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

Protocol Number:	ALK6019-202
Clinical Phase:	2
Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
Study Agent:	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:	V3.0
Version Date:	10JUL2019
Replaces Version:	V2.0, 03DEC2018

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.

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LIST OF ABBREVIATIONS

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

LIST OF DEFINITIONS

Infusion Nurse	The **unblinded study personnel,** qualified by training and experience, responsible for administering the investigational product/placebo. The Infusion Nurse ensures that the investigational product (GRF6019)/placebo is allocated appropriately and administered at the correct infusion rate. The Infusion Nurse is also responsible for ensuring that appropriate blinding techniques are used to prevent inadvertent unblinding of study staff and subjects during and immediately following the Infusion Period.
Infusion Period	The period during which GRF6019/placebo is infused.
Outcomes Assessor	The **blinded study personnel,** qualified by training and experience, responsible for observing study subjects during the infusion of the investigational product/placebo and collecting and/or managing adverse events (AEs) that occur before, during, and after the infusion period.

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PROTOCOL APPROVAL PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer's Disease
Protocol Number:	ALK6019-202
Version/Date:	V3.0_10JUL2019
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 Practice, the Declaration of Helsinki in the latest relevant version, and applicable legal and regulatory requirements.

Approved by:

[redacted]	[redacted]	10-Jul-2019
Sponsor Representative (print)	Signature	Date

STATEMENT OF COMPLIANCE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer's Disease
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Version/Date:	V3.0_10JUL2019

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 agent 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), 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 onsite inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, local governing regulatory bodies, and IRB inspectors.

_____ _____

Investigator's Signature Date

_____

Print Name

PROTOCOL SUMMARY

Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer's Disease
Précis:	This is a randomized, double-blind, placebo-controlled study to assess the safety and tolerability of GRF6019, a [redacted] human plasma protein fraction, administered by intravenous (IV) infusion in subjects with severe Alzheimer's disease (AD). The study consists of approximately 20 subjects who will be randomized in a 2:1 ratio to active GRF6019 or placebo. Treatment groups will be stratified by sex. Subjects will receive one infusion per day of active or placebo treatment for 5 consecutive days during Week 1 of the study. The total study duration for the subjects will be approximately 9 weeks. The infusion procedure of active and placebo agents will be identical to maintain blinding. The following measures will be taken to ensure adequate allocation concealment during infusions: blinding of subjects, study coordinators, physicians, and cognitive test administrators to treatment allocation; use of blinded Outcomes Assessors and unblinded Infusion Nurses; and measures to block view of the [redacted] and other infusion equipment/supplies throughout the infusion. All subjects will undergo a screening visit, baseline visit, treatment period, follow-up visits, and an-end-of-study/early-termination visit. Safety and tolerability assessments will occur at every visit. Cognitive and other assessments will be performed at Baseline and periodically during subsequent visits through End of Study/Early Termination.
Objectives:	The primary objective of the study is to assess the safety and tolerability of an infusion dosing regimen of GRF6019 in subjects with severe AD. As a secondary objective, the study will assess the potential effects of GRF6019 on cognition and function. The exploratory objectives include serial compositional analysis of plasma proteins to identify specific biomarkers associated with cognitive function and/or indicators of disease progression.
Endpoints:	Primary Endpoint(s): • Incidence of treatment-emergent AEs and SAEs identified by MedDRA preferred term (PT) and grouped by MedDRA System Organ Class (SOC) Secondary Endpoint(s): • Changes in safety laboratory parameters • Changes in vital signs • Changes in body weight

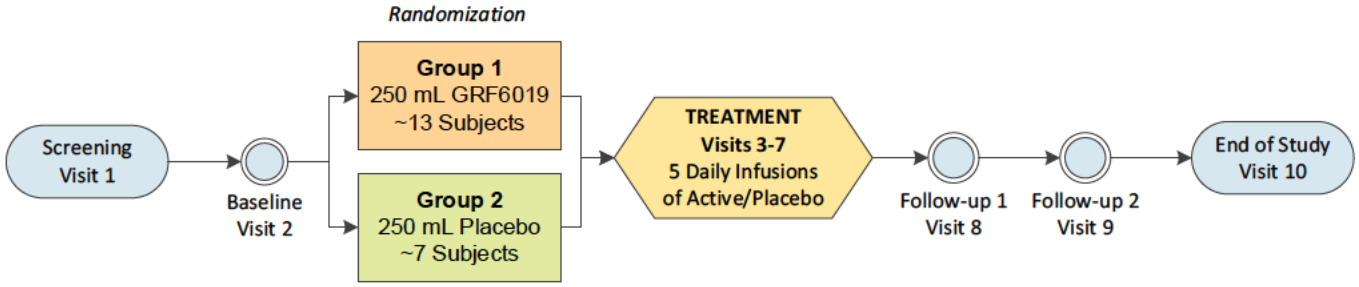
- Changes in physical exam
- Changes in electrocardiogram (ECG) parameters
- Changes in the Mini-Mental Status Examination (MMSE)
- Changes in the Severe Impairment Battery (SIB)
- Changes in the Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL-Severe)
- Changes in the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Caregiver Input (ADCS-CGIC)
- Change on the Neuropsychiatric Inventory (NPI) or NPI Nursing Home Version (NPI-NH)

Exploratory Endpoint(s):

- Proteomic assessment of plasma for investigation of study-related biomarkers

Population:	Approximately 20 subjects between 60 and 95 years of age with severe AD. Assuming a drop-out rate of 20%, enrollment of 20 subjects would yield approximately 16 evaluable subjects.
Phase:	2
Number of Sites:	Up to 4 sites in the United States (US)
Description of Study Agent:	GRF6019: A [redacted] human plasma protein fraction for IV infusion.
Study Duration:	Approximately 12 months
Subject Duration:	Approximately 9 weeks

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, or their designee, and provided to the investigator.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Alzheimer's disease (AD) is a progressive neurodegenerative disease 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 (Alzheimer's Association 2018). During the course of the disease, synapses and ultimately neurons are lost in the cerebral cortex, hippocampus, and subcortical structures (including selective cell loss in the nucleus basalis of Meynert), locus coeruleus, and nucleus raphe dorsalis. Imaging studies have found characteristic changes in perfusion and cerebral glucose metabolism (e.g., reduction in the parietal lobe and temporal cortices in early-stage disease, prefrontal cortex in late-stage disease). Neuropathologically, neuritic or senile plaques (composed of neurites, astrocytes, and glial cells around an amyloid core) and neurofibrillary tangles (composed of tau paired helical filaments) are the hallmarks of AD. Some of these pathologic changes (e.g. plaques) precede symptoms of impaired cognition (Mayeux 2010).

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. It is estimated that by 2050, nearly 1 million new cases will be diagnosed per year (Alzheimer's Association 2018). After being diagnosed with AD, the average life expectancy of a person who is 65 or older is 5.7 years for women and 4.2 years for men, and approximately 1.5-3 years of that time will be spent in the most severe stage of the disease, and this time is commonly spent in a skilled nursing facility (Larson 2004, Alzheimer's Association 2018).

While approved therapies, including acetylcholinesterase inhibitors (e.g., donepezil) and the N-Methyl-D-aspartic acid (NMDA) receptor agonist memantine, ameliorate symptoms, the magnitude of this symptomatic effect is moderate. Moreover, these drugs do not slow the progression of the disease (Alzheimer's Association 2018). 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 from heterochronic parabiosis in mice 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, studies were designed to explore the therapeutic effects of systemic exposure of aged mice to young plasma by direct injection (Villeda 2014). Systemic administration of young plasma in aged mice improved age-related cognitive 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 [redacted] 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

Study ALK6019-202 will evaluate the safety and tolerability of administering GRF6019 via IV infusions in subjects with severe AD. 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, 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 from multiple 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]

Our nonclinical studies were initiated 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 µl 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].

We evaluated the effects of both [redacted] plasma and plasma protein fraction using various dosing paradigms in NODscid, NSG (NODscid Gamma) and C57BL/6J mice. Initially, mice were dosed with 150 µL 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, we elected to assess a novel dosing regimen of 150 µL for 7 consecutive days (referred to as "pulsed dosing"), both alone and compared to other intermittent weekly dosing regimens [redacted]. Our final study examined pulsed dosing of 150 µL for 5 consecutive days [redacted], which is the pulse-dosing regimen chosen for ALK6019-202.

Based on our non-clinical studies, we observed significant improvements in cognitive performance and histological correlates with a [redacted] plasma protein fraction. In addition, studies with [redacted] plasma protein fractions demonstrated that the beneficial effect continued 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, [redacted]. If safety and efficacy are demonstrated with GRF6019, pulsed dosing may be more convenient than weekly or monthly dosing for patients.

Severe AD patients will be selected for inclusion in this clinical study as they have marked 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 favorable.

A randomized, placebo-controlled, double-blind 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 cognitive endpoints, and potential plasma derived factors that may affect these parameters. A 2:1 randomization ratio will increase the number of subjects exposed to active GRF6019 and thus provide additional safety data. Within-subject and between-group cognitive changes associated with the use 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 severe AD and other neurodegenerative disorders typified by cognitive dysfunction.

Human dose levels were selected based on known safety through clinical experience and scaling from efficacy in nonclinical studies. No safety concerns were observed in nonclinical studies using repeated doses of 150 µL in mice.

GRF6019 is a complex mixture consisting of multiple proteins [redacted] and is dosed by infusion of specified volumes, thus, using allometric scaling, a dose of 150 µL 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 <100 kDa, 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 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. Decreased blood pressure may occur, particularly following rapid infusion. The blood pressure may normalize spontaneously after the slowing or discontinuation of the infusion. [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 severe AD.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to assess the safety and tolerability of GRF6019, a [redacted] human plasma protein fraction administered by IV infusion in subjects with severe AD. Secondarily, this study aims to assess the effects of GRF6019 on subjects' cognition and 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.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

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

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

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

During the 5-day dosing period, subjects who do not already reside in a long-term care/skilled nursing facility will be admitted to such a facility to facilitate safety evaluation. Safety and tolerability assessments will occur at every visit. Cognitive and functional assessments will be performed at Baseline and periodically at subsequent visits through End of Study/Early Termination. In the event of early termination of a subject who has received at least one dose, the End of Study procedures will be performed unless the subject/subject's legally authorized representative has withdrawn consent. A comprehensive safety and efficacy assessment of all data *in toto* will be conducted at the end of the study.

The overall duration of the study is approximately 12 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 months. The subject participation period is 9 weeks from Screening through End of Study, unless prematurely discontinued.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

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

The primary safety endpoint is as follows:

- Incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs) identified by MedDRA PT and grouped by MedDRA SOC.

Tolerability endpoint is as follows:

- Number of subjects completing 4 weeks after receiving at least 5 infusions.

4.2.2 SECONDARY ENDPOINTS

This study is not powered to detect statistically significant differences in cognitive domains between the baseline and end of study values. Secondary endpoints will be summarized over the study period from baseline values using descriptive statistics.

Secondary safety endpoints are as follows:

- Changes from baseline in clinical laboratory parameters.
- Changes from baseline in vital sign measurements.
- Changes in body weight from baseline to Visit 8.
- Changes from baseline in physical exam parameters at Visit 10 or End of Study/Early Termination.
- Changes from baseline in ECG recordings.

Secondary efficacy endpoints are as follows:

- Changes in the MMSE (Folstein 1975, Appendix 1).
- Changes in the SIB (Panisset 1994, Appendix 2).
- Changes in the ADCS-ADL-Severe (Galasko 2005, Appendix 3).
- Changes in the ADCS-CGIC (Ferris 1997, Schneider 1997, Appendix 4).
- Change on the NPI/NPI-NH (Cummings 1994, Wood 2000, Appendix 5).

Secondary feasibility endpoints include:

- Subject compliance with the study visit schedule, procedures, infusions, and any required adaptations that are necessary for study completion.
- Success of blinding. This will be assessed based on all occurrences (intentional or unintentional) of unblinding of blinded study subjects 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 biomarkers. 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.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

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

1. Male or female, aged 60-95 years (inclusive).
2. Diagnosis of AD based upon the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria.
3. MMSE Score 0 – 10 (inclusive).
4. Modified Hachinski Ischemia Scale (MHIS) score of ≤ 4.
5. If on medications for cognition (e.g., rivastigmine, galantamine, donepezil, memantine), must be on stable dosage for at least 8 weeks prior to Baseline.

6. If on daily antidepressant medications and/or benzodiazepines and/or typical or atypical antipsychotics, must be on stable dosage for 8 weeks prior to Baseline. If on prn dosing with atypical antipsychotics and/or benzodiazepines, these should not be given within 24 hours before each day of cognitive and other ratings (V1, V2, V8, V9, V10).
7. The subject (with support of a caregiver and/or staff) must be able to follow the study protocol, receive the treatment in the established timeframe, and continue during the follow-up interval.
8. The subject must be sufficiently fluent in English and have visual and auditory acuity sufficient to be capable of reliably completing all study assessments.
9. Provided a signed and dated informed consent form (subject's legal representative) in accordance with local regulations/guidelines/IRB.
10. Adequate renal function as defined by estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation and no microalbuminuria.
11. Systolic ejection fraction of ≥ 55% on trans-thoracic echocardiogram.

5.2 EXCLUSION CRITERIA

An individual will not be eligible for inclusion if any of the following criteria apply:

1. Evidence of clinically relevant neurological disorder(s) other than probable AD.
2. History of 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 allowed.
3. Prior hypersensitivity reaction to any human blood product or intravenous infusion; any known clinically significant drug allergy.
4. Treatment with any human blood product, including transfusions and intravenous immunoglobulin, during the 6 months prior to Screening.
5. History of immunoglobulin A (IgA), haptoglobulin or C1 inhibitor deficiency.
6. History of anaphylaxis or thromboembolic events as a complication of intravenous immunoglobulins.
7. Unstable coronary heart disease, e.g. myocardial infarction or severe or unstable angina in the 6 months prior to dosing.
8. Clinically significant abnormalities on echocardiogram.
9. Moderate to severe congestive heart failure (New York Association Class III or IV).
10. 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.
11. History of Torsades de Pointes dysrhythmia.
12. Clinically significant abnormalities on screening ECG including QTc intervals (using Fridericia's correction formula) of ≥ 450 ms in men and ≥ 470 ms in women.
13. History of hypocalcemia of any kind, including secondary to absorption syndromes secondary to gastric bypass surgery.
14. Clinically significant liver disease or biliary abnormalities.
15. Uncontrolled diabetes defined as HbA1c >7.5%.
16. Malignancy for which the subject has undergone resection and/or radiation and/or chemotherapy in the past 3 years; treated basal cell carcinoma and/or fully cured squamous cell carcinoma is allowed.
17. Clinically significant abnormalities in complete blood count, complete metabolic panel, serum albumin, blood coagulation tests, or the levels of thiamine, pyridoxine, cobalamin and thyroid stimulating hormone.

18. Hemoglobin <10 g/dL in women and <11 g/dL in men.
19. Urine protein-to-creatinine ratio (UPCR) of > 1.5 grams of protein per gram of creatinine.
20. Inadequate venous access to allow IV drug delivery or blood draws.
21. Concurrent participation in any other therapeutic treatment trial. If there was prior clinical trial participation, subject must have discontinued investigational agents for at least 30 days for small molecules, and 1 year for active or passive immunotherapies prior to Screening.
22. Subjects who have a level of agitation that, in the opinion of the investigator, could interfere with study procedures.
23. 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.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The Sponsor does not anticipate any specific challenges in meeting recruitment goals of enrolling and retaining a total of approximately 20 subjects in this study. Subjects will be recruited continuously until the planned sample size is achieved. Subjects who withdraw or are withdrawn during Screening, as well as subjects who discontinue, may be replaced (see Section 5.4.2 Handling of Participant Withdrawals or Termination).

This trial is enrolling subjects with severe AD who have sufficient cognitive impairment to be considered a vulnerable population. In this situation, consent will be obtained from the legally authorized representative. The subject's agreement to participate in the study will be obtained via an informed assent form and/or to their best level of his or her understanding. Recruitment will not proceed if the subject refuses, shows significant distress, or the legally authorized representative refuses.

The expected length of participation in the study, ~9 weeks, is not expected to be unduly onerous on subjects. Financial support for meal, travel, and miscellaneous expenses may be provided, as appropriate, and based on local regulations and guidelines. It is expected that meals will be provided by the study facilities as needed. Use of visit transport services may also be incorporated into the trial to support the subject in maintaining study visit compliance.

A description of the clinical trial will be posted on clinicaltrials.gov to 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 an 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, Sponsor, or medical monitor. The investigator must follow the subject until the AE resolves or is stable, unless the subject is lost to follow up.
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject's legally authorized representative (e.g., withdraws consent),

investigator, Sponsor, or regulatory authority.
- Pregnancy.

5.4.2 HANDLING OF PARTICPANT 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 20 subjects will be enrolled in the study with the intent of obtaining ~16 evaluable subjects who have received at least 5 doses and completed through Visit 8. Subjects who discontinue or are unblinded prior to completing Visit 8 may be replaced. Subjects who withdraw or are withdrawn during Screening will be replaced.

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 approximately 4 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).

5.4 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 statues 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.
- 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

GRF6019 is manufactured by Grifols Therapeutics, Inc. (Clayton, North Carolina, US). The placebo control agent will be 0.9% sodium chloride injection, USP (saline). The study agent and placebo will be supplied to the sites directly from a depot.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

[redacted]

[redacted] Both GRF6019 and the placebo will be labeled for investigational use according to the local regulatory requirements for clinical studies. The label will clearly identify if it is the study agent (GRF6019) or placebo control agent.

6.1.3 PRODUCT STORAGE AND STABILITY

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

Solutions which are turbid should not be used. Administration of the study agent or placebo must begin within 4 hours of the container being entered. [redacted] 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

[redacted] The study agent and placebo should be prepared in accordance with the Infusion Administration Manual that will be provided to sites (see Section 6.1.5 Dosing and Administration).

6.1.5 DOSING AND ADMINISTRATION

The study agent/placebo will be administered in accordance with the Infusion Administration Manual. The purpose of the Infusion Administration Manual is to promote safe administration of GRF6019/placebo and maintain appropriate blinding of staff and study subjects. The Infusion Administration Manual will include provisions for masking study agent/placebo and concealing the IV set-up from view of blinded staff and study subjects during the Infusion Period.

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

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

6.1.6 ROUTE OF ADMINISTRATION

The study agent and placebo will be administered by IV route only.

6.1.7 DOSING SCHEDULE

Subjects will be randomized to receive either GRF6019 or placebo. Randomization to treatment group will be stratified by sex. Subjects will receive one infusion of 250 mL per day for 5 consecutive days at Week 1.

6.1.8 DURATION OF THERAPY

From Screening to End of Study, the duration of study involvement for each subject is approximately 9 weeks.

All subjects will receive 5 consecutive days of therapy during Week 1. Thus, the duration of therapy for all subjects will be 5 exposure days. The duration of therapy for a subject to be considered evaluable in the intent-to-treat population is 4 exposure days.

6.2 STUDY AGENT ACCOUNTABILITY

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

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/placebo accidentally wasted or intentionally disposed of must be maintained.

The disposal of used, partially used, or wasted study agent/placebo must be performed in accordance with the institution's drug disposal policy, or as directed by Sponsor. 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/placebo, including empty containers. A copy of the institution's drug disposal policy should be maintained or referenced in the investigator's study file. A certificate of (study agent/placebo) destruction must be provided to the Sponsor if destroyed on site.

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:

- Assessment of AD
- MMSE
- MHIS
- Medical history
- Demographics
- Review of medications
- Vital signs
- Physical examination
- 12-lead ECG
- Echocardiogram
- Blood and urine collection for laboratory evaluations

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 Assessment of 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 (Refer to Section 7.1.1.1.2) 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:
    - Amnestic 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.
    - Nonamnestic 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 nonfluent/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 cerebrospinal fluid biomarkers will be evaluated, if available, to support the clinical diagnosis of AD.

7.1.1.1.2 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.

7.1.1.1.3 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.

7.1.1.1.4 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject's caregiver(s) during Screening. The medical history should focus on recent history, with an emphasis on the history of cognitive symptoms related to probable AD. Additionally, the medical history should include:

- Current/past illnesses and conditions.
- Current symptoms of any active medical condition.
- Surgeries and procedures.
- Allergies.
- Family history in biological parents, siblings, and offspring of AD, other dementias, or neurological

disorders, if known.
- Social history (e.g. smoking, alcohol, illegal substances), if known.
- Prior imaging, cerebrospinal fluid assessments, or other relevant diagnostic tests, including genetics, if available.

7.1.1.1.5 Demographics
Demographic information such as the subject's education level, ethnicity, and race may be collected at Screening if available.

7.1.1.1.6 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.

7.1.1.1.7 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 body temperature. Vital signs should be measured after the subject has been seated for 5 minutes.

7.1.1.1.8 Physical Examination
A complete physical examination will be performed to assess the following organ systems: skin, ears, nose, throat, head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic, and lymphatic systems. Height and weight will also be documented as specified in Section 15 Schedule of Events.

7.1.1.1.9 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.

7.1.1.1.10 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 ≥55% (Gebhard 2012).

7.1.1.1.11 Biological Specimen Collection
Biological samples will be obtained, analyzed, and stored appropriately for future analysis. Blood 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 in Section 15 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. Subjects (or their legally authorized representatives) can opt out of storage of samples for future analysis.

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
- 12-Lead ECGs
- Targeted physical exams
- Weight
- End of Study (or Early Termination) physical examination
- Blood and urine collection for clinical laboratory evaluations

7.1.1.2.1 Review of Adverse Events

AEs will be reviewed, documented, and reported as required at each visit (from time of consent through End of Study). 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 7.1.1.1.7 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 12-Lead ECG

Refer to Section 7.1.1.1.9 for information pertaining to 12-Lead ECGs.

7.1.1.2.5 Targeted Physical Exams

During the dosing period, 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).

7.1.1.2.6 Physical Examination

Refer to Section 7.1.1.1.8 for a description of the complete physical exam. The complete physical exam will be performed at Screening and repeated at End of Study (or Early Termination).

7.1.1.2.7 Blood and Urine Collection for Laboratory Evaluations

As described in Section 7.1.1.1.11, subjects will have blood and urine samples collected for clinical

evaluation (Section 7.2.1 Clinical Laboratory Evaluations). Refer to Section 15 Schedule of Events for timing and frequency of blood and urine collection for laboratory evaluations.

7.1.1.3 Procedures to Assess Efficacy

Cognitive function will be assessed using assessment scales administered by qualified raters. Raters must be certified, as appropriate. The same rater should be used for the duration of each subject's participation unless a change in rater is unavoidable. Additionally, for scales that require an informant (e.g., caregiver), the informant should be consistent throughout the duration of each subject's participation unless a change is unavoidable. Informants must have frequent contact with the subject (defined as approximately 10 hours per week). The following scales will be used during the course of this study:

- MMSE
- SIB
- ADCS-ADL-Severe
- ADCS-CGIC
- NPI or NPI-NH

Information regarding the timing and frequency of these procedures is provided in 7.3 Study Schedule.

7.1.1.3.1 Mini-Mental Status Examination

Refer to Section 7.1.1.1.2 for information pertaining to the MMSE.

7.1.1.3.2 Severe Impairment Battery

The SIB is designed to assess cognitive abilities in patients with severe AD. The SIB is divided into scorable subscales that cover orientation to time and place, attention, language, praxis, visuospatial ability, construction, memory, orientation to name, and social interaction. Scoring gives credit to nonverbal and partially correct answers, thus decreasing the need for language output. There are 57 items, and it takes approximately 20 minutes to complete. The range of possible scores is 0-133 (Panisset 1994, Appendix 2).

7.1.1.3.3 Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory for Severe Alzheimer's Disease

The ADCS-ADL-Severe assesses the competence of patients with AD in performing basic activities of daily living. The ADCS-ADL-Severe contains 19 items covering physical and mental functioning and independence in self-care (e.g. dressing, grooming, bathing, eating, walking, and toileting). For each ADL, an informant (e.g., caregiver) is first asked if the patient attempted the activity during the past 4 weeks. If a patient did attempt the ADL, the informant is asked to choose the single most accurate definition of the patient's level of performance. The scores range from 0 to 54, with higher scores indicating less functional impairment (Galasko 2005, Appendix 3).

7.1.1.3.4 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Caregiver Input

The ADCS-CGIC is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician. The ADCS-CGIC focuses on clinicians' observations of change in the subject's cognitive, functional, and behavioral performance since the beginning of a trial. It relies on both direct examination of the subject and interview of informants (Ferris 1997, Schneider 1997, Appendix 4).

7.1.1.3.5 Neuropsychiatric Inventory or Neuropsychiatric Inventory – Nursing Home Version

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

The NPI-NH was derived from the NPI (Cummings 1994) to evaluate the neuropsychiatric manifestations and psychopathology of patients with AD and other dementias who reside in nursing homes, extended care facilities, or other long-term care settings. The NPI-NH is an interview-based scale designed to be administered to an informed professional nursing home caregiver (as opposed to a family or home-based caregiver in the standard NPI) involved in the daily care of the subject. Generally, the NPI-NH is used to evaluate changes in subject behavior that have appeared during a given period (Wood 2000, Appendix 5).

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g. whole blood, serum, urine, buccal swab) will be collected for laboratory evaluations in accordance with the Schedule of Events (Section 15). Clinical sample processing and laboratory evaluations will be conducted by certified Clinical Laboratory Improvement Amendments (CLIA) facilities. 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 ε4 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, and other exploratory measures.

7.2.2.2 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 15 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.

7.2.3 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 33 ± 7 days. Study visit procedures are listed in the recommended order in which they should be completed.

7.3.1 SCREENING

Screening Visit (Day -28 to -8)

- □ Obtain informed consent from the subject's legally authorized representative and informed assent from the subject, if applicable, prior to performing any study-related assessments.
- □ Assess for probable AD using NIA-AA criteria and administer the MMSE.
- □ Conduct the MHIS.
- □ Obtain medical history to determine eligibility based on inclusion/exclusion criteria.
- □ Collect demographic information.
- □ Review subject's current and prior medications.
- □ Collect vital signs, height, and weight.
- □ Perform the physical exam.
- □ Perform the 12-lead ECG.
- □ Collect blood and urine specimens for labs.
- □ Perform transthoracic echocardiogram.

Note: The Screening Visit may be split to allow sufficient time to complete all required procedures. AEs and concomitant medications should be recorded during split visits, if applicable.

7.3.2 BASELINE

Baseline Visit (Days -7 to -1)

- □ Re-review Screening assessments for eligibility.
- □ Review AEs and concomitant medications.
- □ Collect vital signs.
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to administering cognitive and functional assessments.
- □ Administer cognitive and functional assessments in the following order:
    1. SIB
    2. ADCS-ADL-Severe
    3. ADCS-CGIC
    4. NPI or NPI-NH

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.

7.3.4 TREATMENT

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

Visits 3 -7 (Days 1-5)

- □ Perform the following procedures prior to administering study treatment:
    - Review AEs and concomitant medications.
    - Obtain samples for proteomics/epigenetics/biobanking; fasting samples preferred (**Visit 3 Only**).
    - Obtain sample for ApoE genotype testing (**Visit 3 Only**).
    - Obtain pre-infusion safety laboratory samples and assess results **prior to the next day's infusion** (**Visits 4, 5, and 6 Only**). (When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion, provided that all pre-infusion safety lab results are available and interpreted prior to the subject's infusion start on Visits 5, 6, and 7.)
    - Collect urine for urinalysis (**Visit 6 Only**).
    - Measure and record the subject's weight in kilograms.
    - Perform targeted physical exam (i.e. auscultation of heart and lungs and assessment of peripheral edema) (**Visits 3, 5, and 7 Only**).
    - Perform 12-lead ECG (**Visits 3 and 5 Only**).
    - Collect pre-infusion vital signs.
- □ Administer study treatment and perform safety assessments per the Infusion Administration Manual.

7.3.5 FOLLOW-UP VISITS

Follow-up Visit 8 (Day 6 + 3 days)

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs and subject's weight in kilograms.
  - Blood and urine samples for safety labs (fasting samples preferred).
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Perform 12-lead ECG.
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to administering cognitive and functional assessments.
- □ Administer cognitive and functional assessments in the following order:
  1. SIB
  2. ADCS-CGIC

Follow-up Visit 9 (Day 12 ± 3 days)

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs and subject's weight in kilograms.
  - Blood samples for safety labs (fasting samples preferred).
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to administering cognitive and functional assessments.
- □ Administer cognitive and functional assessments in the following order:
  1. SIB
  2. ADCS-CGIC
  3. NPI or NPI-NH

7.3.6 FINAL STUDY VISIT

Visit 10, End of Study (Day 33 ± 7 days)

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs and subject's weight in kilograms.
  - Blood and urine samples for exit safety labs (fasting samples preferred).
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Perform the physical exam.
- □ Perform the 12-lead ECG.
- □ Ensure the subject has had an opportunity to eat a meal prior to administering the cognitive and functional assessments.
- □ Administer cognitive and functional assessments in the following order:
  1. MMSE
  2. SIB
  3. ADCS-ADL-Severe
  4. ADCS-CGIC
  5. NPI or NPI-NH

7.3.7 EARLY TERMINATION VISIT

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.

7.3.8 SCHEDULE OF EVENTS TABLE

A tabular summary of all procedures by study visit can be found in Section 15 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., AE, etc.).

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following are prohibited:

- Concurrent participation in any other therapeutic treatment trial. If there was prior clinical trial participation, subject must have discontinued investigational agents for at least 30 days for small molecules, and 1 year for active or passive immunotherapies prior to Screening.
- 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.
- Any drugs of the interferon class.
- Systemic corticosteroids (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 whether GRF6019 or placebo was received by a subject is essential. Any instances of unblinding will be managed as indicated in Section 10.6.3 Breaking the Study Blind/Subject 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 or the subject's caregiver 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/caregiver.
- 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)

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.

Note: 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: the terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE. "Serious" is a regulatory definition.

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 AE is more plausible; a temporal sequence cannot be established with the onset of the AE 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 AE and administration of the study agent, but the AE 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 AE causes.
- Definitely Related: The AE 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/FREQUENCY FOR EVENT ASSESSMENT/FOLLOW-UP

At every study visit, subjects will be assessed for AEs and SAEs. After the subject/subject's caregiver 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 AE AND SAE

The investigator is not obligated to actively seek SAE information in former study subjects, 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 AEs, 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 AEs of special interest (AESI):

- Clinically-significant peripheral edema or pulmonary edema.
- Reduced kidney function (eGFR <45 mL/min/1.73 m^2).
- Suspected transmission of blood-borne infectious agents.

AESIs 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 or female partner of a male subject subsequent to first exposure to the study agent until End of Study, or 3 months following a subject's

last dose in the event of early termination. 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(s) 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 (see Section 8.2.2 Relationship to Study Agent).
- 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 (i.e., 3 related events in the same SOC or a suspicious overall pattern, 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, unless the Sponsor deems unblinding necessary for safety evaluation.

Attendants at the Safety Evaluation Meeting will include the Program Physician of Alkahest (or his/her designee), the CRO Medical Monitor, and available 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 site investigators. There will be no formal Data Safety Monitoring Board (DSMB) established. As needed, 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) 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 tasks and scope 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 or the Sponsor's designee to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL DESIGN MODEL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unblinding of the study data.

10.2 STATISTICAL HYPOTHESES

Because the primary objective of the study is safety and tolerability, it is not designed to detect statistically significant differences between active and placebo on efficacy endpoints. The statistical approach toward secondary efficacy endpoints will be primarily descriptive; 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 subjects.
- **Safety Dataset**: all subjects who received at least one dose of the study agent.
- **Evaluable Dataset:** all subjects who receive at least 4 of the 5 planned doses.
    - **Per Protocol Dataset:** a subset of the Evaluable Dataset. A detailed description of the reasons for exclusion from the Per Protocol population will be included in the Statistical Analysis Plan (SAP).

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 endpoints will be summarized serially over time using descriptive statistics to assess the within-subject changes and between-group differences. Overall baseline and demographic data will be summarized using descriptive statistics; between-groups testing will be used to evaluate the effectiveness of the randomization in producing homogeneous pre-treatment groups.

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 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

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

Summary tabulations of reported AEs 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 EFFICACY ENDPOINTS

The study is not powered to detect significant changes in cognition, function, ADLs, etc.; however, using available data from analysis of the secondary efficacy endpoints, including changes in scores from baseline, descriptive summaries will be developed. Of particular interest will be the within-subject changes from baseline and their distribution around a null value of zero and a comparison between groups to evaluate any trends in differences between subjects randomized to active and placebo agents.

10.4.4 ANALYSIS OF THE SECONDARY SAFETY ENDPOINTS

Actual values and changes from baseline in clinical laboratory measurements, vital signs, and body weight will be assessed and summarized. Abnormal lab or vital sign 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.

For secondary safety endpoints that are continuous in nature (e.g. clinical laboratory parameters, systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, body weight) the mean, median, minimum, maximum, and standard deviation will be plotted over time.

For secondary safety endpoints that are categorical in nature (e.g. physical exam or ECG abnormalities), the frequency counts and percentages will be presented as a descriptive summary.

Per-subject extent of exposure will be listed.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Subject adherence with study visit schedule, visit procedures, infusions, and subject retention will be assessed.

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 interim analysis is conducted, the treatment assignment will remain masked, unless unblinding is deemed necessary by the Sponsor for safety evaluation.

10.4.8 ADDITIONAL SUBGROUP 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

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

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

To minimize the potential bias at the time of randomization, the study will be double-blinded and randomized. A stratified block randomization will be implemented by sex. The randomization codes will be generated by a statistician who has no involvement in the study other than generation and maintenance of the randomization codes.

All study outcome measures will be assessed by blinded Outcomes Assessors or other blinded raters. However, [redacted] GRF6019 or [redacted] placebo will be provided by an unblinded pharmacist, or other qualified staff responsible for drug accountability, to an unblinded Infusion Nurse who will administer the infusion. To ensure that Outcomes Assessors, raters, and other study personnel as well as subjects and their caregivers are unaware of the allocation, appropriate measures will be taken to mask the study agent/placebo containers and IV setup such that they will only be visible as necessary to the unblinded Infusion Nurse. In addition, a curtain, drape, or equivalent may be used to shield the infusion administration setup from view of all but the unblinded Infusion Nurse, and the unblinded Infusion Nurse will be responsible for concealing and returning used containers of the study agent or placebo to the pharmacy at the end of the Infusion Period.

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

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

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Success of blinding will be assessed based on all occurrences (intentional or unintentional) of unblinding of blinded study subjects 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/SUBJECT CODE

The study blind may be broken for safety reasons if the information is required for the management of SAEs or severe AEs or if the investigator believes that the safety of the subject is at stake and that unblinding is necessary. Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor or

their representatives. If unintentional unblinding occurs during the study, root cause analysis will be evaluated, and corrective actions implemented as appropriate.

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 subjects. Each site will permit authorized representatives of regulatory agencies, the IRB, 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, subject'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 subject 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/subject's legally authorized representative (such as advertisements, information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB. Approval from the IRB 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 subjects need to be re-consented.

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

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS

Consent/assent forms describing in detail the study intervention, study procedures, and risks are given to the subject and/or the subject's legally authorized representative and written documentation of informed consent is required prior to performing any study-related procedures.

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 or their legally authorized representative after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to performing any study-related procedures.

Subjects and/or their legally authorized representatives should have the opportunity to discuss the study with family members or other advisors and be given adequate time to consider participation carefully. Subjects or their legally authorized representatives may voluntarily withdraw consent at any time throughout the course of the study. The rights and welfare of subjects will be protected by emphasizing that the quality of their medical care will not be adversely affected if they or their legally authorized representative declines participation in the study.

The investigator or designee must utilize an IRB-approved consent/assent 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 (if appropriate) and/or their legally authorized representative and the person obtaining consent. A copy of the signed consent form (and assent form if applicable) will be provided to the subject and/or their 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 consented subjects 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 the Health Insurance Portability and Accountability Act (HIPAA).

12.4 DATA CONFIDENTIALITY

Subject 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 subjects. 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, 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 subjects in this study. The clinical study site will permit the study monitor to 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. 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 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, de-identified biological samples may be stored at Alkahest, or designee, for future use. These samples could be used for research and to improve treatment. Alkahest will also be provided with a code-link that will allow linking the biological samples with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects/subject's legally authorized representatives may choose whether the Sponsor can store and use samples for further research.

During the conduct of the study, an individual subject (or subject's legally authorized representative) can choose to withdraw consent to have biological samples stored for future research. However, withdrawal of consent for storage of biological samples 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, or designee. 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 investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. 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. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

For each subject who receives the study agent/placebo, the CRF must be completed in a timely manner. 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, 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 procedures 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), ICH GCP, and applicable regulatory requirements. 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, IRB approval with correspondence, informed consents, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and study-specific manuals (e.g., lab manual).

Subject clinical source documents would 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 study 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

Protocol Deviations are any change, divergence, or departure from the study design or procedures defined in the protocol. Noncompliance with the clinical trial protocol 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 a study-specific Protocol Deviation plan.

Major Protocol Deviations are departures from the approved protocol relating to the conduct of the study which may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the rights, safety, or wellbeing of study participants. Major Protocol Deviations may result in data that are not deemed evaluable for the *per protocol* analysis and/or may require that subjects are discontinued from the study.

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.

All deviations will be logged and tracked at the site and study level. Periodic review of Protocol Deviations will

serve as an indicator 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. Notification of Protocol Deviations must be sent to the local IRB per their guidelines. The site investigator and applicable study staff are 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 90 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 disclosure agreement will be made between each principal investigator and Alkahest, Inc. or its authorized representative before the study agent is shipped. Each investigator will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study and 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 SCHEDULE OF EVENTS

15.1 SCHEDULE OF EVENTS TABLE

	Screening[a]/ Baseline Visit		Treatment					Follow-up		End of Study/ Early Termination Visit
Visit	1	2	3	4	5	6	7	8	9	10
Infusion Number			1	2	3	4	5			
Day	Day -28 to -8	Day -7 to -1	1	2	3	4	5	6 + 1-3 days[b]	12 ± 3 days	33 ± 7 days
Week			1						2	5
Informed Consent	X									
Medical History	X									
Demographics	X									
Vital Signs (BP, HR, temp, RR)	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
12-lead ECG	X		X[1]		X[1]			X		X
MHIS	X									
Echocardiogram	X									
Physical Exam	X									X
Height	X									
Weight	X		X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Targeted Physical Exam			X[1]		X[1]		X[1]			
Concomitant Medication	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Adverse Event Review	X[a]	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Drug Administration										
Randomization			X[1]							
GRF6019/Placebo Infusion			X	X	X	X	X			
Labs										
Screening Lab Panel[c]	X									
Urinalysis[d]	X					X[1]		X		X
ApoE Genotype Testing			X[1]							
Proteomics/epigenetics/biobanking			X[1]					X		X
Pre-infusion Safety Labs[e]				X[1]	X[1]	X[1]				
Follow-up Safety Labs[f]								X	X	
Exit Lab Panel[g]										X
Cognitive and Functional Assessments										
MMSE	X							X		X
Severe Impairment Battery		X						X	X	X
ADCS-ADL-severe		X								X
ADCS-CGIC		X						X	X	X
NPI or NPI-NH[h]		X							X	X

Notes:	X[1]: To be performed prior to infusion start. During, and for 2 hours after, each infusion, vital signs should be collected according to the schedule outlined in the Infusion Administration Manual.
	a: Screening visit may be split to allow for sufficient time to complete all procedures. AEs and concomitant medications should be recorded during split visits, if applicable.
	b: The treatment window is 5 days. Visit 8 may occur on Day 6 + 1 to 3 days following treatment to potentially avoid a weekend visit, if needed. The preference for Visit 8 is for the subject to be seen on Day 6.
	c: Includes Comprehensive Metabolic Panel [glucose, ionized calcium, albumin, total protein, sodium (Na), potassium (K), total carbon dioxide (TCO_2), chloride (Cl), urea nitrogen (BUN), creatinine, ALP, ALT, AST, bilirubin]; hematology (CBC and iron); coagulation (PT, INR, PTT); magnesium; phosphate; creatinine phosphokinase (CPK); lactate dehydrogenase (LDH); thyroid-stimulating hormone (TSH); serology (HIV, HBV, HCV); vitamin B1 (Thiamine); vitamin B6 (Pyridoxine); vitamin B12 (Cobalamine); IgA; haptoglobin; C1 Inh, functional; C1 Inh, antigenic; direct antiglobulin test (DAT); RBC antibody screen; and brain natriuretic peptide (BNP); HbA1c.
	d: Urine creatinine, urine albumin, albumin/creatinine ratio, urine sodium, sodium/creatinine ratio, urine potassium, potassium/creatinine ratio.
	e: Samples for pre-infusion safety labs should be collected and results interpreted prior to the next day's infusion start. Pre-infusion safety labs include Na, K, Cl, TCO_2, anion gap, ionized calcium, glucose, BUN, creatinine, hematocrit, hemoglobin. (When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion, provided that all pre-infusion safety lab results are available and interpreted prior to the subject's infusion start on Visits 5, 6, and 7.)
	f: Comprehensive Metabolic Panel [glucose, ionized calcium, albumin, total protein, Na, K, TCO_2, Cl, BUN, creatinine, ALP, ALT, AST, bilirubin]; hematology (CBC and iron); coagulation (PT, INR, PTT); magnesium; phosphate; CPK; LDH.
	g: Includes Chemistry (Glucose, Na, K, TCO_2, Cl, BUN, creatinine); serology (HIV, HBV, HCV); hematology (CBC and iron); DAT; RBC antibody screen.
	h: The NPI should be utilized for subjects who reside in the community; the NPI-NH should be utilized for subjects who reside in nursing homes.

16 REFERENCES

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16.2 UNPUBLISHED REFERENCES

[redacted]

17 APPENDICES

The cognitive and functional assessments in this section and associated information are provided as **EXAMPLES ONLY**. The actual assessments, related source documents, and instructions for administration and scoring are included in a rater reference manual or equivalent.

Appendix 1. The Mini-Mental Status Examination

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 >25	Increased odds of dementia Decreased odds of dementia
Education	21 <23 <24	Abnormal for 8th grade education Abnormal for high school education Abnormal for college education
Severity	24-30 18-23 0-17	No cognitive impairment Mild cognitive impairment 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. Severe Impairment Battery

The SIB is designed to assess cognitive abilities in patients with severe AD. The SIB is divided into 9 subscales, each of which yield scores that are downward extensions of instruments used to assess mild to moderate dementia. These subscales include orientation, attention, language, praxis, visuospatial perception, construction, memory, orientation to name, and social interaction. Language is further divided into several subcategories as listed below. There are 51 items and it takes approximately 20 minutes to complete. The range of possible scores is 0-100.

The items in the SIB are composed of single one-step commands. They are represented in conjunction with gestural cues and can be repeated a number of times to facilitate comprehension. Only one answer is timed (verbal fluency). Scoring gives credit to nonverbal and partially correct responses.

Domain	**Items/Cues**
1. Orientation	• Name • Place (town) • Time (month and time of day)
2. Attention	• Digit span • Counting to visual and auditory stimuli
3. Language	• Auditory and reading comprehension • Verbal fluency (food and months of the year) • Naming from description, pictures of objects, objects, colors, and forms • Repetition • Reading • Writing • Copying of written material
4. Praxis	How to use a cup and a spoon
5. Visuospatial perception	Discrimination of color and forms
6. Construction	Spontaneous drawing, copying, and tracing a figure
7. Memory	Immediate, short- and long-term recall for examiner's name, objects, colors, forms, and a short sentence
8. Orientation to name	When the patient's name is called from behind
9. Social interaction	Shaking hands and following general directions

Reference:

Panisset M, Roudier M, Saxton J, Boller F. Severe Impairment Battery: a neuropsychological test for severely demeted patietns. Arch Neurol. 1994 ;51:41-45.

Appendix 3. Alzheimer's Disease Cooperative Study Group Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL-Severe)

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

ADL	**Point Range**
1. Walks	0-3
2. Grooms	0-3
3. Bathes	0-3
4. Eats	0-3
5. Dresses	0-4
6. Toileting	0-3
7. Turns faucet on	0-1
8. Turns faucet off	0-1
9. Turns lights on	0-1
10. Turns lights out	0-1
11. Finds belongings	0-3
12. Disposes of litter	0-3
13. Clears table	0-3
14. Travels beyond home	0-4
15. Conversation	0-3
16. Watches TV	0-4
17. Uses telephone	0-5
18. Obtains beverage	0-3
19. Can be left alone	0-3
TOTAL	**0-54**

Reference:

Galasko D, Schmitt F, Thomas R, Jin S, Bennett D, Ferris D; Alzheimer's Disease Cooperative Study. Detailed assessment of activities of daily living in moderate to severe Alzheimer's disease. J Int Neuropsychol Soc. 2005 Jul;11(4):446-453.

Appendix 4. Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Caregiver Input (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 informant 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.

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Appendix 5. Neuropsychiatric Inventory and Neuropsychiatric Nursing Home Version

The NPI is an outcome measure designed to assess psychiatric symptoms in patients with dementia in outpatient settings with information provided by a familial and/or professional caregivers (informant). The NPI-NH was developed for use with professional caregivers (informants) in a nursing home setting as a questionnaire about patients for whom they care. Each of the 12 NPI-NH domains contains a screening question that reflects cardinal symptoms of that domain. Initial responses to each domain screening question are "Yes" (present) or "No" (absent). If the response to the domain question is "No", the interviewer goes to the next question. If "Yes," the interviewer proceeds to ask the informant a series of subquestions for that domain. For each behavioral domain, there are 4 scores: frequency, severity, domain total score (frequency x severity), and caregiver distress (NPI)/occupational disruptiveness (NPI-NH). Thus, the NPI and NPI-NH evaluate response to therapy and provide symptom severity and distress ratings for each symptom reported, as well as total severity and distress scores reflecting the sum of individual domain scores. It takes approximately 20-30 minutes to complete the interview.

12 Domains/Screening Questions: NPI

1. Delusions: Does the patient have beliefs you know are not true? For example, insisting that people are trying to harm him/her or steal from him/her? Has he/she said that family members are not who they say they are or that the house is not their home?

2. Hallucinations: Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear, or experience things that are not present?

3. Agitation/Aggression: Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

4. Depression/Dysphoria: Does the patient seem sad or depressed? Does he/she say that he/she is sad or depressed?

5. Anxiety: Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

6. Elation/Euphoria: Does the patient seem too cheerful or too happy for no reason?

7. Apathy/Indifference: Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for participating in new activities? Is he/she more difficult to engage in conversation or doing chores? Is the patient apathetic or indifferent?

8. Disinhibition: Does the patient seem to act impulsively without thinking? Does he/she say or do things that are not usually said or done in public? Does he/she do things that are embarrassing to you or others?

9. Irritability/Lability: Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she extremely impatient?

10. Aberrant Motor Behavior: Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

11. Nighttime Behaviors (only given to caregivers who work the night shift): Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

12. Appetite/Eating: Has he/she had any changes in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in the type of food he/she prefers?

12 Domains/Screening Questions: NPI-NH

1. Delusions: Does the resident have beliefs you know are not true? For example, saying that people are trying to harm him/her or steal from him/her? Has he/she said that family members or staff are not who they say they are or that his/her spouse is having an affair? Has the resident had any other unusual beliefs?

2. Hallucinations: Does the resident have hallucinations – meaning, does he/she see, hear, or experience things that are not present?

3. Agitation/Aggression: Does the resident have periods when he/she refuses to let people help him/her? Is he/she hard to handle? Is he/she noisy or uncooperative? Does the resident attempt to hurt or hit others?

4. Depression/Dysphoria: Does the resident seem sad or say that he/she is depressed? Does the resident cry at times?

5. Anxiety: Is the resident very nervous, worried, or frightened for no reason? Does he/she seem very tense and unable to relax? Is the resident afraid to be apart from you or from others that he/she trusts?

6. Elation/Euphoria: Does the resident seem too cheerful or too happy for no reason? I don't mean normal happiness but, for example, laughing at things that others do not find funny?

7. Apathy/Indifference: Does the resident sit quietly without paying attention to things going on around him/her? Has he/she lost interest in doing things or lack motivation for participating in activities? Is it difficult to involve the resident in conversation or in group activities?

8. Disinhibition: Does the resident do or say things that are not usually done or said in public? Does he/she seem to act impulsively without thinking? Does the resident say things that are insensitive or hurt people's feelings?

9. Irritability/Lability: Does the resident get easily irritated or disturbed? Are his/her moods very changeable? Is he/she extremely impatient?

10. Aberrant Motor Behavior: Does the resident have repetitive activities or "habits" that he/she performs over and over such as pacing, wheeling back and forth, picking at things, or winding string? (Do not include simple tremors or tongue movements).

11. Nighttime Behaviors (only given to caregivers who work the night shift): Does the resident have difficulty sleeping (do not count as present if the resident simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she awake at night? Does he/she wander at night, get dressed, or go into others' room?

12. Appetite/Eating: Does the resident have an extremely good or poor appetite, changes in weight, or unusual eating habits (not applicable if the resident is incapacitated and has to be fed)? Has there been any change in the type of food he/she prefers?

References:

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308-2314.

Wood S, Cummings JL, Hsu MA, Barclay T, Wheatley MV, Yarema KT, Schnelle JF. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. Am J Geriatr Psychiatry. 2000 Winter;8(1):75-83.

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 3.0 dated 10JUL2019
Replaces: Protocol Version 2.0 dated 03DEC2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V2.0 03DEC2018 ***Now reads:*** V3.0 10JUL2019	Version Control
2.3.1	Removed mention of hypotension due to infusions and replaced with "decrease in blood pressure."	Updated to clarify that decreases in blood pressure at a single timepoint are not a chronic diagnosis of hypotension.
7.3.4, 15.1	***Sentence added:*** When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion, provided that all pre-infusion safety lab results are available and interpreted prior to the subject's infusion start on Visits 5, 6, and 7.	Clarified timepoints for the collection and interpretation of the pre-infusion safety labs for sites using an i-STAT Handheld Blood Analyzer. This was previously clarified in Protocol Clarification Memo #2 dated 15APR2019.
8.4.3	[redacted]	[redacted]
10.3	Updated definition of the Per Protocol dataset.	Updated definition for standardization with current Alkahest statistical standards.

Location	Description	Purpose
13.3	Added definition of Protocol Deviation and updated definition of Major Protocol Deviation.	Updated definitions based on Alkahest-revised SOPs.
15.1	Added HbA1c to Screening Lab Panel.	HbA1c is part of the exclusionary criteria but was inadvertently left out of the Schedule of Events table. This was previously clarified in Protocol Clarification Memo #1 dated 25FEB2019.

Protocol Version 2.0 dated 03DEC2018
Replaces: Protocol Version 1.0 dated 07AUG2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V1.0_07AUG2018 ***Now reads:*** V2.0_03DEC2018	Version Control
Throughout	Grammar and style changes.	For protocol clarity and standardization
Title Page	[redacted]	[redacted]
List of Abbreviations, Protocol Summary, 4.2.2, 7.1.1.3, 7.1.1.3.4, 7.3.2, 7.3.5, 15.1, Appendix 4	Removed "Plus" from "Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change" assessment. Also removed "+" from abbreviation of assessment, "ADCS-CGIC" throughout protocol.	Correction of assessment nomenclature.
List of Abbreviations, Protocol Summary, 4.2.2, 7.1.1.3,	Added assessment "Neuropsychiatric Inventory" and abbreviation of assessment, "NPI" throughout protocol.	Protocol previously only included the Neuropsychiatric Inventory-Nursing Home version (NPI-NH). Subjects who reside in the community are now being recruited into the study, and the

Location	Description	Purpose
7.1.1.3.5, 7.3.2, 7.3.5, 7.3.6, 15.1, Appendix 5		standard NPI is the appropriate instrument for assessment of this population.
Protocol Summary, 4.1, 6.1.7, 10.6.1	Added content to indicate treatment groups will be stratified by sex.	Integration of analysis by sex in the research process.
5.1	***Amended Inclusion Criteria as follows:*** • All Inclusion Criteria were previously bulleted; bullets were updated to a numbered list. • ***#6 Previously read:*** If on antidepressant medications and/or benzodiazepines and/or typical or atypical antipsychotics, must be on stable dosage for 8 weeks prior to Baseline. • ***#6 Now reads:*** If on daily antidepressant medications and/or benzodiazepines and/or typical or atypical antipsychotics, must be on stable dosage for 8 weeks prior to Baseline. If on prn dosing with atypical antipsychotics and/or benzodiazepines, these should not be given within 24 hours before cognitive and other ratings (V1, V2, V8, V9, V10).	Updated for clarity and standardization.
5.2	***Amended Exclusion Criteria as follows:*** • All Inclusion Criteria were previously bulleted; bullets were updated to a numbered list. • #10: Refined definitions of "poorly controlled" and "refractory" hypertension. ***Added the following Exclusion Criteria:*** • #16: Malignancy for which the subject has undergone resection and/or radiation and/or chemotherapy in the past 3 years; treated basal cell carcinoma and/or fully cured squamous cell carcinoma is allowed.	Updated for clarity and standardization.
6.2	***Previously read:*** The disposal of used, partially used, or wasted study agent/placebo must be performed in accordance with the institution's drug disposal policy.	Clarification of drug disposal/destruction policies.

Location	Description	Purpose
	Now reads: The disposal of used, partially used, or wasted study agent/placebo must be performed in accordance with the institution's drug disposal policy, or as directed by Sponsor. ***Sentence added:*** A certificate of (study agent/placebo) destruction must be provided to the Sponsor if destroyed on site.	
7.3.5, 15.1	Visit 8 may now occur on Day 6 + 1 to 3 days following treatment (was previously only Day 6 + 1).	Extra days added to visit window to potentially avoid a weekend visit, if needed. The preference for Visit 8 is for the subject to be seen on Day 6.
10.5	[redacted]	[redacted]
15.1	***Footnote previously read:*** X[1]: To be performed prior to infusion start. ***Footnote now reads:*** X[1]: To be performed prior to infusion start. During, and for 2 hours after, each infusion, vital signs should be collected according to the schedule outlined in the Infusion Administration Manual.	Additional vital sign measurements included for increased safety.
Appendix 2	***Previously read:*** There are 57 items and it takes approximately 20 minutes to complete. The range of possible scores is 0-133. ***Now reads:*** There are 51 items and it takes approximately 20 minutes to complete. The range of possible scores is 0-100.	Updated to reflect correct assessment specifications.
Appendix 3	Score range for the following items were revised: "Eats" updated to 0-3 and "Watches TV" updated to 0-4.	Updated to reflect correct assessment specifications.

Location	Description	Purpose
18, 18.1	Added "Revision History" and "Summary of Changes" sections and content.	Sections and content not required for initial version, but necessary for all subsequent versions.