Assessments and Digit Span ([Appendix 7](#)).

Secondary safety endpoints include:

- Changes from baseline in clinical laboratory parameters.
- Changes from baseline in vital sign measurements.
- Changes from baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS) ([Posner 2011](#)) ([Appendix 8](#)).
- Changes on MRI scans designed to assess for ARIA.

Secondary feasibility endpoints include:

- Subject compliance with the study visit schedule, procedures, and infusions, and any required adaptations that are necessary for the study completion.
- Success of blinding. This 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).

4.2.3 EXPLORATORY ENDPOINTS

The exploratory endpoints include 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.

The serial compositional analysis of individual subject's plasma will be performed to identify specific biomarkers associated with cognitive functional changes and/or indicators of AD progression. DNA will be extracted from blood samples to explore epigenetic changes. In addition, subjects who consent to participate in the optional CSF biomarker research will undergo two lumbar punctures for CSF collection, the first occurring prior to initial dosing, and the second occurring following final dosing. The CSF will be utilized to assess the potential therapeutic effects of GRF6019 on AD biomarkers of neuronal death, synaptic function, inflammation, and growth factors.

5.1 INCLUSION CRITERIA

In order to be eligible for inclusion, all subjects must meet the following criteria:

- Male or female, aged 60-90 years (inclusive).
- Diagnosis of probable AD based upon the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria.
- MMSE Score 12-24 inclusive.
- Modified Hachinski Ischemia Scale (MHIS) score of ≤ 4 .
- Have a dedicated, reliable and competent trial partner (e.g., caregiver or family member) who has frequent contact with the subject (defined as approximately 10 hours per week) who is willing to provide support to the subject to ensure compliance with study requirements. The trial partner should understand the nature of the study and be willing to complete the trial partner scales and functional assessments throughout the study.
- The subject (with support of a trial partner) must be able to follow the study protocol, receive the treatment in the established timeframe, and continue during the follow-up interval.
- The subject and trial partner must be sufficiently fluent in English and have visual and auditory acuity sufficient to be capable of reliably completing all study assessments.

- Provided a signed and dated informed consent form (either the subject and/or subject's legal representative as well as the trial partner) in accordance with local regulations/guidelines/IRB/IEC.
- Adequate renal function as defined by estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation ([MDRD for Adults \(Conventional Units\) | NIDDK, n.d.](#)).
- Systolic ejection fraction of $\geq 55\%$ on trans-thoracic echocardiogram.
- Willing to spend up to 7 nights in an inpatient study unit during both dosing periods.

In order to be eligible for inclusion in the optional CSF biomarker research, all subjects must meet the following criteria:

- Currently enrolled in the ALK6019-201 study.
- Provided a signed and dated informed consent form for CSF collection (either the subject and/or subject's legal representative) in accordance with local regulations/guidelines/IRB/IEC.
- Not yet dosed in the ALK6019-201 study.

5.2 EXCLUSION CRITERIA

A subject will not be eligible for inclusion if any of the following criteria apply:

- Positive screening for Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV).
- Evidence of clinically relevant neurological disorder(s) other than AD.
- History of blood coagulation disorders or hypercoagulability; any concurrent use of an anticoagulant therapy. (e.g., heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors). Use of antiplatelet drugs (e.g., aspirin or clopidogrel) is acceptable.
- Initiation or change in the dosage of cholinesterase inhibitors (AChEI), memantine, Axona, vitamin E supplementation, or selegiline within 3 months prior to screening.
- Prior hypersensitivity reaction to any human blood product or intravenous infusion; any known clinically significant drug allergy.
- Treatment with any human blood product, including transfusions and intravenous immunoglobulin, during the 6 months prior to screening.
- History of immunoglobulin A (IgA), haptoglobin or C1 inhibitor deficiency; stroke, anaphylaxis, or thromboembolic complications of intravenous immunoglobulins.
- Heart disease, including myocardial infarction, unstable, new onset or severe angina, or congestive heart failure (New York Association Class II, III or IV) in the 6 months prior to dosing;
- Poorly controlled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite treatment during the 3 months prior to dosing, or treatment refractory high blood pressure, defined as treatment requiring 3 or more antihypertensives from different classes.
- History of Torsades de Pointes dysrhythmia or hypocalcemia of any kind, including secondary to absorption syndromes secondary to gastric bypass surgery.
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- Uncontrolled diabetes defined as HbA1c $> 7.5\%$ or requiring insulin.
- Clinically significant abnormalities in complete blood count, complete metabolic panel, serum albumin, serum lipids, blood coagulation tests, or the levels of thiamine, pyridoxine, cobalamin and thyroid stimulating hormone.

- Hemoglobin < 10 g/dL in women and < 11 g/dL in men.
- Urine protein-to-creatinine ratio (UPCR) of > 1.5 grams of protein per gram of creatinine.
- Clinically significant abnormalities on screening electrocardiogram (ECG) including QTc intervals (using Fridericia's correction formula) of ≥ 450 ms in men and ≥ 470 ms in women.
- Clinically significant abnormalities on echocardiogram.
- Inadequate venous access to allow IV drug delivery or multiple blood draws.
- 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.
- Concurrent daily treatment with benzodiazepines, long-acting opioids, or other medications that, in the investigator's opinion, interfere with cognition. [Note: intermittent treatment with low-doses of shorter half-life benzodiazepines (e.g. lorazepam, alprazolam) may be permitted, provided that no dose is administered within the 72 hours preceding any cognitive assessment].
- 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.
- Active suicidal ideation with at least some intent to act, with or without a specific plan, in the past 6 months.
- Presence of a pacemaker or any other implant that would be a contraindication to an MRI exam or claustrophobia that would not enable the subject to undergo an MRI.
- >2 lacunar strokes or other imaging abnormality on baseline MRI that would make the interpretation of subsequent MRI scans of the brain difficult.
- 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.

A subject will not be eligible for inclusion in the optional CSF biomarker research if any of the following criteria apply:

- Allergy or sensitivity to lidocaine or other local anesthetics to be used for the lumbar puncture.
- Skin infection near the site of the lumbar puncture.
- Suspicion of cord mass or signs of cord compression.
- Suspicion of intracranial mass or raised intracranial pressure (e.g., as evidenced by papilledema).
- Altered mental status (from baseline).
- Use of oral antiplatelet therapy (e.g. clopidogrel, prasugrel, ticagrel) within 5 days prior to the lumbar puncture. Use of aspirin is permitted.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

We do not anticipate any particular challenges in meeting recruitment goals of enrolling a total of 20 subjects per group in this study. Similarly, as AD has a higher prevalence in women, we do not anticipate difficulties in enrolling female subjects. Subjects will be recruited continuously until the desired sample size is achieved. Subjects who withdraw or are withdrawn during screening or prior to completing Visit 8 may be replaced to enroll sufficient evaluable subjects.

We expect enrollment in this trial to be consistent with the observation that typically the majority of subjects enrolled in clinical trials conducted in the United States are non-Hispanic whites. If the risk/benefit analysis of GRF6019 justifies larger subsequent trials, special efforts will be made to enroll subjects from diverse ethnic and racial groups.

This trial is enrolling subjects with AD who may have sufficient cognitive impairment to be considered a vulnerable population. In this situation, the subject’s agreement to participate in the study will still be obtained to their best level of his or her understanding, and recruitment will not proceed if the subject refuses, shows significant distress or the trial partner and/or legally authorized representative refuse. For subjects who are, in the opinion of the investigator, unable to give informed consent, consent will be obtained from the legally authorized representative. Subjects will receive a modest stipend for participation in the study.

The expected length of participation in the study, seven months, is not expected to be unduly onerous on subjects or their trial partners. During the two treatment periods at weeks 1 and 13, subjects will be housed in inpatient clinical trial units. If the trial partner does not reside within a reasonable distance from the inpatient facility, they will be given the option to stay with the subjects or to stay in a nearby hotel/motel. Financial support for meal and miscellaneous expenses may be provided as appropriate (it is expected that meals will be provided by the study facilities as needed). Use of visit transport services and study buddies (registered and trained personnel that can stand in for the trial partner for required visits) may also be incorporated into the trial to support both the subject and their trial partner in maintaining study visit compliance.

A description of the clinical trial will be posted on clinicaltrials.gov that will provide additional transparency to the public and possibly aid study recruitment. In addition, advocacy groups and patient networks will be approached for recruitment as needed.

5.4 SUBJECT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

A subject will be withdrawn from the study for the following medical or administrative reasons:

- Occurrence of a treatment-emergent AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the investigator. The investigator must follow the subject until the AE resolves or is stable, unless the subject is lost to follow up.
- Subject and/or trial partner noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject or the subject’s legally authorized representative (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.
- Pregnancy.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Subjects will be encouraged to complete the study and all assessments. However, subjects may voluntarily withdraw at any time, and the investigator may discontinue individual subjects from the study at any time.

Approximately 40 subjects (approximately 20 in the 100 mL group and 20 in the 250 mL group) will be enrolled in the study with the intent of obtaining at least 30 evaluable subjects who have received at least 5 doses and completed through Visit 8.

Subjects who have received at least one infusion but are withdrawn or withdraw from the study will be encouraged to complete the end of study procedures within 4-6 weeks of their last visit. For post-study AE and SAE reporting, see [Section 8.3.1](#). The primary reason for study discontinuation will be documented on the case report form (CRF).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor and/or their representatives will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs. In terminating the study, the Sponsor and the investigator will continue to protect the subjects’ privacy and identity as required by relevant statutes and regulations.

Alkahest, Inc. has the right to terminate a study site from participating in the study at any time. Reasons for study or site termination may include, but are not limited to:

- (Immediate) risk to subject safety.
- Unsatisfactory subject enrollment.
- Unacceptable Protocol Deviations as assessed by Sponsor.
- Inaccurate or incomplete data entry and recording; fabricated data.
- Investigational site non-compliance with ICH/GCP.
- Unacceptable emergent safety profile.

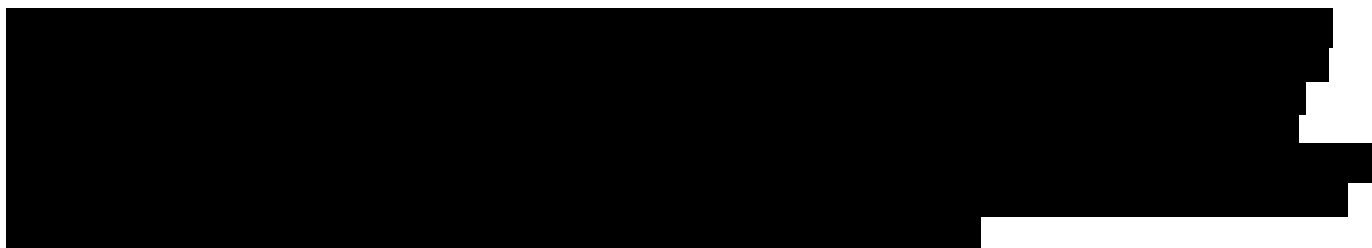
6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The study agent will be commercially manufactured by Grifols in their Clayton, North Carolina facility in accordance with license BL 101140. The material will be supplied to the sites directly from a study drug depot.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING



GRF6019 will be supplied in 250 mL glass vials bearing a label that meets applicable regulations for investigational protein products (further manufactured) per 21 CFR 312.6. The label will clearly identify the study agent and manufacturer, and will display other required information specifically applicable to its intended use, including but not limited to:

- Federal law statement
- Storage information
- Volume (accurate within ± 10%)
- Expiration date

6.1.3 PRODUCT STORAGE AND STABILITY

The study agent should be stored at room temperature not exceeding 30°C (86°F). Solution that has been frozen should not be used. Do not use after expiration date.

Solutions which are turbid should not be used. Administration of the study agent must begin within 4 hours of the container being entered. Vials which are cracked or have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms. [REDACTED]

6.1.4 PREPARATION

The study agent is compatible with the usual carbohydrate and electrolyte solutions. Remove seal to expose stopper. Always swab stopper top immediately with suitable antiseptic prior to entering the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Only 16-gauge (or larger) needles or dispensing pins should be used with 250 mL vials. Needles, dispensing pins, or equivalent should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring. IV tubing should be vented, as the study agent is supplied in glass bottles.

6.1.5 DOSING AND ADMINISTRATION

The study agent will be infused in accordance with the Infusion Administration Manual provided to sites. The purpose of the Infusion Administration Manual is to promote safe administration of GRF6019 and maintain appropriate blinding of staff and study subjects. The manual will include provisions for masking study agent and concealing the IV apparatus from view of blinded staff and study subjects during the Infusion Period.

The study agent and dose to be administered will be provided by an unblinded pharmacist (or other qualified personnel responsible for drug accountability) to an unblinded Infusion Nurse. Administration of the study agent will be performed by the unblinded Infusion Nurse, and study outcome measures (including AEs and vital signs) will be assessed by a blinded Outcomes Assessor.

Infusion Nurses will be qualified by training and experience to administer infusions under the direction of the Principal Investigator. Only authorized Infusion Nurses may administer the study agent, and only subjects enrolled in the study may receive the study agent in accordance with applicable regulatory requirements.

6.1.6 ROUTE OF ADMINISTRATION

The study agent will be administered by IV route only.

6.1.7 DOSING SCHEDULE

Subjects will be randomized to a dose level of 100 mL or 250 mL of study agent, and they will remain on the same dose for the duration of the study. Subjects will receive one infusion per day for 5 consecutive days at Weeks 1 and 13.

Randomization to all dosing groups will be stratified by sex.

6.1.8 DURATION OF THERAPY

From screening to exit, the duration of study involvement for each subject and their trial partner is ~7 months.

All subjects will receive 5 consecutive days of therapy at the beginning of weeks 1 and 13. Thus, the cumulative duration of therapy for all subjects will be 10 exposure days. The duration of therapy for a subject to be considered evaluable in the intent-to-treat population is 5 exposure days.

6.2 STUDY AGENT ACCOUNTABILITY

Under the supervision of the Principal Investigator, the unblinded study pharmacist or other qualified personnel is responsible for ensuring adequate accountability of all used and unused study agent. This includes acknowledgment of receipt of each shipment of study agent (quantity and condition), subject dispensing records, and returned or destroyed study agent. Dispensing records will document quantities received and quantities dispensed to subjects including the date dispensed, the intended subject's study identifier, the initials of the individual responsible for dispensing the study agent, and the initials of the Infusion Nurse administering the study agent. Drug accountability will be monitored by an unblinded CRA.

Accountability records must be maintained and readily available for inspection by representatives of Alkahest, Inc. or their designee and are open to inspection by regulatory authorities at any time. The accounts of any study agent accidentally wasted or intentionally disposed of must be maintained.

The disposal of used, partially used, or wasted study agent must be performed in accordance with the institution's drug disposal policy. At study initiation, the clinical study monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with study requirements. At the end of the study, following final drug reconciliation by the monitor, the study site will be instructed by the Sponsor to return or destroy all unused study agent, including empty containers. A copy of the institution's drug disposal policy should be maintained or referenced in the site's regulatory binder.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

7.1.1.1 Screening Procedures

During screening, the following will be performed:

- C-SSRS
- Assessment of probable AD including MMSE
- MHIS
- Medical history
- Demographics
- Review of medications
- Vital signs
- Physical examination
- 12-Lead ECG
- Blood and urine collection for laboratory evaluations
- Echocardiogram*
- MRI*
- PET Scan (optional; to be performed after all screening procedures have been completed, and the subject meets criteria for inclusion)

***Note:** the echocardiogram and screening MRI should be performed after all other screening procedures have been completed, and the subject meets all other criteria for inclusion. The echocardiogram and screening MRI may be completed in any order.

Detailed descriptions of each of these procedures are provided in the sections immediately following. Information pertaining to all study activities performed during screening, and the sequence of events, is provided in [Section 7.3.1 Screening](#).

7.1.1.1.1 Columbia-Suicide Severity Rating Scale

The C-SSRS is a simple series of questions for the assessment of suicidal ideation and behavior in clinical trials ([Posner 2011](#)) ([Appendix 8](#)). The C-SSRS was designed to distinguish the domains of suicidal ideation and suicidal behavior in subjects who have expressed wishes to be dead or suicidal thoughts. Four constructs are measured. The first is the severity of ideation, which is rated on a 5-point ordinal scale in which 1=wish to be dead, 2=nonspecific active suicidal thoughts, 3=suicidal thoughts with methods, 4=suicidal intent, and 5=suicidal intent with plan. The second is the intensity of ideation subscale, which comprises 5 items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation. The third is the behavior subscale, which is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. And the fourth is the lethality subscale, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale. The use of a standardized measure such as the C-SSRS comprehensively assesses suicidal behavior and ideation.

The C-SSRS will be administered by interview at screening to assess suicidal ideation and behavior over the course

of the subject's lifetime and in the past 6 months. The C-SSRS will be repeated on Visits 8 and 16 to assess suicidal ideation and behavior for the time period since the subject's last C-SSRS assessment.

7.1.1.1.2 Assessment of Probable Alzheimer's Disease

Subjects will undergo an assessment for AD using NIA-AA criteria ([McKhann 2011](#)). Probable AD is diagnosed when the subject meets criteria for dementia per MMSE score (12-24 inclusive) (Refer to [Section 7.1.1.1.3](#)), and in addition, has the following characteristics:

- Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
- Clear-cut history of worsening of cognition by report or observation; and
- The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
 - Amnesic presentation: It is the most common syndromic presentation of AD. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
 - Nonamnesic presentations:
 1. Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
 2. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
 3. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

The diagnosis of probable AD should not be applied when there is evidence of one or more of the following:

- Substantial concomitant cerebrovascular disease defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment.
- The presence of multiple or extensive infarcts or severe white matter hyperintensity burden.
- Core features of dementia with Lewy bodies other than dementia itself.
- Prominent features of behavioral variant frontotemporal dementia.
- Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia.
- Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Previous radiologic imaging and/or assessment of AD CSF biomarkers will be collected, if available, to support the clinical diagnosis of AD. Amyloid imaging by Positron Emission Tomography (PET) performed within 12 months of screening will be used, if available, to estimate beta-amyloid neuritic plaque density at baseline (See [Section 7.2.2.2](#)).

7.1.1.1.3 Mini-Mental Status Examination

The MMSE ([Folstein 1975](#)) ([Appendix 1](#)) 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), and language (6 items). The scores from the 5 components are summed to obtain the overall MMSE total score.

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. The MMSE total score can range from 0 to 30, with higher scores indicating better mental status. Change scores will not be calculated for the individual items.

7.1.1.1.4 Modified Hachinski Ischemic Scale

The MHIS ([Rosen 1980](#)) is an 8-item scale that examines clinical features that may be consistent with vascular dementia and is commonly used as a screening tool to exclude patients with multi-infarct dementia from entrance into clinical trials assessing neuropsychopharmacologic therapy in patients with AD. The scale is completed by the physician based on clinical information obtained from diagnostic information and physical examination. The scale takes about 10 to 15 minutes to complete, depending on the availability of the data needed. Scores for the 8 items are added together for a total score. Subjects who score 5 or greater are more likely to have a dementia of vascular etiology and thus are excluded from participating in the trial.

7.1.1.1.5 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 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)

7.1.1.1.6 Demographics

Information pertaining to the subject's socioeconomic status (e.g. highest level of income achieved, education, longest held occupation), ethnicity, race, marital status, and family size will be collected by interview with the subject and the subject's trial partner at screening.

7.1.1.1.7 Review of Medications

The investigator or designee should obtain a complete list of the 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. Assessment of eligibility should include a review of permitted and prohibited medications. Any additions, discontinuation or dosage changes in medication during the course of the study will be recorded.

7.1.1.1.8 Vital Signs

Vital signs will include seated systolic and diastolic blood pressure (mmHg), heart rate (beats per minute [bpm]), respiration rate (breaths per minute), and oral temperature. Vital signs will be measured after the subject has been seated for 5 minutes.

7.1.1.1.9 Physical Examination

A full physical examination will be performed to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic and lymphatic systems. Height and weight will also be documented.

7.1.1.1.10 12-Lead ECG

A 12-lead ECG will be performed after the subject has rested quietly for at least 5 minutes in a supine position. In some cases, it may be appropriate to repeat abnormal ECGs to rule out technical factors contributing to ECG artifacts or abnormality. It is important that leads are placed in the same positions each time for consistency. The overall conclusion with the interpretation of the ECGs will be recorded on the appropriate CRF. The interpretation of the ECGs will be recorded as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Corrected QTc intervals will be calculated using Fridericia's correction formula.

7.1.1.1.11 Echocardiogram

During screening, an echocardiogram will be performed to evaluate the subject's left ventricular (LV) systolic function to ensure the subject's ejection fraction is $\geq 55\%$ ([Gebhard 2012](#)).

7.1.1.1.12 Biological Specimen Collection

Biological samples will be obtained, analyzed, and stored appropriately for additional analysis. Blood and CSF (in participating subjects) will be drawn by a qualified medical provider, and urine specimens will also be collected. These samples may be used for re-testing, further evaluation of an AE and/or assessment, and follow-up of other exploratory endpoints. The timing and frequency for specimen collection and laboratory evaluations to be performed are described in the study's laboratory manual and [Section 17 Schedule of Events](#).

Samples that remain after study testing is complete will be stored in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. Samples will be stored in a deidentified coded form.

7.1.1.1.13 Magnetic Resonance Imaging

The screening MRI should only be performed after the subject has met all other inclusion criteria and none of the exclusion criteria (except the echocardiogram, which can be performed before or after the MRI). The sequence may also include vMRI, fMRI, and/or ASL. Additional information is provided in [Section 7.2.2.3](#).

7.1.1.2 Procedures to Assess Safety

Subjects enrolled in the trial will be monitored closely to assess safety and tolerability of the study agent and intervention. Study-specific procedures that will be used for this purpose are summarized below. Information regarding the timing and frequency of these procedures is provided in [Section 7.3 Study Schedule](#).

- Review of AEs
- Review of medications
- Vital signs
- C-SSRS
- 12-Lead ECGs
- Targeted physical exams
- End of Study (or Early Termination) Physical Examination
- Blood Draw and Urine Collection for Laboratory Evaluations
- MRI to assess for ARIA

7.1.1.2.1 Review of Adverse Events

AEs will be reviewed, documented, and reported as required at each visit. For definitions, guidance, and additional information regarding AEs, refer to [Section 8](#).

7.1.1.2.2 Review of Medications

The investigator or designee should review the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject since the last visit. Changes to the subject's list of medications should be reviewed and recorded. Review of medications should occur at every visit.

7.1.1.2.3 Vital Signs

Refer to [Section 7.1.1.1.8](#) for a description of Vital Signs. Vital Signs will be collected at every visit. During infusions, vital signs will be collected according to the Infusion Administration Manual by the blinded Outcomes Assessor.

7.1.1.2.4 Columbia-Suicide Severity Rating Scale

Refer to [Section 7.1.1.1.1](#) for a description of the C-SSRS.

7.1.1.2.5 12-Lead ECG

Refer to [Section 7.1.1.1.10](#) for information pertaining to 12-Lead ECGs.

7.1.1.2.6 Targeted Physical Exams

While the subject is inpatient, a targeted physical exam, including auscultation of the heart and lungs, an assessment of peripheral edema, and weight, will be performed per the Study Schedule ([Section 7.3](#)).

7.1.1.2.7 Physical Exam

Refer to [Section 7.1.1.1.9](#) for a description of the physical exam. The physical exam, including measurements of height and weight, will be performed at screening and repeated at End of Study (or early termination).

7.1.1.2.8 Blood and Urine Collection for Laboratory Evaluations

As described in [Section 7.1.1.1.12](#), subjects will have blood and urine specimens collected for clinical evaluation ([Section 7.2.1 Clinical Laboratory Evaluations](#)). Refer to [Section 17 Schedule of Events](#) for timing and frequency of blood and urine collection for laboratory evaluations.

7.1.1.3 Procedures to Assess Efficacy

Procedures to assess efficacy include neuropsychological and motor function testing and radiologic imaging. Information regarding the timing and frequency of these procedures is provided in [7.3 Study Schedule](#).

Cognitive and motor function will be assessed using neuropsychological and motor function testing performed by qualified evaluators who have undergone standardized rater training. Raters must be certified, as appropriate. The same evaluator should be used for the duration of each subject's participation unless a change in rater is unavoidable. The established order of behavioral and cognitive testing during visits with multiple assessments will be as follows (unless otherwise specified):

1. C-SSRS* (refer to [Section 7.1.1.1.1](#))
2. MMSE* (refer to [Section 7.1.1.1.3](#))
3. Savonix Neurocognitive Assessments and Digit Span

4. ADAS-Cog/11
5. Grooved Pegboard
6. CFT
7. CDR-SOB (subject and trial partner)
8. ADCS-ADL₂₃ (trial partner)
9. ADCS-CGIC (subject and trial partner)
10. NPI-Q (trial partner self-administered). *Note:* The trial partner may complete the NPI-Q at any available time during applicable visits

Assessments with an asterisk (*) should only be performed during follow-up when required per protocol. Descriptions of each neuropsychological and motor function assessment are provided below.

7.1.1.3.1 Savonix Neurocognitive Assessments and Digit Span

Assessments of cognitive function will be performed throughout the study using the Savonix Neurocognitive Assessments, a digitized neurocognitive testing app on a compatible iPad device. The Savonix digitized neurocognitive testing platform is a multi-faceted 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant computer-based application for iOS or Android devices that integrates multiple aspects of common neurocognitive tests into one computerized assessment. Measured elements across brain domains include instant verbal memory, delayed verbal memory, impulse control, focus, attention, emotional regulation, emotion identification, information processing, flexible thinking, working memory, executive function, spatial memory, decision making, and emotionality ([Appendix 7](#)).

Assessments using a digital interface are expected to provide more granular neurocognitive data while at the same time being less burdensome to the subject. This pilot experience will also lay the foundation for use of this digital platform in future trials.

Subjects will be provided instructions and asked to complete either a full or brief battery at every study visit, starting at baseline. The full battery of tests includes the Savonix-8 and Digit Span (forwards and backwards) and takes approximately 30-40 minutes to complete. The Savonix-8 consists of:

- Verbal Memory – immediate and delayed
- Go/No-Go
- Verbal Interference
- Complex Figure Copy
- N-back
- Maze Task
- Emotion Identification Task
- Trails A and B

The brief battery will be administered during infusion visits and should be completed prior to starting the infusion. The brief battery takes approximately 15-20 minutes to complete and consists of:

- Go/No-Go
- Color Interference
- N-back
- Trail-Making tasks
- Digit Span

7.1.1.3.2 The Alzheimer's Disease Assessment Scale – Cognitive Subscale

The ADAS-Cog/11 ([Rosen 1984](#)) ([Appendix 2](#)) includes 11 items assessing cognitive function ([Skinner 2012](#)). The domains include memory, language, praxis, and orientation. There are 70 possible points, 48 for the first 9 items, and 22 for the last two items, word recall, and recognition. Test performance is assessed for errors in following ordered commands, naming of real objects and of fingers, constructional praxis (copying of geometric forms), ideational praxis (preparation of a letter for mailing), orientation, a 10-item word recall task and a 12-item and 12 foils word recognition task. Higher scores reflect greater cognitive impairment. Individual testing domains may be separated out for the purposes of statistical analysis.

7.1.1.3.3 Grooved Pegboard Test

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.

7.1.1.3.4 Category Fluency Test

The CFT is one of the validated nine components of the neuropsychological test battery. Category fluency tasks are an important component of neuropsychological assessment, especially when evaluating for dementia syndromes. Subjects are asked to name as many different types of animals, vegetables, and fruits, in that order, as they can in a 60 second period. The number of correct, non-repeated responses for each individual category constitute the raw score for the specific category. The total category fluency score is calculated by adding the number of correct responses for the pooled categories ([Acevedo 2000](#)).

7.1.1.3.5 Clinical Dementia Rating Scale – Sum of Boxes

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 and provides more information than the global CDR score in patients with mild dementia ([O'Bryant 2008](#)) ([Appendix 3](#)). Individual testing domains may be separated out for the purposes of statistical analysis.

7.1.1.3.6 Alzheimer's Disease Cooperative Study Group – Activities of Daily Living₂₃

The ADCS-ADL₂₃ assesses the competence of patients with AD in performing basic and instrumental activities of daily living. The ADCS-ADL₂₃ contains 23 items covering physical and mental functioning and independence in self-care. For each activity of daily living (ADL), an informant (e.g., trial partner) is first asked if the patient attempted the activity during the past 4 weeks. If a patient did attempt the ADL, the informant (e.g., trial partner) is asked to choose the single most accurate definition of the patient's level of performance. The scores range from 0 to 78, with higher scores indicating less functional impairment ([Galasko 1997](#)) ([Appendix 4](#)).

7.1.1.3.7 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change

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 ([Ferris 1997](#), [Schneider 1997](#)) ([Appendix 5](#)). 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 (e.g. trial partner).

7.1.1.3.8 Neuropsychiatric Inventory Questionnaire

The NPI-Q evaluates the most frequent neuropsychiatric manifestations of dementia and determines their frequency and intensity ([Kaufer 2000](#)) ([Appendix 6](#)). 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.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g. whole blood, serum, urine) will be collected for laboratory evaluations in accordance with the Schedule of Events ([Section 17](#)). Clinical sample processing and laboratory evaluations will be conducted by a central lab's registered and certified Clinical Laboratory Improvement Amendments (CLIA) facilities. STAT laboratory evaluations will be conducted at the clinical site. Refer to the study's laboratory manual for complete information regarding all laboratory evaluations to be performed, sample collection procedures, and related requirements.

The investigator is responsible for determining and documenting if out of range laboratory values are clinically significant or not. All clinically significant values will be recorded as AEs in the CRF and followed until resolution, unless the subject is lost to follow up. Once resolved, the appropriate CRF page(s) will be updated.

7.2.2 OTHER ASSAYS OR PROCEDURES

7.2.2.1 Apolipoprotein E (ApoE) Genotype Testing

ApoE genotype is a known risk factor for AD pathogenesis, with presence of the ApoE ϵ 4 allele carrying increased risk. This risk is further influenced by age, sex, race, and ethnicity. Thus, determining ApoE genotype at baseline will allow for the assessment of possible differential effects of ApoE genotype on safety, treatment efficacy, neuroimaging and other exploratory measures.

7.2.2.2 Positron Emission Tomography (Optional)

Documented PET Scan is optional and not required for inclusion in the study.

Subjects who have had a PET Scan using any radioligand within 12 months of screening will be asked to provide copies of the images and results. The historical scan will be used to estimate the density of beta-amyloid neuritic plaque.

Subjects who meet eligibility criteria and who have not had a PET Scan within 12 months of screening will be given the option of having a PET Scan performed and read by a central reader. The results of the scan will be made available to the subject.

7.2.2.3 Magnetic Resonance Imaging

MRI [3 Tesla (T) preferred but 1.5T will be accepted] will be used to evaluate subjects' eligibility for inclusion in the study and to assess safety (ARIA) at Visit 8. MRI may also be used to compare neural activity and brain atrophy at screening/baseline, after the first series of pulsed doses, and at end of study. During the MRI, the subject will be asked to lie on a narrow bed in a large tunnel while images are captured by the MRI machine. The screening and Visit 8 scans will be interpreted by local radiologists to confirm eligibility and the continued safety of subjects. The MR images may also be analyzed centrally at the end of the study by an outside party.

The MRI exam after dosing on Visit 8 will be used to evaluate subjects for possible ARIA. ARIA are MRI abnormalities, including signal changes thought to represent vasogenic edema and/or microhemorrhages that have been seen in subjects enrolled in clinical trials of experimental amyloid-modifying therapies. [REDACTED]

7.2.2.4 Proteomic and Genetic Biobanking

Blood and plasma will be collected from subjects at multiple timepoints throughout the trial for biobanking. For information regarding the timing and procedures for sample collection and related requirements, refer to the study's laboratory manual and [Section 17 Schedule of Events](#).

Plasma will be analyzed by proteomics using mass spectrometry and targeted approaches to assess the specific signature of proteins in subjects at baseline and to assess the changes in the proteome with repeated GRF6019 infusions. These methodologies will provide a broad overview of the proteins that are present in the plasma sample by assessing 1000-5000 analytes and allow generation of a proteomic signature. From this signature, we hope to identify key proteins that are drivers of cognitive function and/or indicators of disease progression. Blood samples will be retained for analysis of emergent genetic markers of disease. By understanding the composition and function of plasma samples from the trial, we seek to identify the biomarkers relevant to further optimizing treatment in AD. For information regarding future use of stored samples, see [Section 12.5 Future Use of Stored Specimens](#).

7.2.2.5 Cerebrospinal Fluid Biomarker Collection (Optional)

Participation in the cerebrospinal fluid (CSF) biomarker research is optional and not required for inclusion in the study.

The CSF collection procedure, as well as the potential risks and benefits, will be explained to all study participants at participating sites. Subjects who are eligible and consent to participate will undergo two lumbar punctures for CSF collection, the first occurring prior to initial dosing, and the second occurring following final dosing. If a subject withdraws from the study early but is willing to provide the second (final) CSF sample, this can be obtained as long as the subject received at least two infusions of GRF6019. If the subject is currently taking antiplatelet therapy (e.g. clopidogrel, prasugrel, ticagrel), this medication must be withheld for 5 days prior to each lumbar puncture (treatment with aspirin can continue).

The lumbar punctures should be performed by a physician experienced in the procedure and according to the site's standard procedures. Both lumbar punctures should be performed at approximately the same time of day and the time should be recorded. For each lumbar puncture, 12-15 mL of CSF will be collected by gravity (not aspiration).

The first 2 mL should be collected for erythrocyte analysis. The remainder should be collected into a low-protein-binding polypropylene CSF collection tube without additives. The CSF should be kept at room temperature until centrifugation. The centrifugation should occur within 1 hour of collection, and the time documented. The tube should be centrifuged at 2,000 g for 10 minutes. The supernatant will be divided into approximately 10 aliquots of approximately 1 mL each. The aliquots should be pipetted into polypropylene tubes with screw caps and immediately frozen. Each aliquot tube should be at least 75% filled, and the number of aliquots should be adjusted to achieve this (depending on the final CSF volume collected).

CSF aliquots will be thawed and analyzed for specific AD biomarker assessments including [REDACTED]. CSF samples will also be analyzed by proteomics using mass spectrometry and targeted approaches to assess the specific signature of proteins in subjects at baseline and to assess the changes in the proteome with repeated GRF6019 infusions. These methodologies will provide a broad overview of the proteins that are present in the CSF samples and allow generation of a proteomic signature. From this signature, we hope to identify key proteins that are drivers of cognitive function and/or indicators of disease progression. For information regarding future use of stored samples, see [Section 12.5 Future Use of Stored Specimens](#).

7.2.3 SPECIMEN PREPARATION, HANDLING, STORAGE, AND SHIPPING

Refer to the study’s laboratory manual for specimen preparation, handling, storage, and shipping procedures.

7.3 STUDY SCHEDULE

Visit windows (when noted) should be benchmarked relative to Visit 3 for a subject, such that subjects complete the entire study by Day 168 (±7 days). Study visit procedures are listed in the recommended order in which they should be completed.

7.3.1 SCREENING

Visit 1, Screening (Day -28 to -8)

- Informed consent of subject (and/or the subject’s legally authorized representative) and the subject’s trial partner must be obtained prior to any study-related assessments
- Administer the C-SSRS
- Assess for probable AD using NIA-AA criteria including MMSE
- Conduct the MHIS
- Obtain medical history, including medical records to support AD diagnosis if available
- Collect demographic information
- Review subject’s current and prior medications
- Review and provide the subject (and subject’s trial partner) with a list of permitted and prohibited medications
- Collect vital signs, height, and weight
- Perform the physical exam
- Perform 12-Lead ECG
- Collect specimens for the laboratory panel
- Perform transthoracic echocardiogram
- Complete MRI
- Complete PET Imaging (optional)

Note: The Screening Visit may be split to allow for sufficient time to complete all required procedures. AEs and concomitant medications should be collected during split visits, as applicable. Any PET Imaging should be completed after the MRI but before Visit 3. The optional PET scan should only be performed after the subject has met criteria for inclusion in the study.

7.3.2 BASELINE

Visit 2, Baseline (Days -7 to -1)

- Re-review screening assessments for eligibility (e.g., MMSE scores, lab values)
- Review AEs and concomitant medications
- Collect the following:
 - Vital signs
 - Samples for proteomics/epigenetics/biobanking (fasting samples are preferred)
 - Buccal swab for ApoE Genotype testing
- Ensure the subject has had an opportunity to eat a meal prior to commencing cognitive and motor testing
- Perform cognitive and motor testing in the following order unless otherwise specified:
 1. Savonix Full Battery
 2. ADAS-Cog/11
 3. Grooved Pegboard
 4. CFT
 5. CDR-SOB (subject and trial partner)
 6. ADCS-ADL₂₃ (trial partner)
 7. ADCS-CGIC (subject and trial partner)
 8. NPI-Q (trial partner self-administered; may be completed by the trial partner at any available time during the visit)
- Confirm subject eligibility prior to initiating treatment
- In consenting, eligible subjects, perform initial lumbar puncture and obtain CSF samples for optional biomarker research.

Note: The Baseline Visit may be split to allow collection of all required assessments.

7.3.3 RANDOMIZATION

It is recommended that subjects be randomized at the start of Visit 3, prior to receiving their first dose. However, subjects may be randomized at any time after eligibility has been confirmed but prior to receiving their first dose on Visit 3.

Subjects who are randomized but do not receive any dose of the study agent, may be re-screened and randomized if they meet all of the study eligibility requirements.

7.3.4 TREATMENT

There are two inpatient treatment periods scheduled during the trial, each with a total of 5 infusions. 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 each inpatient treatment period.

Visits 3-7 (Days 1-5) and 11-15 (Days 85*-89):

*Day 85 has a ± 7-day window. Visits 12-16 should follow consecutively.

- Perform the following procedures prior to administering study treatment:
 - Review AEs and concomitant medications
 - Obtain blood and urine samples for comprehensive laboratory panel; fasting samples preferred **(Visits 4, 6, 12, and 14 Only)**
 - Obtain samples for proteomics/epigenetics/biobanking; fasting samples preferred **(Visits 3 and 11 Only)**
 - Obtain i-STAT safety laboratory test samples and assess results before each infusion
 - Perform targeted physical exam (i.e. auscultation of heart and lungs and assessment of peripheral edema)
 - Measure and record the subject’s weight in kilograms
 - Perform 12-lead ECG **(Visit 11 Only)**
 - Ensure the subject has had an opportunity to eat a meal prior to cognitive and motor testing
 - Administer the Savonix Brief Battery
 - Perform ADAS-Cog/11 **(Visit 11 Only)**
 - Collect pre-infusion vital signs
- Administer study treatment and perform safety assessments per the Infusion Administration Manual
- Post-infusion: perform 12-lead ECG **(Visits 7 and 15 Only)**

7.3.5 FOLLOW-UP

Visits 8 and 16 (Day 6 and Day 90 – Last Day of Inpatient Stay):

- Review AEs and concomitant medications
- Collect the following:
 - Vital signs and subject’s weight in kilograms
 - Blood and urine samples for comprehensive laboratory panel (fasting samples preferred)
 - Samples for proteomics/epigenetics/biobanking (fasting samples preferred)
 - i-STAT safety laboratory test samples and assess results before discharge
- Perform targeted physical exam (i.e. auscultation of heart and lungs and assessment of peripheral edema)
- Ensure the subject has had an opportunity to eat a meal prior to cognitive and motor testing
- Perform cognitive assessments in the following order:
 1. C-SSRS
 2. MMSE
 3. Savonix Full Battery
 4. ADAS-Cog/11
- Complete MRI **(Visit 8 + 4 days Only)**
- In consenting, eligible subjects, perform final lumbar puncture (after final dosing) and obtain CSF samples for optional biomarker research **(Visit 16 or within 5 days following)**

Visit 9 (Day 28 ±7 days) and Visit 17 (Day 112 ±7 days)

- Review AEs and concomitant medications
- Collect the following:
 - Vital signs
 - Blood samples for interim safety labs (Note: Subjects randomized prior to August 30, 2018, will not participate in the additional interim safety labs at Visit 9 and Visit 17.)
 - Samples for proteomics/epigenetics/biobanking (fasting samples preferred)
- Ensure the subject has had an opportunity to eat a meal prior to cognitive and motor testing
- Perform cognitive and motor testing in the following order unless otherwise specified:
 1. Savonix Full Battery
 2. ADAS-Cog/11
 3. Grooved Pegboard
 4. CFT
 5. CDR-SOB (subject and trial partner)
 6. ADCS-ADL₂₃ (trial partner)
 7. ADCS-CGIC (subject and trial partner)
 8. NPI-Q (trial partner self-administered; may be completed by the trial partner at any available time during the visit)

Visit 10 (Day 56 ±7 days) and Visit 18 (Day 140 ±7 days)

- Review AEs and concomitant medication
- Collect the following:
 - Vital signs
 - Blood and urine samples for comprehensive laboratory panel (fasting samples preferred)
 - Samples for proteomics/epigenetics/biobanking (fasting samples preferred)
- Ensure the subject has had an opportunity to eat a meal prior to cognitive and motor testing
- Perform cognitive assessments in the following order unless otherwise specified:
 1. Savonix Full Battery
 2. ADCS-ADL₂₃ (trial partner)
 3. NPI-Q (trial partner self-administered; may be completed by the trial partner at any available time during the visit)

7.3.6 FINAL STUDY VISIT

Visit 19, End of Study (Day 168 ±7 days)

- Review AEs and concomitant medication
- Collect the following:
 - Vital signs and subject's weight in kilograms
 - Blood and urine samples for exit laboratory panel (fasting samples preferred)
 - Samples for proteomics/epigenetics/biobanking (fasting samples preferred)
- Perform the physical exam
- Ensure the subject has had an opportunity to eat a meal prior to cognitive and motor testing
- Perform cognitive and motor testing in the following order unless otherwise specified:
 1. MMSE
 2. Savonix Full Battery
 3. ADAS-Cog/11
 4. Grooved Pegboard
 5. CFT
 6. CDR-SOB (subject and trial partner)
 7. ADCS-ADL₂₃ (trial partner)
 8. ADCS-CGIC (subject and trial partner)
 9. NPI-Q (trial partner self-administered; may be completed by the trial partner at any available time during the visit)
- Complete MRI

Note: Visit 19 may be split to allow for sufficient time to complete all required procedures.

7.3.7 EARLY TERMINATION

If a subject has received at least one infusion but is terminated or terminates from the study early, the site should try to perform all assessments scheduled at the End of Study Visit. In addition, if a subject withdraws from the study early but is willing to provide the second (final) CSF sample (and has consented and is eligible to participate in the optional CSF biomarker research), this can be obtained as long as the subject received at least two infusions of GRF6019.

7.3.8 SCHEDULE OF EVENTS TABLE

A tabular summary of all procedures that will be accomplished at each study visit can be found in [Section 17 Schedule of Events](#).

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All prescription, over-the-counter, and non-prescription medications (including herbal therapies and supplements) must be documented in the source documents and CRFs. All subjects should be maintained on the same medications at the same dosage and administration for treatment of AD throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Any changes in medications should be documented with reason for change (e.g., adverse event, etc.).

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following are prohibited:

- Concurrent participation in another therapeutic treatment trial for AD. If there was prior clinical trial participation, then the last dose of the investigational agent for symptomatic therapies must have been 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.
- Concurrent daily treatment with benzodiazepines, long-acting opioids, or other medications that, in the investigator’s opinion, interfere with cognition. [Note: intermittent treatment with low-doses of shorter half-life benzodiazepines (e.g. lorazepam, alprazolam) may be permitted, provided that no dose is administered within the 72 hours preceding any cognitive assessment].
- Any anticoagulant therapy; antiplatelet drugs (e.g., aspirin or clopidogrel) are acceptable.
- Any drugs of the interferon class.
- Systemic steroids (e.g., hydrocortisone, cortisone, betamethasone, prednisone, prednisolone, triamcinolone, dexamethasone, fludrocortisone) for longer than 5 consecutive days; ophthalmic, topical, intra-articular and inhaled steroids are allowed.

8 ASSESSMENT OF SAFETY

Assessment of safety will be conducted by blinded study personnel except in extraordinary circumstances where knowledge of the dose received by a subject is essential. Any instances of unblinding will be managed as indicated in [Section 10.6.3 Breaking the Study Blind/Participant Code](#).

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Per 21 CFR 312.32(a) an AE is any untoward (unfavorable, harmful, or pathologic) medical occurrence in a subject administered a medicinal (investigational) product even if the event does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is deemed clinically significant), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

An AE does include any:

- Exacerbation of a pre-existing illness
- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff
- Increase in frequency or intensity of a pre-existing episodic event or condition

- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study (unless it can be demonstrated by medical record review that the onset of the event preceded the date/time of Informed Consent)
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study
- Symptoms associated with disease not previously reported by the subject
- Lack of efficacy in the acute treatment of a life-threatening disease
- Untoward medical occurrences considered by the investigator to be related to study-mandated procedures
- Abnormal assessments (e.g., change on physical examination, ECG findings), if they represent a clinically significant finding, that were not present at Baseline or worsened during the course of the study
- Laboratory test abnormalities, if they represent a clinically significant finding, symptomatic or not, which were not present at Baseline or worsened during the course of the study

An AE DOES NOT include a/an:

- Elective medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion)
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions)
- The disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition
- Overdose of either study drug or concurrent medication without any signs or symptoms.
- Symptoms associated with AD that are consistent with the subject's usual clinical course unless the symptom(s) meet(s) the criteria for "serious"
- Pregnancy

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is any AE occurring at any dose that results in any of the following outcomes (note that if either the investigator or the Sponsor believes that the event is serious, the event must be considered serious and evaluated for expedited reporting). Note that the terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE. "Serious" is a regulatory definition. A serious adverse event (experience) or reaction is an untoward medical occurrence that, at any dose, fulfills one or more of the following criteria:

- a. Results in death (i.e., the AE actually causes or leads to death)
- b. Is life-threatening
 - An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death; it does not include AEs which, had it occurred in a more severe form, might have caused death
- c. Results in inpatient hospitalization or prolongation of existing hospitalization.
 - Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE

- Complications that occur during hospitalization are AEs; if a complication prolongs hospitalization, the event is an SAE
 - “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons that may or may not be overnight; it does not include presentation at a casualty or emergency room unless the event meets the definition of an Important Medical Event (in the opinion of the Investigator or Sponsor)
- d. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- The term ‘disability’ means a substantial disruption of a person’s ability to conduct normal life functions; this definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption
- e. Results in a congenital anomaly in the offspring of a subject who received drug
- f. Results in an Important Medical Event. Important Medical Events are events that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition; examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse
- Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Each AE or suspected adverse reaction must be assessed for its seriousness and severity. Severity will be assessed by the investigator or designee using the following definitions:

SEVERITY	DEFINITION
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

Outcome will be assessed using the following categories: recovered/resolved, not recovered/ not resolved, recovered/resolved with sequelae, fatal, or unknown.

8.2.2 RELATIONSHIP TO STUDY AGENT

Investigators are required to assess the causal relationship (i.e., whether there is reasonable possibility that the study drug caused the event) using the following definitions:

- Unrelated: another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the study agent; or a causal relationship is considered biologically implausible.

- **Possibly Related:** There is a clinically plausible time sequence between onset of the adverse event and administration of the study agent, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the study agent is one or several biologically plausible adverse event causes.
- **Definitely Related:** The adverse event is clearly related to use of the study agent.

If either the investigator or the Sponsor considers the event related, then the event will be considered related for reporting purposes.

8.2.3 EXPECTEDNESS

The Sponsor or designee will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Reference Safety Information described in the Investigator's Brochure.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the Investigator's Brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes ([FDA 2012](#)).

This definition of "unexpected" relies entirely on the Reference Safety Information in the Investigator's Brochure as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is unexpected. The suspected adverse reactions listed in the Investigator's Brochure (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed.

Sponsor assessment of expectedness and relationship to study drug/causality will determine the need for expedited reporting of AEs.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At every clinic visit, subjects will be assessed for AEs and SAEs. After the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking a non-leading question such as the following:

1. "How are you feeling?"
2. "Have you had any changes since your last assessment/visit?"
3. "Have you taken any new medicines since your last assessment/visit?"

8.3.1 POST-STUDY AEs AND SAEs

The investigator is not obligated to actively seek SAE information in former study participants, but the investigator is encouraged to notify Alkahest, Inc. or their designee of any AE or SAE occurring within 30 days after a subject completes the study (or has their last visit) that the investigator judges may be reasonably related to study treatment or study participation.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All subjects who have given informed consent will be evaluated for AEs. All AEs that occur after the time of treatment with the study agent will be considered Treatment Emergent AEs. Subjects with Treatment-Emergent AEs must be followed until the AE is resolved or is stable, unless the subject is lost to follow up.

Each AE or suspected adverse reaction must be described as follows: the date of onset, date of resolution, severity (mild, moderate, severe), frequency of the event (single episode, intermittent, continuous), action taken with study treatment (no action taken, treatment held, treatment discontinued), outcome, causality* (unrelated, possibly related, definitely related), and seriousness criteria. Each AE or suspected adverse reaction must be recorded separately.

***Note:** Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the study agent. An AE occurring before the subject’s exposure to study agent will always be labeled as “unrelated”.

Any AE occurring during the study must be documented in the subject’s medical records and as an AE in the CRF. Any SAE occurring during the study must be documented in the subject’s medical records and as an SAE in the CRF.

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE page.

The investigator should attempt to establish a diagnosis of the event (that meets the definition of an AE or SAE) based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs or symptoms. The diagnosis will become the basis for the verbatim term as reported by the investigator. If no diagnosis is known and clinical signs and symptoms are not present, the abnormal finding should be recorded.

In addition to the investigator’s own description of the AE, each AE will be encoded according to the MedDRA.

The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE. Any medication necessary for the treatment of an AE must be recorded on the concomitant medication CRF.

The SAE pages of the CRF should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the study Contract Research Organization (CRO). It is very important that the investigator provide his/her assessment of causality to study drug as well as an applicable diagnosis at the time of the initial SAE report.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

8.4.2.1 Timeframes for Reporting SAEs

Under 21 CFR 312.32(c), the Sponsor is required to notify FDA and all participating investigators in a safety report of potentially serious risks from clinical trials [i.e., Suspected Unexpected Serious Adverse Reactions (SUSARS)], as soon as possible after the Sponsor receives the safety information and determines that the information qualifies for reporting:

- No later than 7 calendar days for events that are life threatening (in the opinion of the investigator or the Sponsor) or that involve Death as an outcome.
- No later than 15 calendar days for all other SUSARS.

As such, prompt notification of the Sponsor, and/or the Sponsor's representatives, and promptly providing requested follow-up information regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. Investigators are responsible for reporting SAEs according to the following timeframes:

- All SAEs occurring during the study should be reported immediately.
- The SAE Report Form and relevant source documents, if applicable, must be completed and emailed to Safety.Alkahest@apcerls.com within 24 hours of observation or learning of the event.
- Follow-up information must be sent to the CRO within 24 hours of receipt of information by the investigational site.

SAEs will be followed until resolution, the condition stabilizes, the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow up.

8.4.2.2 SAE Information to Report

All information available regarding an SAE must be submitted in the timeframes indicated. At a minimum, SAE reports must contain the subject ID, the SAE verbatim term, onset date, relationship to study drug/causality, and a brief narrative of the event. Please note that **relationship to study drug/causality as well as the reported verbatim term are very important** and should be included in the initial report as it may impact expedited regulatory reporting requirements for the event. The date of SAE discovery by the site staff should be documented in the source documents.

The investigator must record all relevant information regarding an AE/SAE in the applicable sections of the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by the CRO and/or the Sponsor. If medical records are submitted to the CRO then all subject personal identifiers must be completely and thoroughly redacted prior to submission.

A blank SAE Report Form and instructions for SAE reporting will be provided to the site and will be maintained in the investigator's study file. The SAE Report Form must be completed and emailed to Safety.Alkahest@apcerls.com according to the timeframes specified in [Section 8.4.2.1](#). The SAE Report Form should include copies of relevant source documents, if applicable. Reconciliation of any discrepancy noted during monitoring and amending the CRF is required.

If new information about an SAE is received or corrections to data are needed, the investigator should complete a new SAE Report Form and check the "follow-up" box on the form. This follow-up SAE Report Form should be

submitted within 24 hours of learning of the information, especially if the new information concerns seriousness, relatedness, or the event term of an AE.

Sites acting under their local IRB should submit all applicable events, unanticipated problems, and safety reports to the site's local IRB, if applicable. All safety reporting deviations should also be submitted to their local IRB, if applicable.

8.4.3 ADVERSE EVENTS OF SPECIAL INTEREST

The following will be considered adverse events of special interest (AESI):

- Clinically-significant peripheral edema or pulmonary edema.
- Systolic blood pressure (BP) < 90 or > 160 mm Hg and/or diastolic BP < 60 or > 100 mm Hg, or a change of > 25% from Day 1 (Visit 3) pre-infusion systolic and/or diastolic BP.
- Reduced kidney function (eGFR < 45 mL/min/1.73 m²).
- Suspected transmission of blood-borne infectious agents.

AESI occurring during the study should be reported within 48 hours of observation or learning of the event, unless the event is serious, in which case the event must be reported according to the timeframes specified in [Section 8.4.2.1](#).

8.4.4 REPORTING OF PREGNANCY

While pregnancy itself is not considered an AE, pregnancy occurring in a clinical study must be followed to collect information regarding the experiences of gestation and pregnancy with study agent exposure. The investigator must report any pregnancy that occurs in a female study subject subsequent to first exposure to the study agent until End of Study, or 3 months following a subject's last dose. All pregnancies will be reported to the IRB, Sponsor, and CRO. In the event of a pregnancy, treatment will be discontinued, and the subject will undergo continued safety follow-up through pregnancy outcome.

Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as an SAE within 24 hours of the investigator or study personnel's first knowledge.

8.5 STUDY HALTING RULES

If any of the following safety events occur, a Safety Evaluation Meeting (defined below) will be triggered:

- Three or more SAEs in the same system/organ/class (SOC) that are assessed as possibly or definitely related to the study agent by the investigator and confirmed as such by the Sponsor (see [Section 8.2.2 Relationship to Study Agent](#)).
- Within or between any of the dosing groups: an overall pattern of symptomatic, clinical, or laboratory events associated with the study agent that the Sponsor's Program Physician or designee consider a serious potential safety concern (e.g. suspicious overall pattern).

Events that are more likely related to the infusion procedure, such as infiltration or hematoma, will not be considered "drug related" and will not contribute to the count of definitely-related SAEs that would trigger a Safety Evaluation

Meeting.

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (as defined above) a Safety Evaluation Meeting will be triggered, and dosing may be temporarily halted based on the observations. The Sponsor will inform investigators and the FDA in the event of any temporary halt in dosing at any time during the conduct of the study. The purpose of the meeting is for investigators, the Sponsor, and the CRO Medical Monitor to discuss and evaluate the safety of the subjects using available aggregated safety data and without compromising study blinding.

Attendants at the Safety Evaluation Meeting will include the Alkahest Program Physician (or his/her designee), the CRO Medical Monitor, and a majority of active investigators participating in the trial. After sufficient data review the Sponsor will choose one of the following courses of action:

1. Continue dosing with no change to protocol.
2. Halt dosing in all groups and stop the study.
3. Continue with a modified protocol design and amend the protocol as appropriate.

8.6 SAFETY OVERSIGHT

Safety oversight will be provided by the Sponsor's Program Physician or his or her designee and the CRO's Medical Monitor in concert with the Principal Investigators at each participating site. As all subjects are on active drug, there will be no formal Data Safety Monitoring Board (DSMB) established. As needed, blinded Safety Evaluation Meetings will be convened as described in [Section 8.5](#) to monitor the ongoing safety of the study. The Sponsor's Program Physician or designee is the final authority for safety oversight in the study.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Study CRO in accordance with the Clinical Monitoring Plan (CMP).
- A mix of on-site and centralized risk-based monitoring will be performed to ensure the safety of clinical subjects and the accuracy and completeness of study data.
- The Sponsor will be provided with copies of monitoring reports per the timelines specified within the CMP.
- Details of clinical site monitoring are documented in the Study's CMP. The CMP describes in detail who will conduct monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by the Sponsor in accordance with the Sponsor's clinical quality oversight plan or equivalent to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed during the conduct of the study. The finalization of the SAP will occur prior to clinical database lock and unblinding of the study data.

10.2 STATISTICAL HYPOTHESES

In as much as the study design is focused on safety and tolerability, the statistical approach toward the secondary endpoints will be primarily descriptive with only modest amounts of hypothesis testing; within-subject changes from baseline for each dosing group and among-group differences will be evaluated.

10.3 ANALYSIS DATASETS

Four analysis datasets are possible however, analyses may not necessarily be conducted with all four:

- **Intention-to-Treat (ITT) Dataset:** all randomized participants.
- **Safety Dataset:** all subjects who received at least one dose of the study agent.
- **Evaluable Dataset:** all subjects who receive at least 5 of the 10 planned doses.
 - **Per Protocol Dataset:** a subset of the Evaluable Dataset comprised of subjects who have no Major Protocol Deviations.

The presentation of baseline characteristics will be conducted on the ITT dataset. All safety analyses will be performed for the Safety Dataset. Analyses of the secondary endpoints will focus on the Evaluable and/or Per Protocol Datasets.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Using the Evaluable and/or Per Protocol Datasets, all secondary cognitive-score endpoints (e.g., MMSE, ADAS-Cog, etc.) will be summarized serially over time using descriptive statistics to assess the within-subject changes and among-group differences. Overall baseline and demographic data will be summarized using descriptive statistics; among-groups testing will be used to evaluate the effectiveness of the randomization in producing homogeneous pre-treatment groups.

For analysis of the primary and secondary endpoints, the following will be considered:

- 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 inferential statistics:
 - If the Normality assumption is met, Paired t-test, or Analysis of Covariance (ANCOVA) using the baseline value as a covariate will be used.

- If the Normality assumption is not met, a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used.
- For endpoints that are categorical in nature:
 - Frequency counts and percentages will be presented as descriptive summary.
 - Chi-square test or Logit model will be used for inferential statistics.

Subject disposition (e.g., the number of subjects randomized, completed, and discontinued) will be summarized and medical history data will be listed. Prior and concomitant medications taken from screening and during the study will be categorized by World Health Organization (WHO) classification for therapeutic class and drug name, listed and summarized by number and percentage of subjects.

Final analyses are not limited to the summaries described herein. As noted above, analytical details and assumptions will be fully presented in the SAP.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Summary tabulations of the reported adverse events will be presented by group after the Verbatim Terms have been coded to PTs and SOCs using the MedDRA Version 21.0 coding dictionary. The summaries will include severity and attribution to the study agent. Multiple reports of the same AE by the same subject will be counted only once at the highest severity and strongest attribution to the study agent.

The AE analyses will focus on those that are Treatment-Emergent, however any AEs that are reported after consent has been signed and prior to initial dosing will be tabulated as Intercurrent Events.

Additional details are presented in [Section 10.4.4](#).

10.4.3 ANALYSIS OF THE SECONDARY ENPOINT(S)

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 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. Appropriate paired sample tests (paired t-test or Wilcoxon Signed Rank tests) may be conducted to evaluate within-subject changes from baseline, using a two-tailed α -level of 0.05. Among-group differences may be assessed by One-way ANCOVA or its nonparametric equivalent test. Alternatively, since the dose groups are ordinal, regression and graphical methods may be employed to evaluate any dose-response trends.

10.4.4 SAFETY ANALYSES

Safety, tolerability, and feasibility will be evaluated by examining the occurrence of AEs, including Treatment-Emergent AEs, and AEs leading to discontinuation from the study. AEs will be summarized by severity and by study drug dose.

Actual and changes from baseline in clinical laboratory measurements and vital signs will also be assessed and summarized. Abnormal values will be determined and flagged in the listings. Laboratory shift tables or graphics displaying the change (number of subjects) relative to the reference range from baseline to each study visit may also be presented for each test. The investigator should exercise his or her medical and scientific judgment in

deciding and documenting whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

Per-subject extent of exposure will be listed.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Feasibility as measured by subject adherence with the study visit schedule, visit procedures, infusions, and subject retention. Subject adherence may vary across the different groups offering another feasibility measurement as would a comparison of the number of subjects who complete two series of 5 pulsed doses to subjects who complete only the first series. Reasons for study discontinuation will be compared across groups and across other subgroups of subjects, as appropriate.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

See [Section 10.4.1](#).

10.4.7 PLANNED INTERIM ANALYSES

No interim analyses are planned. If a Safety Evaluation Meeting is triggered (see [Section 8.5](#)), an ad hoc interim safety analysis will be performed. If such an ad hoc safety interim analysis is conducted, the dose assignment will remain masked.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Not applicable.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments for multiplicity will be employed.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

This will be further defined in the SAP.

10.4.11 EXPLORATORY ANALYSES

Not applicable.

10.5 SAMPLE SIZE

A total of 40 subjects (20 in the 100 mL group and 20 in the 250 mL group) 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 completing Visit 8 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced. Subjects who are randomized but do not receive any dose of the study agent, may be re-screened and randomized if they meet all of the study eligibility requirements.

The study is not powered for detecting statistically significant differences in pharmacodynamic parameters or to assess the cognitive effects of GRF6019 infusions in AD. However, 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 5.0% (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 response.

10.6 MEASURE TO MINIMIZE BIAS

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

To minimize the potential bias, the study will be double-blinded at randomization and through the end of study. A stratified permuted block randomization will be implemented 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. However, study agent and information regarding the volume to be administered, will be provided by an unblinded pharmacist, or other qualified staff responsible for drug accountability, to an unblinded Infusion Nurse. Administration of the study agent will be performed by the unblinded Infusion Nurse. 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 vial(s) 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, and the unblinded Infusion Nurse will be responsible for concealing and returning used and partially used vials to the pharmacy at the end of the Infusion Period.

Communication between the Outcomes Assessor and the Infusion Nurse will be restricted to only that required to ensure immediate safety of subjects (e.g. requests to start/stop/change infusion rates outside of the standard infusion protocol due to AEs). The Outcomes Assessors will observe the subject during the infusion of the study agent and collect and/or manage/report AEs and SAEs.

[REDACTED]

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

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Evaluation of success of blinding will be assessed as part of study feasibility. 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). All intentional and unintentional unblinding will be documented and reported.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Due to the dose-comparison concurrent control study design, it is not expected that the study blind would need to be broken for safety reasons. Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor’s Study Team Lead. Subjects who have been unblinded prior to dosing day 5 will be replaced. If unintentional unblinding occurs during the study, root cause analysis will be evaluated, and corrective actions implemented.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of regulatory agencies, the IRB/IEC, the Sponsor, or the Sponsor’s representatives to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant’s memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable for the CRF to be the only record of a subject’s participation in the study. This is to ensure that anyone who would access the subject’s medical record has adequate knowledge that the subject is participating in a clinical trial. Source document templates will be developed for this study.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, ICH E6 R2, 21 CFR, part 320, 1993, Retention of Bioavailability and Bioequivalence Testing Samples and the Declaration of Helsinki.

12.2 INSTITUTIONAL REVIEW BOARD

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Any modifications or amendment to the protocol must also be submitted to the IRB/IEC for approval prior to implementation.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject (or the subject’s legally authorized representative) and trial partner. Written documentation of informed consent is required prior to any invasive study procedures. The following consent materials are submitted with this protocol:

- ALK6019-201 Informed Consent Form

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study and/or their legally authorized representative and the subject’s trial partner (if not the same person as the legally authorized representative) after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

Subjects and/or trial partners should have the opportunity to discuss the study with their family members or other advisors and the time to consider participation in the trial carefully. Participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator or designee must utilize an IRB/IEC-approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and/or their legally authorized representative and the subject’s trial partner (if not the same person as the legally authorized representative) and the person obtaining consent. A copy of the signed consent form will be provided to the subject and/or their legally authorized representative and the trial partner (if not the same person as the legally authorized representative). By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited

information about the potential candidate (e.g., date of screening).

All subjects who provide consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to the study subject. Once a number is assigned to a subject, that number will remain with that study subject and will not be reused.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used for screening, written informed consent must be obtained prior to review of that information in accordance with HIPAA.

The Screening period for a subject commences at the point at which the subject signs the informed consent form and must be completed within 28 days prior to study drug treatment.

Due to the nature of the assessments in the trial, subjects and trial partners will need to speak English. Therefore, there will be no need to translate the informed consent form into other language versions.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Subject and trial partner confidentiality is held in strict trust by the participating investigators, their staff, the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC or government regulatory agencies may inspect documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and an identification code (i.e., not names) should be recorded on non-local lab samples, requisitions and any documents submitted to the CRO, Sponsor and/or IRB/IEC. The investigator must keep a subject log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

12.5 FUTURE USE OF STORED SPECIMENS

With the subject's (or the subject's legally authorized representative's) approval and as approved by local IRBs under separate consent, de-identified biological samples may be stored by Alkahest, or designee, indefinitely for future use. These samples could will be used for research into the causes of AD, its complications, and other conditions for which elderly individuals are at increased risk, and to improve treatment options. Alkahest will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each subject, maintaining the masking of the identity of the study subject.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens

stored for future research. However, withdrawal of consent for biospecimen storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be managed by Alkahest. In the event Alkahest transfers ownership to another commercial sponsor, ownership of the samples may be transferred as well.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.**

For each subject who receives an infusion, the CRF must be completed within approximately 14 days of each completed visit. The investigator will review and approve the CRF for each study subject after all data have been entered, the CRFs have been source document verified by the CRA, and all queries have been resolved. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

All data collection and recordkeeping procedure must be compliant with applicable ICH GCP.

13.1.1 INVESTIGATOR RESPONSIBILITIES

The investigator will comply with the protocol (which has been approved/given favorable opinion by an IRB/IEC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term “investigator” as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator’s signature is specifically required.

13.1.2 STUDY FILES

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 two separate categories (although not limited to) the following: (1) investigator’s study file, and (2) subject clinical source documents.

The investigator’s study file will contain the protocol/amendments, CRF and query forms (if paper CRFs are utilized), IRB/IEC approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents would 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.

13.2 STUDY RECORDS RETENTION

All clinical study documents must be retained by the investigator until two years after the Investigational New Drug (IND) application is discontinued and regulatory authorities have been notified. Before the investigator destroys any material related to the clinical study, he/she must obtain approval in writing from the Sponsor.

The investigator should keep a file where the full name and address of the subject and all signed informed consents are included for at least 15 years after completion of the trial. Any original study-related information that permits verification of inclusion and exclusion criteria, including clinical history, a copy of all data collection logs, and documents on the use of the study agent, must be stored for as long a time period as permitted by the center.

Should the investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the Subject, appropriate copies should be made for storage outside of the site.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or with GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. When deviations occur, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol Deviations will be categorized as either Major or Minor and will be defined in the study-specific Protocol Deviation Plan.

Major Protocol Deviations are departures from the approved protocol relating to the conduct of the study which may affect the rights, safety and/or wellbeing of study participants, or the study outcomes or data quality. Major Protocol Deviations may result in data that are not deemed evaluable for the per protocol analysis and/or may require that subjects be discontinued from the study. Major Protocol Deviations are Significant Clinical Issues.

Minor Protocol Deviations are departures from the approved protocol relating to the conduct of a study that does not affect the rights, safety and/or wellbeing of study participants, or the study outcomes or data quality. Minor Protocol Deviations do not require review by the medical monitor. Minor Protocol Deviations would not generally preclude subject data from the per protocol analysis population.

Note: persistently missed or incomplete study procedures and/or study evaluations will be considered Major Protocol

Deviations.

All deviations will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will inform assessment of site performance.

It is the responsibility of the site to use continuous vigilance to identify and report deviations promptly to the study CRO and/or Sponsor. All deviations must be addressed in study source documents. Protocol Deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

In compliance with The International Committee of Medical Journal Editors (ICMJE) clinical trials registration policy and Section 801 of the Food and Drug Administration Amendments Act of 2007, this study will be registered by the Sponsor in ClinicalTrials.gov, a public trials registry which is sponsored by the National Library of Medicine.

Notwithstanding the Sponsor's requirements for registration and data sharing in ClinicalTrials.gov, any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and the Sponsor. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final Clinical Study Report. The resulting publication will name investigators according to the policy of the chosen journal. Where it is not permitted for all investigators to be included as authors, the publication will name all investigators within the publication.

Individual investigators may publish data arising from their own subjects. The investigator will provide the Sponsor with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit the Sponsor to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged ([REDACTED]), to allow adequate input or supplementary information that may not have been available to the investigator, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication, unless this has been agreed otherwise by all other investigators and the Sponsor. However, in the event that no publication of the overall results has been submitted after approval of the Clinical Study Report, investigators may publish results of one or more center's subjects to the same review as outlined above. The Sponsor will circulate proposed multicenter publications to all investigators for review.

Data will be reviewed by all participating investigators prior to publication. The study Sponsor will have 60 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

14 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY

A separate financial agreement will be made between each principle investigator and Alkahest, Inc. or its authorized representative before the study drug is shipped. For this study, each investigator and sub-investigator (as designated on the FDA Form 1572) will provide a signed Financial Disclosure Form in accordance with 21 CFR 54. Each investigator

will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study for 1 year after the study has been completed. Alkahest and the study CRO will evaluate any disclosed conflicts of interest and will establish a mechanism for their management.

15 LITERATURE REFERENCES

Acevedo A. Category fluency test: normative data for English and Spanish-speaking elderly. *J Int Neuropsych Soc.* 2000;6(7):760-769.

ALK-2015-R002. Effects of young and old human plasma on cognition in NODscid mice.

Alzheimer’s Association. 2018 Alzheimer’s Disease Facts and Figures. *Alzheimers Dement.* 2018;14(3):367-429.
 Benton AL. Development of a multilingual aphasia battery: progress and problems. *J Neurol Sci.* 1969;9:39-48.

[REDACTED]

Burnouf T. Modern plasma fractionation. *Transfus Med Rev.* 2007;21(2):101-17.

Cai K, Miller JL, Stenland CJ, Gilligan KJ, Hartwell RC, Terry JC, et al. Solvent-dependent precipitation of prion protein. *Biochim Biophys Acta.* 2002;1597:28-35.

Food and Drug Administration (FDA), U.S. Department of Health and Human Services. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. December, 2012.

Ferris SH, Mackell JA, Mohs R, Scheider LS, Galasko D, Whitehouse P, et al. A multicenter evaluation of new treatment efficacy instruments for Alzheimer’s disease clinical trials: overview and general results. *Alz Dis Assoc Dis.* 1997;11(Suppl 2):S1-S12.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res.* 1975;12(3):189-198.

[REDACTED]

Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer’s Disease. *Alz Dis Assoc Disord.* 1997;11 (Suppl 2):S33-39.

Gebhard C, Stahli B, Jenni R, Tanner FC. Effect of age on left ventricular ejection fraction assessed by echocardiography. *Eur Heart J.* 2012;33:1.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Brit J Psychiat.* 1982;140:566-572.

Kaufers DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci*. 2000 Spring;12(2):233-239.

Lafayette Instrument Company. Grooved Pegboard Test User Instructions (Model 32025); 2002.
 Mayeux R. Early Alzheimer's disease. *N Engl J Med*. 2010;362:2194-2201.

McKhann GM, Knopman, DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011 May;7(3):263-269.

MDRD for Adults (Conventional Units) | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases Available at: <https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units>. (Accessed: 16th February 2018)

O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's Research Consortium study. *Arch Neurol*. 2008;65:1091-1095.

Polacchini A, Metelli G, Francavilla R, Baj G, Florean M, Mascaretti LG, et al. A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. *Sci Rep*. 2015;5:17989.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am Psychiatry*. 2011 December;169(12):1266-1277.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.

Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. 1980. Pathological verification of ischemic score in differentiation of dementia. *Arch Neurology*. 1980;7:486-488.

Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg, B, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *Alzheimers Dis Assoc Disord*. 1997;11 (Suppl 2):S22-S52.

Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, et al. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. *Brain Imaging Behav*. 2012;6 (4):1-24.

Stenland CJ, Lee DC, Brown P, Petteway SR Jr, Rubenstein R. Partitioning of human and sheep forms of the pathogenic prion protein during the purification of therapeutic proteins from human plasma. *Transfusion*. 2002;42:1497-500.

Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*. 2011;477:90-94.

Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, Luo J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med. 2014 Jun;20(6):659-663.

[REDACTED]

16 APPENDICES

The neurocognitive assessments in this section and associated information are provided as **EXAMPLES ONLY**. The actual neurocognitive assessments, related source documents, and instructions for administration and scoring are included in the **Rater Reference Manual**.

Appendix 1. Mini-Mental State Examination (MMSE)**Instructions for Administration and Scoring**Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, ""Can you tell me the name of this facility (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.

- **Reading:** On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- **Writing:** Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- **Copying:** Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Reference:

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 1975;12(3):189-198.

Appendix 2. Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-COG/11): Assessment Categories, Descriptions, and Scoring**1. Immediate word recall**

In this task, the subject is given **3** tries to learn a list of **10** words. The subject must first read the words aloud, memorize them and then reproduce them. The subject’s score is the average number of words not recalled in **3** trials (maximum 10).

2. Naming objects and fingers

For this item, the subject is asked to name the 12 real objects presented randomly as well as the fingers of his/her dominant hand. The objects presented: flower, bed, whistle, pencil, rattle, mask, scissors, comb, wallet, harmonica, stethoscope, and tweezers. The score varies from 0 to 5.

3. Commands

The subject is asked to carry out **1** to **5** commands. Score varies from 0 to 5.

4. Constructional praxis

This task assesses the subject’s ability to copy **4** geometric forms: a circle, a superimposed rectangle, a diamond and a square. Score varies from 0 to 4.

5. Ideational praxis

This task is designed to determine whether the individual can perform a complex sequence of actions. The score varies from 0 to 5.

6. Orientation

The components of this task are person, day of the week, day of the month, month, year, season, time of day, and specific place. One point is given for each incorrect answer (maximum 8).

7. Word recognition

In this task, the subject must read and memorize a list of 12 words. These words are then randomly mixed with 12 words the subject has not seen, and the subject is asked to decide whether or not the word has already been read. The subject has **3** tries, in each of which, the word order is changed. The score is calculated.

8. Remembering test instructions

This item evaluates the individual's ability to remember the instructions of the recognition task. Score varies from 0 to 5.

9. Spoken language ability

This item is an overall rating of the quality of speech, such as clarity and capacity to make someone understand. Score varies from 0 to 5.

10. Word-finding difficulty in spontaneous speech

This task analyzes the decrease in expressive speech, but only as refers to difficulty in word choice. Score varies from 0 to 5.

11. Comprehension

This item evaluates the individual's ability to understand the examiner's speech. Score varies from 0 to 5.

References:

Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementia. *Arch Neurology*. 1980;7:486-488.

Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, et al. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. *Brain Imag Behav*. 2012;6:489-501.

Appendix 3. Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB)

The CDR rates the severity of AD using a 5-point scale assessing signs and symptoms of the disease as they affect the patient’s ability to function in the 6 cognitive categories of memory, orientation, judgment and problem solving, community affairs/involvement, home life and hobbies and personal care. The CDR is completed by a specially trained researcher or clinician after performing a face-to-face, semi-structured interview with the patient and a reliable informant (e.g., trial partner). The informant is interviewed first, and the results of that interview are used to assess patient recall of events and to confirm the accuracy of patient responses. In each cognitive category, the patient receives a score of 0 (no cognitive impairment) to 3 (severe cognitive impairment). The CDR can be scored to obtain a global score by using an algorithm that weights memory more heavily than the other categories, or it can be scored using the sum of boxes (SOB) method in which all categories are weighted equally; in general, the higher the score, the greater the severity of dementia

The memory, orientation, judgment and problem solving, community affairs/involvement, and home life and hobbies categories are scored using a 5-point ordinal scale, as follows:

- 0 indicates no impairment
- 0.5 indicates very mild impairment
- 1 indicates mild impairment
- 2 indicates moderate impairment
- 3 indicates severe impairment

The personal care category is scored using a 4-point ordinal scale, as follows:

- 0 indicates no impairment
- 1 indicates mild impairment
- 2 indicates moderate impairment
- 3 indicates severe impairment

The descriptors for each score on the CDR scoring sheet vary based on the category being evaluated; the selection criteria for each score are clearly described on the scoring sheet. In the CDR-SOB scoring method, all 6 categories are weighted equally, and the scores for each of the categories are summed to obtain a total score; the total score can be 0 to 18. The advantages of the SOB scoring method include greater ease in calculating dementia severity, the ability to better detect subtleties in dementia severity and increased precision in serially tracking the severity of dementia. SOB scores are used to rate dementia severity as follows:

- 0 indicates normal cognitive functioning
- 0.5–4.0 indicates questionable cognitive impairment

- 0.5–2.5 indicates questionable impairment
- 3.0–4.0 indicates very mild dementia
- 4.5–9.0 indicates mild dementia
- 9.5–15.5 indicates moderate dementia
- 16.0–18.0 indicates severe dementia

References

Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer’s Disease. *Alz Dis Assoc Disord.* 1997;11 (Suppl 2):S33-39.

O’Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer’s Research Consortium study. *Arch Neurol.* 2008;65:1091-1095.

Appendix 4. Alzheimer’s Disease Cooperative Study – Activities of Daily Living (ADCS-ADL23)

The ADCS-ADL₂₃ contains 23 items covering physical and mental functioning and independence in self-care. For each ADL, an informant/trial partner is first asked if the patient attempted the activity during the past 4 weeks. If a patient did attempt the ADL, the informant/trial partner is asked to choose the single most accurate definition of the patient’s level of performance. The scores range from 0 to 78, with higher scores indicating less functional impairment. Included below are the standard questions used for assessment of mild to moderate AD.

1. Regarding eating: Which best describes subjects’ usual performance during the past 4 weeks?

- Ate without physical help
- Used a fork or spoon, but not a knife to eat
- Used fingers to eat
- Usually or always was fed by someone else

2. Regarding walking (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her optimal performance:

- Mobile outside of home without physical help
- Mobile across a room without physical help
- Transferred from bed to chair without help
- Required physical help to walk or transfer

3. Regarding bowel and bladder function at the toilet, which best describes his/her usual performance in the past 4 weeks:

- Did everything necessary without supervision or help
- Needed supervision, but no physical help, and was usually continent
- Needed physical help, and was usually continent
- Needed physical help, and was usually incontinent

4. Regarding bathing, in the past 4 weeks, which best describes his/her usual performance:

- Bathed without reminding or physical help
- No physical help, but needed supervision/reminders to bathe completely
- Needed minor physical help (e.g., with washing hair) to bathe completely
- Needed to be bathed completely

5. Regarding grooming, in the past 4 weeks, which best describes his/her optimal performance:

- Cleaned and cut fingernails, without physical help

Brushed or combed hair without physical help

Kept face and hands clean without physical help

Needed help for grooming of hair, face, hands, and fingernails

6a. Regarding dressing, in the past 4 weeks, did subject select his/her first set of clothes for the day?

Yes / No / don't know - If Yes, which best describes his/her usual performance:

Without supervision or help

With supervision

With physical help

6b. Regarding physically getting dressed, which best describes his/her usual performance in the past 4 weeks (check one):

Dressed completely without supervision or physical help

Dressed completely with supervision, but without help

Needed physical help only for buttons, clasps, or shoelaces

Dressed without help if clothes needed no fastening or buttoning

Always needed help, regardless of type of clothing

Don't know

7. In the past 4 weeks, did subject use a telephone

Yes / No / don't know - If Yes, which best describes his/her highest level of performance:

Made calls after looking up numbers in white or yellow pages, or by dialing directory assistance

Made calls only to well-known numbers without referring to a directory, list, or preprogrammed numbers

Made calls only to well-known numbers by using a directory or list

Answered the phone; did not make calls

Did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did subject watch television?

Yes / No / don't know - If Yes, ask each of the following (Yes / No):

a. Did subject usually select or ask for different programs or his/her favorite show?

b. Did subject usually talk about the content of a program while watching it?

c. Did subject talk about the content of a program within a day (24 hours) after watching it?

9. In the past 4 weeks, did subject ever appear to pay attention to conversation or small talk for at least 5 minutes?

(note subject did not need to initiate the conversation)

Yes / No / don't know - If Yes, which best describes his/her usual degree of participation:

Usually said things what were related to the topic

Usually said things that were not related to the topic

Rarely or never spoke

10. Did subject clear the dishes from the table after a meal or snack?

Yes / No / don't know - If Yes, which best describes how he/she usually performed:

Without supervision or help

With supervision

With physical help

11. In the past 4 weeks, did subject usually manage to find his/her personal belongings at home?

Yes / No / don't know - If Yes, which best describes how he/she usually performed:

Without supervision or help

With supervision

With physical help

12. In the past 4 weeks, did subject obtain a hot or cold beverage for him/herself?

Yes / No / don't know - If Yes, which best describes his/her highest level of performance:

Made a hot beverage, usually without physical help

Made a hot beverage, usually if someone else heated the water

Obtained a cold beverage, usually without physical help

13. In the past 4 weeks, did subject make him/herself a meal or snack at home?

Yes / No / don't know - If Yes, which best describes his/her highest level of performance:

Cooked or microwaved food, with little or no help

Cooked or microwaved food, with extensive help

Mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich)

14. In the past 4 weeks, did subject dispose of garbage or litter in an appropriate place or container at home?

Yes / No / don't know - If Yes, which best describes how he/she usually performed:

Without supervision or help

With supervision

With physical help

15. In the past 4 weeks, did subject get around (or travel) outside of his/her home?

Yes / No / don't know - If Yes, which best describes his/her optimal performance:

Alone, went at least 1 mile away from home

Alone, but remained within 1 mile of home

Only when accompanied and supervised, regardless of the trip

Only with physical help, regardless or the trip

16. In the past 4 weeks, did subject ever go shopping?

Yes / No / don't know - If yes, ask A and B

A) Which one best describes how subject usually selects items?

Without supervision or physical help

With some supervision or physical help

Not at all, or selected mainly random or inappropriate items

B) Did subject usually pay for items without supervision or physical help?

Yes

No

17. In the past 4 weeks, did subject keep appointments, meetings with other people, such as relatives, a doctor, the hairdresser, etc.?

Usually remembered, may have needed written reminders, e.g., notes, a diary, or calendar

Only remembered the appointment after verbal reminders on the day

Usually did not remember, in spite of verbal reminders on the day

18. In the past 4 weeks, was subject ever left on his/her own?

Yes / No / don't know - If yes, ask all questions:

Was subject left:

Yes / No

a) away from home for 15 minutes or longer, during the day?

b) at home for an hour or longer, during the day

c) at home, for less than 1 hour during the day

19. In the past 4 weeks, did subject talk about current events? (This means events or incidents that occurred during the past month.)

Yes / No / don't know - If yes, ask all questions:

Did subject talk about events that (Yes / No):

- a) he/she heard or read about or saw on TV but did not take part in?
- b) he/she took part in outside home involving family, friends, or neighbors?
- c) events that occurred at home that he/she took part in or watched

20. In the past 4 weeks, did subject read a magazine, newspaper or book for more than 5 minutes at a time?

Yes / No / don't know - If yes, ask all questions:

Did subject usually (Yes / No):

- a) talk about details of what he/she read while or shortly (less than 1 hour) after reading?
- b) talk about what he/she read 1 hour or longer after reading?

21. In the past 4 weeks, did subject ever write things down?

Yes / No / don't know (Note: if subject wrote things only after encouragement or with help, the response should still be 'Yes'.)

If yes, which best describes the most complicated things that he/she wrote:

- Letters or long notes that other people understood
- Short notes or messages that other people understood
- His/her signature or name

22. In the past 4 weeks, did subject perform a pastime, hobby, or game?

Yes / No / don't know - If yes, how did subject usually perform his/her most common pastimes:

- Without supervision or help
- With supervision
- With help

If subject performs hobbies/pastimes only at day care, check here

23. In the past 4 weeks, did subject use a household appliance to do chores?

Examples include washer, dryer, vacuum, dishwasher, toaster, toaster oven, range, microwave, food processor

Yes / No / don't know

Reference:

Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's Disease. *Alz Dis Assoc Disord.* 1997;11 (Suppl 2):S33-39.

Questionnaire modified from electronic form developed at the Palo Alto Veterans Affairs Hospital by Wes Ashford, M.D., Ph.D., Jerome Yesavage, M.D. Available at: <http://www.medafile.com/cln/ADCSADLm.htm>

Appendix 5. Alzheimer’s Disease Cooperative Study- Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC evaluates the patient in five treatment domains: 1) cognition (immediate and delayed memory, praxis, attention, and executive function); 2) clinical global change; 3) activities of daily living; 4) behavioral symptoms (agitation and other noncognitive symptoms); 5) cognition in severely impaired patients.

Instructions for Administration of the ADCS-CGIC

The ADCS-CGIC consists of two parts; Part I, the baseline evaluation (includes information from both the subject and informant); Part II, ADCS_CGIC forms for both subject and informant.

The overall intent of the ADCS-CGIC is to provide a reliable means to assess global change from baseline in a clinical trial. It provides a semi structured format to enable clinicians to gather necessary clinical information from both the patient and informant to make a global impression of change.

Part I is used to record baseline information to serve as a reference for future ratings. Part II is composed of two sections, a subject interview form and an informant interview form. These forms are used to record information from separate interviews with both the subject and informant from which an impression of change score is made.

Baseline Evaluation

At baseline, the clinician interviews the patient and caregiver, recording onto Part I notes about baseline status for later reference. At baseline only, clinical information about the subject from any source can be used. The clinician indicates on a checklist the sources of information compiled during the baseline evaluation.

Parts I and II share a similar format for recording relevant clinical information. The column headed “Area” identifies various areas that a clinician might consider while evaluating a patient for potential clinical change, including what might be expected to be assessed in performing an ordinary but brief comprehensive office interview to determine a subject’s baseline status and eligibility for a clinical trial. The “Probes” column provides sample items that a clinician might find useful in assessing an area, and these are intended as guides for collecting relevant information. The last column provides space for notes. For the baseline form, there are separate spaces for notes taken from the informant and patient interviews.

There is no specified amount of time to complete the baseline form.

Follow-up Visits

Part II is administered at each follow-up visit. At each follow-up visit, the order of interviews should be the same for all participants, with all subjects being interviewed first or, alternatively, all informants being interviewed first.

After completing the interviews, the clinician records the clinical impression of change on a 7-point Likert-type scale (from marked improvement to marked worsening). The ADCS-CGIC is a rating of change and not of severity. The clinician may refer to the baseline data in Part I.

The clinician, alone, must make decisions about change, without consulting other staff. The clinician should avoid asking opinions of the interviewee, which may contaminate the ratings, such as opinions regarding change in symptoms or side effects. At the beginning of the interview, the clinician may wish to caution the informant to refrain from mentioning this information.

The time allotted for the subsequent ratings of change is 20 minutes each per subject or information interview. This time was chosen on the basis of the mean time reported by clinicians who often assess clinical change.

References:

- Ferris SH, Mackell JA, Mohs R, Scheider LS, Galasko D, Whitehouse P, et al. A multicenter evaluation of new treatment efficacy instruments for Alzheimer's disease clinical trials: overview and general results. *Alz Dis Assoc Dis*. 1997;11(Suppl 2):S1-S12.
- Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg, B, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *Alzheimers Dis Assoc Disord* 1997;11 (Suppl 2):S22-S52.

Appendix 6. Neuropsychiatric Inventory-Questionnaire (NPI-Q)

The NPI-Q is designed to be a self-administered questionnaire completed by informants about patients for whom they care. Each of the 12 NPI-Q domains contains a survey question that reflects cardinal symptoms of that domain. 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. Caregiver Distress) using a 5-point scale. The NPI-Q provides symptom Severity and Distress ratings for each symptom reported, and total Severity and Distress scores reflecting the sum of individual domain scores.

Most informants will be able to complete the NPI-Q in 5 minutes or less. It is recommended that responses to the NPI-Q be reviewed for completeness by a clinician and for clarifying uncertainties after each administration. The first time an informant completes the NPI-Q, it may be useful to verbally review the instructions. In some instances, it may be necessary to conduct the NPI-Q in part or entirely as an interview.

Questions

- 1. Delusions:** Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?
- 2. Hallucinations:** Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear things that are not present?
- 3. Agitation/Aggression:** Is the patient resistive to help from others at times, or hard to handle?
- 4. Depression/Dysphoria:** Does the patient seem sad or say that he/she is depressed?
- 5. Anxiety:** Does the patient become upset when separated from you? Does he/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?
- 6. Elation/Euphoria:** Does the patient appear to feel too good or act excessively happy?
- 7. Apathy/Indifference:** Does the patient seem less interested in his/her usual activities or in the activities/plans of others?
- 8. Disinhibition:** Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?

9. Irritability/Lability: Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?

10. Motor Disturbance: Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

11. Nighttime Behaviors: Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?

12. Appetite/Eating: Has the patient lost or gained weight, or had a change in the type of food he/she likes?

Reference:

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci.* 2000 Spring;12(2):233-239.

Appendix 7. Savonix 8 Mobile Application: Overview

Savonix Mobile is a battery of digitized neurocognitive assessments delivered via HIPPA and COPPA compliant Android and iOS mobile operating systems and supported by a web-based client dashboard system for data tracking and analytics.

Savonix Mobile provides a screening tool for markers of multiple domains of cognitive and emotional function that are impaired in a wide range of mental health problems. Savonix Mobile delivers tests that are capable of assessing function in 14 cognitive and emotional domains:

- Verbal Memory (Immediate)
- Verbal Memory (Delayed)
- Impulse Control
- Focus
- Sustained Attention
- Emotion Regulation
- Emotion Recognition
- Information Processing Speed
- Cognitive Flexibility
- Working Memory
- Executive Function
- Visual Spatial Memory
- Decision Making (Risk Taking/Loss Aversion Scale)
- Emotionality (Positivity/Negativity Bias)

Features of Savonix Mobile

Age-Gated and Color-Blind versions

Modified versions of the Savonix Mobile accommodate children and color-blind individuals.

Savonix Mobile Assessment Administration

Within the application, users are presented with a short demographics questionnaire to establish factors such as identity, gender, age and education level to provide normative/percentile scores in the results section. A brief screen is presented that demonstrates how to take the Savonix Mobile assessment and gives the user instructions to follow to begin the assessment. In addition to written instructions, audio instructions are available for the user to toggle on and off.

Users are informed that they may take short breaks between tasks but may not exit the app until the entire assessment is complete.

A practice condition precedes each task to give the user a chance to learn the interface before scoring begins. Before each task, countdown screens are used to prepare the user to begin.

Repeat Assessment

Savonix Mobile uses parallel forms of configurable tasks as a built-in method for controlling for practice effects

across repeat administrations. Pseudorandomization of remaining tasks ensures that the same test is not repeated for the same user.

Savonix Mobile Task	Parallel Forms
Verbal Memory Recognition	3
Go / No-Go Task	Randomized
Verbal Interference	Randomized
N-back Task	Randomized
Emotion Identification	Randomized
Trailmaking Task	6
Maze Task	6
Complex Figure Copy	3
Digit Span	Randomized

Reporting

Scores will be provided directly to the CRO for data analysis via a CSV file that includes each user’s demographic information, performance across domains on each administration of Savonix Mobile, raw trial-by-trial data, as well as descriptive means and variances of response times, correct and incorrect responses, and completion times for applicable tasks. Scores will not be available to subjects or study staff. To support quality data collection, statistics regarding whether tests were completed or not will be provided to study staff on an ongoing basis.

Description of Savonix Mobile Tasks

Verbal Memory Recognition Task

This task measures immediate and delayed verbal learning. Users are presented with a list of words, which they are asked to memorize and later recognize from memory. Words are closely matched on concreteness, length, and frequency of use. After the memorization period, the user is asked to recognize as many words from the list as possible from a series of words, comprised of listed words and foil words. A delayed memory recognition trial is completed approximately 30 minutes later after a number of intervening tasks. The outcome variables are the number of words correctly and incorrectly recognized across the immediate and delayed trials.

Go / No-Go Task

This task measures impulse control. A green circle is presented frequently (Go) and a red square infrequently (No-Go) on the screen. The user is required to inhibit the screen tap responses on the square and tap quickly on the circle when presented. This task measures target detection rate; response time and errors of commission and omission. It is used to assess the capacity for suppressing well-learned, automatic responses. The outcome variables are the number correct and incorrect responses, and response times for correct and incorrect responses.

Verbal Interference Task

This task taps the ability to inhibit automatic and irrelevant responses as a measure of focus. The user is presented with colored words, one at a time. Each word is drawn from the following set of words: red, yellow, green and blue. Below each colored word is a response pad with the four possible colors displayed in black and in fixed format. The test has two parts. In trial 1, the user is required to identify the name of each word as quickly as possible. In trial 2, the user is required to name the color each word is printed in on the screen as quickly as possible. Each part lasts for 1 minute.

Responses are made on the screen by tapping the appropriate color word on the touch screen. The outcome variables are the number of correct responses and response times compared between the two trials.

N-Back Task

This is a measure of sustained attention in a continuous performance task. Users are presented with a sequence of stimuli on the screen and asked to indicate when the current stimulus matches the one from n steps earlier in the sequence. The load factor n can be adjusted to make the task more or less difficult. 1-N means that you have to remember the position of the item, ONE turn back. 2-N means that you have to remember the position of the item TWO turns back, and so on. A 1-back is used in the child's version of the assessment, and a 2-back is used in the adult version. The outcome variables include response times and number correct and in correct.

Emotion Identification Task

This is test of emotional recognition. Users are presented with a series of faces with different emotional expressions (i.e. surprise, fear, disgust, happy, sad, neutral). Users tap a button on the touch screen to correctly match the name of the emotion expressed on the face for each trial in the test. The goal is to identify the correct emotional expression presented by the faces. The outcome variable is the total correct versus incorrect and the response time for each face presented.

Trail Making Task

Part 1 of this task is a measure of visual scanning and information processing speed. The user is presented with a pattern of 13 numbers (1-13) on the screen and is required to touch numbers in ascending sequence (i.e., 1, 2, 3...). As each number is touched in correct order, a line is drawn automatically to connect it to the preceding number or letter in the sequence. This allows the user to visualize the path touched. The outcome variable is time to completion as well as number of correct responses versus incorrect responses.

Part 2 of this task is a measure of cognitive flexibility and attention switching. The user is presented with a pattern of 13 numbers (1-13) and 12 letters (A-L) on the screen and is required to touch numbers and letters alternatively in ascending sequence (i.e. 1, A, 2, B, 3, C...). As each number or letter is touched in correct order, a line is drawn automatically to connect it to the preceding number or letter in the sequence. This allows the user to visualize the path touched. The outcome variable is time to completion as well as number of correct responses versus incorrect responses in comparison with results from Trail Making Part 1.

Maze Task

This task is used as a measure of working memory and executive function. The user is presented with a 6x6 grid of tiles on the device screen. The object of the task is to identify the hidden path through the grid, from the beginning point at the bottom of the grid to the end point at the top. The user is able to navigate around the grid by tapping on individual tiles in the grid. The hidden path must be discovered in order by tapping on consecutive tiles. A total of 15 correct moves are required to complete the maze. The user is presented with a green "check mark" if they make a correct move, red "x" if they make an incorrect move, and a blue "?" if they have tapped out of order. The task serves to assess how quickly the user learns the route through the maze and their ability to remember that route. One maze is presented across two trials to assess for learning between trials. The outcome variable is the total number of correct responses versus errors and time to completion.

Complex Figure Copy Task

This task is a measure of visual spatial memory. Users are required to view and memorize a complex figure made of lines and shapes. Then they are asked to reproduce the figure from memory by drawing lines and dragging shapes on the touchscreen device. Each shape has foils that are similar but not identical to the original shape. Incorrect lines, omitted lines, incorrect shapes, and omitted shapes each count as errors. The outcome variable is accuracy of the reproduced figure against the original figure, as measured by errors versus correct features.

Digit Span Task

This task is used as a measure of attention and working memory. The Forward Digit Span task consists of a number of trials in which a series of digits are presented at a constant rate on the device screen. Immediately after each trial, the user is required to enter the digits on a keypad in the order in which they were flashed. In the Reverse Digit Span task, the user is required to enter the digits in reverse order. Sequence length varies between three and ten, with two trials for each length and with trials presented in ascending sequence order. The task ends when the participant fails 2 trials of any sequence length or when all trials are completed. The outcome variables are the longest sequence lengths correctly completed forwards and backwards.

Additional Reading

Clark CR, Paul RH, Williams LM, Arns M, Fallahpour K, Handmer C, et al. Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Arch Clin Neuropsychology*. 2006;21:449-467.

Mathersul D, Palmer D, Gur R, Gur R, Cooper N, Gordon E, et al. Explicit identification and implicit recognition of facial emotions: II. Core domains and relationships with general cognition. *J Clin Exp Neuropsych*. 2009;31(3):278-291.

Paul RH, Haque O, Gunstad J, Tate DF, Grieve SM, Hoth K, et al. Subcortical hyperintensities impact cognitive function among a select subset of healthy elderly. *Arch Clin Neuropsych*. 2005;20(6): 697-704.

Paul RH, Gunstad J, Cooper N, Williams LM, Clark R, Cohen RA, Lawrence JJ, et al. Cross-cultural assessment of neuropsychological performance and electrical brain function measures: additional validation of an International brain database. *Int J Neurosci*. 2007;117:549-568.

Rowe DL, Cooper NJ, Liddell BJ, Clark RC, Gordon E, Williams LM. Brain structure and function correlates of General and Social Cognition. *J Integ Neurosci*. 2007;6(1):35-74.

Williams L, Mathersul D, Palmer D, Gur R, Gur R, Gordon E. Explicit identification and implicit recognition of facial emotions: I. Age effects in males and females across 10 decades. *J Clin Exp Neuropsych*. 2009;31:257-277.

Appendix 8. Columbia Suicide Severity Rating Scale (C-SSRS)

SUICIDAL IDEATION		Lifetime: Time He/She Felt Most Suicidal
<i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>		
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
INTENSITY OF IDEATION		
<i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>		Most Severe
Most Severe Ideation: _____		
<i>Type # (1-5)</i>	<i>Description of Ideation</i>	
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts		_____
Deterrants <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrants definitely stopped you from attempting suicide (4) Deterrants most likely did not stop you (2) Deterrants probably stopped you (5) Deterrants definitely did not stop you (3) Uncertain that deterrants stopped you (0) Does not apply		_____
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (0) Does not apply		_____

<p>SUICIDAL BEHAVIOR <i>(Check all that apply, so long as these are separate events; must ask about all types)</i></p>				<p>Lifetime</p>		
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>				<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>		
<p>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p>				<p><input type="checkbox"/> <input type="checkbox"/></p>		
<p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>				<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>		
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>				<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>		
<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>				<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>		
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period?</p>				<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>		
<p>Answer for Actual Attempts Only</p>				<p>Most Recent Attempt Date:</p>	<p>Most Lethal Attempt Date:</p>	<p>Initial/First Attempt Date:</p>
<p>Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>				<p>Enter Code _____</p>	<p>Enter Code _____</p>	<p>Enter Code _____</p>
<p>Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>				<p>Enter Code _____</p>	<p>Enter Code _____</p>	<p>Enter Code _____</p>

17 SCHEDULE OF EVENTS

Visit	Screening/ Baseline Visit ^a		Treatment ^b					Follow-up			Treatment ^b					Follow-up			End of Study/Early Termination Visit ^a
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Infusion Number			1	2	3	4	5				6	7	8	9	10				
Day	Day -28 to -8	Day -7 to -1	1	2	3	4	5	6	28 ± 7 days	56 ± 7 days	85 ± 7 days	86	87	88	89	90	112 ± 7 days	140 ± 7 days	168 ± 7 days
Week			1					4	8		13					16	20	24	
Informed Consent/Optional Biomarkers Consent	X																		
Medical History	X																		
Demographics	X																		
12-lead ECG	X						X ²			X ¹				X ²					
Physical Exam/Height/Weight	X																		X
GRF6019 Infusion			X	X	X	X	X			X	X	X	X	X					
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam/Weight			X ¹	X ¹	X ¹	X ¹	X ¹	X		X ¹	X ¹	X ¹	X ¹	X ¹	X				
Concomitant Medication ^a	X	X	X ¹	X ¹	X ¹	X ¹	X ¹	X	X	X	X ¹	X ¹	X ¹	X ¹	X ¹	X	X	X	X
Adverse Event Review ^a		X	X ¹	X ¹	X ¹	X ¹	X ¹	X	X	X	X ¹	X ¹	X ¹	X ¹	X ¹	X	X	X	X
Labs																			
Screening panel ^c	X																		
Exit Panel ^d																			X
Stat labs (performed onsite) ^e			X ¹	X ¹	X ¹	X ¹	X ¹	X ¹		X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹			
Comprehensive Labs ^f			X ¹		X ¹			X		X		X ¹	X ¹		X			X	
Interim Safety Labs ^g									X								X		
Samples for proteomics/epigenetics/biobanking		X	X ¹					X	X	X	X ¹				X	X	X	X	X
ApoE Genotype testing		X																	
Imaging/Lumbar Puncture for CSF Biomarkers																			
Transthoracic echocardiogram	X*																		
MRI Testing	X*						X ^h												X
PET Scan (optional)	X*																		
Lumbar Puncture/CSF Fluid Collection (optional) ⁱ		X													X ²				
Cognitive Testing																			
MHIS	X																		
C-SSRS	X							X							X				
MMSE	X							X							X				X
Savonix Full Battery (Savonix-8 + Digit Span)		X						X	X	X					X	X	X	X	X
Savonix Brief Battery			X ¹	X ¹	X ¹	X ¹	X ¹				X ¹	X ¹	X ¹	X ¹	X ¹				
ADAS-Cog/11		X						X	X		X ¹				X	X			X
Grooved Pegboard		X							X						X				X
CFT		X							X						X				X
CDR-SOB (subject and trial partner)		X							X						X				X
ADCS-ADL (trial partner)		X							X	X					X	X			X
ADCS-CGIC (subject and trial partner)		X							X						X				X
NPI-Q (trial partner, self-administered)		X							X	X					X	X			X

Notes:	<p>*To be performed during screening period after all other criteria have been met. Transthoracic echocardiogram and MRI may be performed in either order, but prior to the optional PET Scan. The optional PET Scan should only be performed after all screening procedures have been completed, and the subject meets criteria for inclusion.</p> <p>X¹: to be performed prior to infusion start.</p> <p>X²: to be performed after infusion.</p> <p>a: Screening, Baseline, and EOS/ET visits may be split to allow for sufficient time to complete all procedures. AEs and concomitant medications should be reviewed during split visits, as applicable.</p> <p>b: The treatment window is 5 + 1 days. If study treatment is administered over a period of 6 days, then Visits 8 and/or 16 may occur 1 day later. The visit window for Visit 11 is Day 85 ± 7 days; visits 12-16 should follow consecutively.</p> <p>c: includes all comprehensive labs^f, infectious serology (HIV, hepatitis B, hepatitis C), cobalamin (vitamin B12) level, pyridoxine (vitamin B6) level, thiamine (vitamin B1) level, thyroid-stimulating hormone (TSH) level, direct antiglobulin test, RBC antibody screen, brain natriuretic peptide (BNP), serum IgA, haptoglobin, and C1 inhibitor. Urine drug screen: cannabinoids, benzodiazepine, barbiturates, opiates, cocaine, amphetamines, methadone, phencyclidine. Urinalysis: urine protein, UPCR.</p> <p>d: includes all comprehensive labs^f, infectious serology, direct antiglobulin test, RBC antibody screen.</p> <p>e: Samples for i-STAT labs should be collected and results interpreted PRIOR to infusion start. Using i-STAT Chem-8+ cartridge: sodium (Na), potassium (K), chloride (Cl), total carbon dioxide (TCO₂), anion gap, ionized calcium, glucose, urea nitrogen (BUN)/urea, creatinine (Crea), hematocrit, hemoglobin.</p> <p>f: comprehensive labs: alkaline phosphatase (ALP), ALT (SGPT), amylase, AST (SGOT), bicarbonate, bilirubin (direct, indirect, and total), ionized calcium, chloride, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine kinase (CK or CPK), creatinine, gamma-GT (GGT), glucose (random), iron, lactate dehydrogenase (LDH or LD), lipase, magnesium, phosphate, potassium, protein total, sodium, triglycerides, blood urea nitrogen (BUN), eGFR, albumin, aPTT, PT, INR, complete blood count (CBC) with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils). Urinalysis: blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, urobilinogen, urine creatinine, urine albumin, albumin/creatinine ratio, urine sodium, sodium/creatinine ratio, urine potassium, potassium/creatinine ratio, and reflex urine microscopy if indicated.</p> <p>g: interim safety labs: blood creatinine, BUN, eGFR. Note: Subjects randomized prior to August 30, 2018, will not participate in the additional interim safety labs at Visit 9 and Visit 17.</p> <p>h: Window for completing the MRI is Visit 8 + 4 days.</p> <p>i: In consenting, eligible subjects, the optional lumbar puncture should be performed at any time during the Baseline Visit window. The second (final) lumbar puncture should be performed within 5 days following the final dose.</p>
--------	---

18 REVISION HISTORY

**Protocol Version 7.0 dated 02NOV2018
Replaces: Protocol Version 6.0 dated 12OCT2018**

In this table, changes from Version 6.0 dated 12OCT2018 are described and their rationale is given.

Location	Description	Purpose
Throughout	<i>Protocol Version previously read:</i> v6.0_12OCTMAR2018 <i>Now reads:</i> v7.0_02NOV2018	Version control.
[REDACTED]	[REDACTED]	[REDACTED]
Throughout	Grammar and style changes	For protocol clarity and standardization.
List of Definitions, Protocol Summary	The Infusion Period will be now be between 2 hours to a maximum of 3 hours.	The Infusion Period was previously increased to from 2.0 to 2.5 hours to 2.5 to 3 hours; to maintain blinding and continuity, all patients will now be infused between 2 hours to a maximum of 3 hours.
Protocol Summary, 4.1 Description of the Study Design	Extension of study duration to ~19 months was reverted to ~15 months and recruitment period of ~12 months was reverted to ~8 months.	Study duration and recruitment period were decreased as additional subjects will not be needed [REDACTED]
2.2 Rationale	Text content and Table 1 changed to reflect revised dosing.	Required changes [REDACTED]
7.3.3 Randomization, 10.5 Sample Size	The following sentence was added to both sections, "Subjects who are randomized but do not receive any dose of the study agent, may be re-screened and randomized if they meet all of the study eligibility requirements."	Content added to clarify potential re-screening for eligible subjects.
17 Schedule of Events	Note "c": removed propoxyphene from urine drug screen.	Screening for this substance is not required.

Protocol Version 6.0 dated 12OCT2018
Replaces: Protocol Version 5.0 dated 30AUG2018

In this table, changes from Version 5.0 dated 30AUG2018 are described and their rationale is given.

Location	Description	Purpose
7.3 Study Schedule / 17 Schedule of Events	<ul style="list-style-type: none"> Amended the Study Schedule and Schedule of Events to include i-STAT labs on V4, V6, V8, V12, V14, and V16. Amended the Study Schedule and Schedule of Events to include the following per Clarification Memo #4: “Note: subjects randomized prior to August 30, 2018, will not participate in the additional interim safety labs at Visit 9 and Visit 17.” 	<ul style="list-style-type: none"> Added i-STAT lab evaluations for increased safety monitoring after FDA request. Per Protocol V5.0 (30AUG2018), blood samples are to be collected at Visit 9 and Visit 17 for interim safety labs. However, subjects who were randomized prior to August 30, 2018, will not participate in the additional interim safety labs at Visit 9 and Visit 17 since they will be following the previous protocol version.

Protocol Version 5.0 dated 30AUG2018
Replaces: Protocol Version 4.0 dated 27MAR2018

In this table, changes from Version 4.0 dated 27MAR2018 are described and their rationale is given.

Location	Description	Purpose
Title Page, Protocol Approval Page, 1.1 Authorized Representative (Signatory) / Responsible Party	Updated Sponsor’s mailing address and authorized representative.	Administrative.
Throughout	<p><i>Protocol Version Previously read:</i> v4.0_27MAR2018</p> <p><i>Now reads:</i> v5.0 30AUG2018</p>	Version control.
[REDACTED]	[REDACTED]	[REDACTED]

Location	Description	Purpose
List of Definitions / Protocol Summary	Extended the Infusion Period to be a maximum of 3 hours.	Infusion rates will be adjusted such that the Infusion Period will be of approximately the same duration for all doses (e.g., 100 mL, 250 mL, [REDACTED]).
Protocol Summary, 4.2.2 Secondary Endpoints, 7.1.1.2 Procedures to Assess Safety	Moved the following from list of exploratory endpoints to secondary safety endpoints: “Changes on MRI scans designed to assess for Amyloid Related Imaging Abnormalities (ARIA)” and updated other sections of the Protocol accordingly.	Evaluating changes on MRI scans to assess for ARIA is a secondary safety endpoint.
Protocol Summary, 4.1 Description of the Study Design	Extended study duration to ~19 months.	To account for extended recruitment period to enroll an additional 20 subjects.
2.2 Rationale	Incorporated isometric scaling as rationale for human dosage levels.	Isometric scaling may be the most likely to accurately estimate the human potential effective dose.
4.1 Description of the Study Design, 5.4.2 Handling of Participant Withdrawals or Termination, 7.3.7 Early Termination	Updated language to clarify that subjects who have received at least one dose of GRF6019 but withdraw/terminate from the study early may be invited to complete the end of study procedures.	To clarify that end of study procedures do not need to be completed for subjects who terminate from the study prior to initial dosing (e.g. Visit 3).
5.1 Inclusion Criteria, 7.1.1.1.11 Echocardiogram	Removed the upper limit for systolic ejection fraction. Subjects will be eligible for inclusion if they have a systolic ejection fraction that is greater than or equal to 55% and no other clinically significant abnormalities are noted.	Unless there is evidence of cardiac pathology on echocardiography, an elevated ejection fraction is not a safety concern. Echocardiography will be used at screening to exclude subjects with an ejection fraction of less than 55% and subjects with other echocardiographic abnormalities, including impaired diastolic function (e.g. impaired diastolic relaxation) or hypertrophic cardiomyopathy.
5.2 Exclusion Criteria	<p>Previously read:</p> <ul style="list-style-type: none"> Heart disease (or history thereof), as evidenced by myocardial infarction, unstable, new onset or severe angina, or congestive heart failure (New York Association Class II, III or IV) in the 6 months prior to dosing; uncontrolled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite treatment during the 3 months prior to 	<p>Protocol clarity and standardization.</p> <p>Addition of exclusion criterion for subjects with treatment-refractory hypertension because such subjects may be more likely to experience a hypertension during GRF6019 infusions.</p>

Location	Description	Purpose
	<p>dosing.</p> <p>Now reads:</p> <ul style="list-style-type: none"> Heart disease, including myocardial infarction, unstable, new onset or severe angina, or congestive heart failure (New York Association Class II, III or IV) in the 6 months prior to dosing; Poorly controlled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite treatment during the 3 months prior to dosing, or <u>treatment refractory high blood pressure, defined as treatment requiring 3 or more antihypertensives from different classes.</u> 	
5.2 Exclusion Criteria, 7.5 Prohibited Medications, Treatments, and Procedures	Removed typical and atypical antipsychotics from the list of prohibited medications.	Determined that typical and atypical antipsychotics would not have a significant impact on cognition, therefore concurrent use is allowed.
5.2 Exclusion Criteria	<p>Previously read: Any major psychiatric disorder including psychosis, claustrophobia, major depression or bipolar disorder, and/or alcohol/substance dependency.</p> <p>Now reads: <u>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.</u></p>	Protocol clarity and standardization.
5.4.1 Reasons for Withdrawal or Termination	Removed the following bullet point: “Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.”	Treatment with a prohibited concomitant medication will be considered on a case-by-case basis as a reason for withdrawal or termination, but not result in automatic subject withdrawal.
5.4.1 Reasons for Withdrawal or Termination	Removed “or change in trial partner” to reflect Protocol Clarification Memo #3.	Protocol clarity and standardization.
5.5 Premature Termination or	Amended to state that the Sponsor reserves the right to terminate the study at any time and	To clarify that the Sponsor, not the investigator, may terminate the study;

Location	Description	Purpose
Suspension of Study	included minor updates to the list of potential reasons for study or site termination.	investigators may terminate the study at their site at any time.
7.1.1.1 Screening Procedures, 17 Schedule of Events	Modified to reflect that the echocardiogram and MRI performed at screening may be completed in either order after all other screening procedures have been completed.	To enhance feasibility, as the sequence of these procedures is inconsequential.
7.1.1.2.1 Review of Adverse Events	Previously read: AEs will be reviewed, documented, and reported as required at each visit, beginning at baseline. Now reads: AEs will be reviewed, documented, and reported as required at each visit.	Modified to reflect that AEs and concomitant medications may need to be assessed during split screening visits, as applicable.
3 Objectives and Purpose, 7.1.1.1.13 Magnetic Resonance Imaging, 7.2.2.3 Magnetic Resonance Imaging	Amended to reflect Protocol Clarification Memos #1 and #2.	Protocol clarity and standardization.
7.3 Study Schedule	Previously read: Visit windows (when noted) should be benchmarked relative to the baseline visit for a subject, such that subjects complete the entire study by Day 168 (± 7 days). Now reads: Visit windows (when noted) should be benchmarked relative to <u>Visit 3</u> for a subject, such that subjects complete the entire study by Day 168 (± 7 days).	Protocol clarity; Visit 3 corresponds to Day 1.
7.3.1 Screening, 17 Schedule of Events	Clarified that AEs and concomitant medications should be collected during split visits, as applicable.	Protocol clarity and standardization.
7.3.4. Treatment, 17 Schedule of Events	Added a ± 7 -day window for Visit 85.	To enhance protocol feasibility.
7.3.4. Treatment, 7.3.5 Follow-Up, 17 Schedule of Events	Modified the schedule for collecting STAT safety laboratory samples.	Based on data from 24 subjects dosed, no clinically significant changes in Na, K, Ca, creatinine, or hematocrit have been detected during the dosing period. Therefore, the frequency of pre-infusion i-STAT lab monitoring has been reduced to every other day during each dosing period.
7.3.5 Follow-Up, 17 Schedule of Events	Added interim safety labs (blood creatinine, blood urea nitrogen, and glomerular filtration rate) at Visits 9 and 17.	To more precisely evaluate potential changes in creatinine levels kidney function over time.
8 Assessment of Safety	Amended the Safety Section to clarify reporting	For protocol clarity and standardization.

Location	Description	Purpose
	requirements for SAEs, AESI, and pregnancy.	
8.2.2 Relationship to Study Agent	<p>Previously read: Final assessment of causality will be made by the Sponsor.</p> <p>Now reads: If either the investigator or the Sponsor considers the event related, then the event will be considered related for reporting purposes.</p>	Sponsor decided to use a more conservative approach to causality determination.
8.4.3 Adverse Events of Special Interest	<p>Previously read:</p> <ul style="list-style-type: none"> • AEs related to increased blood volume or shifts of fluid between the intravascular and extravascular space • Suspected transmission of blood-borne infectious agents <p>Now reads:</p> <ul style="list-style-type: none"> • <u>Clinically-significant peripheral edema or pulmonary edema.</u> • <u>Systolic blood pressure (BP) <90 or >160 mm Hg and/or diastolic BP <60 or >100 mm Hg, or a change of >25% from Day 1 (Visit 3) pre-infusion in systolic and/or diastolic BP.</u> • <u>Reduced kidney function (eGFR < 45 mL/min/1.73 m²).</u> • Suspected transmission of blood-borne infectious agents. 	Protocol clarity and standardization.
8.5 Study Halting Rules	Modified to state that if a Safety Evaluation Meeting is triggered, dosing may be temporarily halted.	Depending on the reason for the Safety Evaluation Meeting, dosing may or may not need to be halted.
9 Clinical Monitoring	Minor updates and clarifications.	To align with study plans and processes.
10.4.5 Adherence and Retention Analyses	Removed the “overall trial partner survey” as a measure of feasibility.	Currently, there is no plan to administer an overall trial partner survey as an assessment of feasibility.
12.3.1 Consent/Assent and Other Informational Documents Provided to Participants	Removed CSF Consent Form (optional).	A separate ICF has not been utilized. Rather, the main ICF includes a description of the optional CSF collection procedure and a separate signature line for subjects/LARs to provide informed consent for the optional procedure.
13.3 Protocol Deviations	Amended the definitions of Major and Minor Protocol Deviations.	Modified to align with Sponsor’s definitions.
15 Literature References	Updated the following references to most recent versions: Alzheimer’s Association 2018, [REDACTED]	Administrative.

Location	Description	Purpose
	[REDACTED]	

Protocol Version 4.0 dated 27MAR2018
Replaces: Protocol Version 3.1 dated 21FEB2018

In this table, changes from Version 3.1 dated 21FEB2018 are described and their rationale is given.

Location	Description	Purpose
7.2.3 Specimen Preparation, Handling, Storage, and Shipping	Removed reference to laboratory manual addendum.	Standard and specialty lab specimen preparation, handling, storage, and shipping procedures are described in the body of the laboratory manual.
7.3 Study Schedule / 17 Schedule of Events	Amended the Study Schedule such that STAT labs will only be performed on V3-6, V8, V11-14, and V16.	Removed the STAT labs on V7/V15 to reduce subject burden without compromising safety.
Throughout	Clarified that the optional CSF collection will only be performed at participating sites.	For protocol clarity, as not all sites will perform this optional procedure.
Throughout	Changed all references to the GRF6019 Infusion Administration Guidelines to reflect the actual document title: Infusion Administration Manual.	For protocol clarity.
Throughout	<i>Protocol Version Previously read:</i> v3.1_21FEB2018 <i>Now reads:</i> v4.0_27MAR2018	Version control.

Protocol Version 3.1 dated 21FEB2018
Replaces: Protocol Version 3.0 dated 16FEB2018

In this table, changes from Version 3.0 dated 16FEB2018 are described and their rationale is given.

Location	Description	Purpose
5.2 Exclusion Criteria	<i>Previously read:</i> Clinically significant abnormalities on screening electrocardiogram (ECG) including QTc intervals (using Fridericia’s correction formula) of \geq	Modified to be less restrictive.

Location	Description	Purpose
	430 ms in men and \geq 450 ms in women. <i>Now reads:</i> Clinically significant abnormalities on screening electrocardiogram (ECG) including QTc intervals (using Fridericia’s correction formula) of \geq 450 ms in men and \geq 470 ms in women.	
7.3 Study Schedule / 17 Schedule of Events	Extended the visit window for Visit 8 MRI, such that the MRI may be performed at Day 6 + 4 days.	To enhance protocol feasibility.
Throughout	<i>Protocol Version Previously read:</i> v3.0_16FEB2018 <i>Now reads:</i> v3.1_21FEB2018	Version control.

Protocol Version 3.0 dated 16FEB2018
Replaces: Protocol Version 2.0 dated 09NOV2017

In this table, changes from Version 2.0 dated 09NOV2017 are described and their rationale is given.

Location	Description	Purpose
List of Definitions	Specified that the Outcomes Assessor is responsible for monitoring subjects before, during, and after the infusion period.	For protocol clarity and standardization.
5.1 Inclusion Criteria	<i>Previously read:</i> Willing to spend up to 6 nights in an inpatient study observation unit during both dosing periods. <i>Now reads:</i> Willing to spend up to 7 nights in an inpatient study observation unit during both dosing periods.	To account for new treatment visit window.
5.2 Exclusion Criteria	Added exclusion criteria pertaining to the C-SSRS administered at screening.	Subjects reporting active suicidal ideation with at least some intent to act in the past 6 months will be excluded from the trial for safety reasons.
5.2 Exclusion Criteria	<i>Previously read:</i> Prior hypersensitivity reaction to any human blood product or intravenous infusion; any known drug allergy. <i>Now reads:</i> Prior hypersensitivity reaction to any human blood product or intravenous infusion; any known clinically significant drug allergy.	Modified to be less restrictive, such that subjects with drug allergies deemed not clinically significant who meet all other eligibility criteria may be enrolled.
7.3.3	Added section to the Study Schedule so that	To allow sites flexibility as to when

Randomization	randomization may occur any time after confirmation of eligibility (following Baseline) but prior to the subject’s first infusion on Visit 3. Included a recommendation to randomize subjects at the start of Visit 3, as this may reduce the risk of randomizing a subject to treatment who discontinues/withdraws prior to Visit 3.	randomization occurs.
7 Study Procedures and Schedule / 17 Schedule of Events	UPCR to be performed at screening ONLY. Added the following urine tests as part of comprehensive labs: albumin/creatinine, sodium/creatinine, and potassium/creatinine. Removed stat urinalysis and amended the tests performed as part of the urinalysis for comprehensive labs.	Added additional testing for safety. Determined that stat urinalysis would not be necessary for guiding dosing decisions.
7 Study Procedures and Schedule / 17 Schedule of Events	Added a targeted physical exam prior to dosing on Visits 3-7 and 11-15; and prior to discharge on V8 and V16.	To assess for safety.
7 Study Procedures and Schedule / 17 Schedule of Events	Fasting lab samples are preferred for all visits except screening; amended the order of procedures on applicable visits accordingly.	Fasting samples are preferable for proteomics.
7 Study Procedures and Schedule / 17 Schedule of Events	Added ECGs to V7 (after dosing), V11 (prior to dosing), and V15 (after dosing).	To assess for safety.
7 Study Procedures and Schedule / 17 Schedule of Events	Added weight measurements prior to dosing on Visits 3-7 and 11-15; and prior to discharge on V8 and V16.	To assess for fluid retention during dosing based on changes in weight.
7.3 Study Schedule / 17 Schedule of Events	Removed NPI-Q from Visits 8 and 16.	Do not expect the NPI-Q to provide relevant data immediately post-inpatient.
7 Study Procedures and Schedule	Where applicable, added a note indicating that the NPI-Q may be completed by the trial partner at any available time during applicable visits.	To enhance protocol feasibility.
7.3 Study Schedule / 17 Schedule of Events	Added ADCS-ADL to Visits 9 and 17.	To assess activities of daily living at additional timepoints.
7.3 Study	Added visit window for Visit 8 MRI, such that the	To enhance protocol feasibility.

Schedule / 17 Schedule of Events	MRI may be performed at Day 6 + 2 days.	
8.5 Study Halting Rules	Clarified that the Sponsor is responsible for deciding whether to halt the study.	Protocol clarity and standardization.
10.6 Measures to Minimize Bias	[REDACTED]	[REDACTED]
13.3 Protocol Deviations	Previously, protocol noncompliance was categorized as either a violation or deviation. Now, Protocol Deviations will be categorized as either Major or Minor.	Protocol clarity and standardization.
15 Literature References	Added reference for MDRD for Adults (Conventional Units) calculator.	To provide a resource for calculating MDRD.
16 Appendices	Added a preface to the Appendices that reads: Please be advised that the neurocognitive assessments in this section and associated information are provided as EXAMPLES ONLY . The actual neurocognitive assessments, related source documents, and instructions for administration and scoring are included in the Rater Reference Manual .	To clarify that the Appendices should not be the primary source of reference for performing the neurocognitive assessments. Rather, all essential documents, materials, and instructions are provided in the Rater Reference Manual which is maintained separately from the protocol.
Throughout	Previously, subjects would receive the infusion at a standardized flow rate. As a result, the interval for administering 100 mL was shorter than the interval for administering the 250 mL dose. To maintain blinding, all subjects would remain connected to the IV apparatus for a set period of time. The Infusion Period has been modified so that all subjects, regardless of dose level, will receive their assigned dose over the course of 2 – 2.5 hours to maintain blinding. Flow rates will be titrated according to the GRF6019 Infusion Administration Guidelines. Masking procedures have been updated accordingly.	It was determined that subjects would likely be able to tell when their infusion had stopped. Thus, the infusion administration and masking procedures were revised to maintain blinding.
Throughout	Modified applicable sections of the protocol to reflect the updated schedule for administering the C-SSRS.	The C-SSRS will be administered at screening to evaluate subject eligibility. The C-SSRS will be repeated following each dosing interval but prior to discharge to evaluate for safety.
Throughout	Clarified testing schedules for the Savonix full and brief batteries. Updated Schedule of Events accordingly.	The brief battery will be performed at the start of the infusion visits. The full battery will be performed at all other visits, beginning at Baseline.

Throughout	Added Cerebrospinal Fluid (CSF) biomarker analysis as an exploratory aim. Added CSF collection as an optional procedure. Amended applicable sections of the Protocol accordingly.	To assess potential therapeutic effects of GRF6019 on AD biomarkers of neuronal death, synaptic function, inflammation, and growth factors.
Throughout	<i>Protocol Version Previously read:</i> v2.0_09NOV2017 <i>Now reads:</i> v3.0 16FEB2018	Version Control.
Throughout	Grammar and style changes	For protocol clarity and standardization.

Protocol Version 2.0 dated 09NOV2017

Replaces: Protocol Version 1.0 dated 02AUG2017

In this table, changes from Version 1.0 dated 02AUG2017 are described and their rationale is given.

Location	Description	Purpose
Throughout	<i>Protocol Title Previously read:</i> An Open Label, Multiple-Dose Study to Assess the Safety and Tolerability of GRF6019 Infusions in Subjects with Mild to Moderate Alzheimer’s Disease (AD) <i>Now reads:</i> 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 (AD)	Updated study design pursuant to direction from the agency
Throughout	Update of study design description from an open label multiple dose study to a prospective, randomized, double-blind dose comparison concurrent control study	Updated study design pursuant to direction from the agency
Throughout	<i>Protocol Version Previously read:</i> v1.0_02AUG2017 <i>Now reads:</i> v2.0_09NOV2017	Version Control
Throughout	Grammar and style changes	For protocol clarity and standardization
Throughout	Update duration of treatment to be <u>approximately</u> 6 months, and total duration in the study to be <u>approximately</u> 7 months.	Improved protocol clarity
Page 8	Measures added to ensure adequate allocation concealment. Added List of Definitions for Infusion Nurse, Infusion Period and Outcomes Assessor	For clarity of updated study design pursuant to direction from the agency

Location	Description	Purpose
Protocol Summary/Precis	Measures added to ensure adequate allocation concealment. Paragraph 3 added to summarize the infusion process and methods for blinding during infusion.	Updated study design pursuant to direction from the agency
2.2 Rationale, Paragraph 8	<p>Previously read: <u>An open-label, two-arm study design</u> has been selected to identify a safe and feasible dosing paradigm, trends in changes of neurocognitive endpoints, and potential plasma derived factors that may affect these parameters.</p> <p>Now reads: <u>A prospective, randomized, double-blind, dose-comparison concurrent control study design</u> has been selected to <u>reduce or eliminate bias while facilitating the identification of</u> a safe and feasible dosing paradigm, trends in changes of neurocognitive endpoints, and potential plasma derived factors that may affect these parameters.</p>	Updated study design pursuant to direction from the agency
2.2 Rationale, Paragraph 9	<p>Previously read: ... the results (of this trial) are nevertheless expected to lay the foundation for larger trials <u>exploring</u> the potential benefit of GRF6019 in AD and other neurodegenerative disorders typified by cognitive dysfunction.</p> <p>Now reads: ... the results (of this trial) are nevertheless expected to lay the foundation for larger trials <u>designed and powered to characterize</u> the potential benefits of GRF6019 in AD and other neurodegenerative disorders typified by cognitive dysfunction.</p>	Clarification of purpose of study design pursuant to direction of the agency
3. Objectives and Purpose	<p>Previously read: As an exploratory objective, <u>serial compositional analysis of subject plasma will be performed</u> to identify specific biomarkers...</p> <p>Now reads: As an exploratory objective, <u>blood and plasma will be collected and analyzed</u> to identify specific biomarkers...</p>	Improved protocol clarity
4.2.2 Secondary Endpoints, Paragraph 1	Confirmation that “This study is neither designed nor powered to detect <u>statistically significant differences</u> in cognitive and motor outcomes...”	Clarification of purpose of study design pursuant to direction of the agency
4.2.2 Secondary Endpoints	Addition of secondary feasibility endpoint related to success of blinding	Updated study design pursuant to direction from the agency
4.2.3 Exploratory Endpoints	Previously read: <u>Cellular samples will be recovered from subject’s plasma</u> to explore epigenetic changes.	Improved protocol clarity

Location	Description	Purpose
	<p>Now reads: DNA will be extracted from blood samples to explore epigenetic changes.</p>	
5.3 Strategies for Recruitment and Retention, Paragraph 4	<p>Clarification that if a trial partner <u>does not reside within a reasonable distance from the inpatient facility</u>, they will be given the option to stay with the subjects or to stay in a nearby hotel/motel.</p>	Improved protocol clarity
5.4.2 Handling of Participant Withdrawals or Termination	<p>Addition that subjects who <u>discontinue or are unblinded</u> prior to Visit 8 may be replaced.</p>	Updated study design pursuant to direction from the agency
6.1.3 Product Storage and Stability	<p>Previously read: Partially used vials must be discarded. Vials which are cracked or have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms.</p> <p>Now reads: Vials which are cracked or have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms.</p>	Correction to enable drug accountability
6.1.4 Preparation	<p>Added: IV tubing should be vented. [REDACTED]</p>	Clarification
6.1.5 Dosing Administration	<p>Measures added to ensure adequate allocation concealment. Section updated to include provisions for the management and maintenance of study blinding during dosing, including the use of unblinded Infusion Nurses and blinded Outcomes Assessors.</p> <p>Administration Guidelines changed from Appendix 9 to a stand-alone manual.</p>	Updated study design pursuant to direction from the agency
6.2 Study Agent Accountability	<p>Measures added to ensure adequate allocation concealment. Addition and explanation of the role of unblinded study staff (study pharmacist, Infusion Nurse, CRA) in accountability of the study agent.</p>	Updated study design pursuant to direction from the agency
7.1.1.2.3 Vital Signs	<p>Previously read: Vital signs will be collected at every visit and at multiple time points during the infusion (Appendix 9).</p> <p>Now reads: Vital Signs will be collected at every visit. During infusions, vital signs will be collected within an hour of infusion start, every 15 minutes during the ~2.5 hour infusion period, and at 3 and 6 hours following conclusion of the infusion period.</p>	Updated for clarity of study procedures. Updated for study design pursuant to direction from the agency

Location	Description	Purpose
	Vital signs will be collected by the blinded Outcomes Assessor.	
7.1.1.3.1 Savonix Neurocognitive Assessments	Clarification that administration of the test should begin <u>no later than one hour after starting the infusion.</u>	Improved protocol clarity
7.2.2.2 PET; 7.3.1 Screening, Visit 1	Section updated to remove use of specific radioligand (Florbetapir) for PET testing. Any radioligand will be accepted for this optional procedure.	Parameters eased for this non-critical test
7.2.2.4 Proteomic and Genetic Biobanking, Paragraph 1	<i>Previously read:</i> <u>Plasma and cellular samples</u> will be collected... <i>Now reads:</i> <u>Blood and plasma</u> will be collected...	Improved protocol clarity
7.2.2.4 Proteomic and Genetic Biobanking, Paragraph 2	<i>Previously read:</i> <u>Cellular samples derived from plasma</u> will be retained... <i>Now reads:</i> <u>Blood samples</u> will be retained...	Improved protocol clarity
7.2.2.4 Proteomic and Genetic Biobanking, Paragraph 2	<i>Added:</i> For information regarding future use of stored samples, see Section 12.5 Future Use of Stored Specimens.	Updated pursuant to direction from the agency
8. Assessment of Safety	<i>Added:</i> <u>Assessment of safety will be conducted by blinded study personnel except in extraordinary circumstances where knowledge of the dose received by a subject is essential. Any instances of unblinding will be managed as indicated in Section 10.6.3.</u>	Updated study design pursuant to direction from the agency
8.4.3 Adverse Events of Special Interest	<i>Previously read:</i> <ul style="list-style-type: none"> Adverse Events related to increased blood volume <i>Now reads:</i> <u>The following will be considered adverse events of special interest:</u> <ul style="list-style-type: none"> <u>AEs related to increased blood volume or shifts of fluid between the intravascular and extravascular space</u> <u>Suspected transmission of blood-borne infectious agents</u> 	Expanded AESI
8.5 Study Halting Rules, Safety Eval. Meeting	Amended outcomes from Safety Evaluation Meeting to align with blinded study design. Measures added to ensure adequate allocation concealment.	Updated study design pursuant to direction from the agency
8.6 Safety Oversight	Updated Safety Oversight section and role of Safety Evaluation Meetings for blinded study design	Updated study design pursuant to direction from the

Location	Description	Purpose
		agency
10.1 Statistical and Analytical Plans	Added: The finalization of the SAP will occur prior to clinical database lock <u>and unblinding of the study data.</u>	Updated study design pursuant to direction from the agency
10.2 Statistical Hypothesis	Within-subject changes from baseline for each dosing group and among-group differences will (changed from “may”) be evaluated.	Updated study design pursuant to direction from the agency
10.4.1 General Approach	Further details on the analysis of the primary and secondary endpoints have been clarified. Increased robustness of general statistical approach regarding primary and secondary analysis of endpoints that are continuous as well as categorical. Update to include subjects randomized as part of the disposition summary.	Updated study design pursuant to direction from the agency
10.4.3 Analysis of Secondary Endpoint(s)	Previously read: Among-group differences may be assessed by One-way Analysis of <u>Variance</u> or its nonparametric equivalent <u>Kruskal-Wallis</u> test. Now reads: Among-group differences may be assessed by One-way Analysis of <u>Covariance (ANCOVA)</u> or its nonparametric equivalent test.	Improved protocol clarity
10.4.7 Planned Interim Analyses	Added: <u>If such an ad hoc safety interim analysis is conducted, the treatment assignment will remain masked.</u>	Updated study design pursuant to direction from the agency
10.5 Sample Size	Updated to reflect target of 40 subjects <u>randomized</u> (vs. enrolled)	Updated study design pursuant to direction from the agency
10.6.1 Enrollment/ Randomization/ Masking Procedures	Section updated to address design deficiencies and measures to minimize bias are elucidated. The trial continues to be randomized and is now designed to be blinded to the study subjects, sponsor, investigators, medical providers, and outcome assessors. The details of the enrollment, randomization and masking procedures to minimize bias are detailed in this section, including labs.	Updated study design pursuant to direction from the agency
10.6.2 Evaluation of Success of Blinding	Section added.	Updated study design pursuant to direction from the agency
10.6.3 Breaking the Study Blind/ Participant Code	Section added.	Updated study design pursuant to direction from the agency
12.5 Future Use of Stored Specimens	Amended to address potential privacy issues subjects need to be aware of at time of informed consent regarding future use of retained samples, including how confidentiality will be maintained, how long samples will be held by Alkahest,	Updated pursuant to direction from the agency

Location	Description	Purpose
	how they will be used, and what happens if Alkahest transfers ownership to another commercial sponsor.	
19. Revision History	Addition of revision history table for Protocol Version 2.0 dated 09NOV2017	Version control