ALKAHEST

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of GRF6021 Infusions in Subjects with Parkinson's Disease and Cognitive Impairment

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Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
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Indications:	Parkinson's Disease with Mild Cognitive Impairment or Parkinson's Disease with Dementia
Authorized Representative:	[redacted] 125 Shoreway Road, Suite D San Carlos, CA 94070 Telephone: 650-801-0469 Fax: 650-801-0480
Principal Investigator:	[redacted]
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LIST OF ABBREVIATIONS

α-Syn	Alpha-synuclein
ACE	Angiotensin converting enzyme
AD	Alzheimer's disease
AE	Adverse event
AESI	Adverse event of special interest
AIC	Ambulatory infusion center
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ApoE	Apolipoprotein E
APTT	Activated partial thromboplastin time
ASL MRI	Arterial-spin labeling magnetic resonance imaging
AST	Aspartate transaminase
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CDR-CCB	Cognitive Drug Research Computerized Cognition Battery
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CISI-PD	Clinical Impression of Severity Index – Parkinson's Disease
CJD	Creutzfeldt-Jakob disease
CK	Creatinine kinase
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CRA	Clinical research associate
CRF	Case Report Form
CRO	Contract Research Organization
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
dCDT	Digital clock drawing test
D-KEFS	Delis-Kaplan Executive Function System
DNA	Deoxyribonucleic acid
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ENT	Ear, nose, throat
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS-15	Geriatric Depression Scale-15
GGT	Gamma-glutamyl transpeptidase

HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C antibody
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
HR	Heart rate
ICH	International Conference on Harmonization
ICH E6 R2	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IMP	Investigational medical product
IND	Investigational New Drug Application
IRB	Investigational Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LV	Left ventricular
MCI	Mild cognitive impairment
MDRD	Modification in diet in renal disease
MDS-PD	Movement Disorder Society's Clinical Diagnostic Criteria for Parkinson's Disease
MDS-UPDRS	Movement Disorder Society's Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NODscid	Non-obese diabetic severe combined immunodeficiency
NSG	NODscid gamma
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PD-MCI	Parkinson's disease with mild cognitive impairment
PDQ-39	Parkinson's Disease Quality of Life Questionnaire-39
PT	Preferred Term
PT/INR	Prothrombin time/international normalized ratio

PTT	Prothrombin time
RBC	Red blood cell
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical Analytical Plan
SBP	Systolic blood pressure
SE-ADL	Schwab and England Activities of Daily Living
SOC	System Organ Class
SOP	Standard operating procedure
S-STS	Sheehan-Suicidality Tracking Scale
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
tf-fMRI	Task-free functional magnetic resonance imaging
TGA	Therapeutic Goods Administration
TSH	Thyroid-stimulating hormone
UPCR	Urine protein-to-creatinine ratio
US	United States
vCJD	Variant Creutzfeldt-Jakob disease
WBC	White blood cell
WOCBP	Women of childbearing potential

LIST OF DEFINITIONS

Infusion Nurse	The **unblinded study personnel,** qualified by training and experience, responsible for administering the study agent/placebo. The Infusion Nurse ensures that the study agent (GRF6021/placebo) is allocated appropriately, administered at the correct infusion rate, and appropriate blinding techniques are used to prevent inadvertent unblinding of study staff and study subjects.
Infusion Period	The period during which GRF6021/placebo is infused (estimated to be approximately [redacted]).
Outcomes Assessor	The **blinded study personnel** qualified by training and experience to be responsible for observing study subjects during the infusion of GRF6021/placebo and collecting and/or managing adverse events (AEs) that occur before, during, and after the Infusion Period.

PROTOCOL APPROVAL PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of GRF6021 Infusions in Subjects with Parkinson's Disease and Cognitive Impairment
Protocol Number:	ALK6021-201
Version/Date:	V5.0_23SEP2019
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] September 23, 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 GRF6021 Infusions in Subjects with Parkinson's Disease and Cognitive Impairment
Protocol Number:	ALK6021-201
Version/Date:	V5.0_23SEP2019

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 United States (US) Food and Drug Administration (FDA) regulations, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of all source documents by Alkahest, Inc. or designee and to onsite inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, local governing regulatory bodies, and IRB/IEC inspectors.

_____ _____

Investigator's Signature Date

_____

Print Name

PROTOCOL SUMMARY

Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of GRF6021 Infusions in Subjects with Parkinson's Disease and Cognitive Impairment
Précis:	This is a randomized, double-blind, placebo-controlled study to assess the safety and tolerability of GRF6021, a [redacted] human [redacted] fraction, administered by intravenous (IV) infusion to subjects with Parkinson's disease (PD) and cognitive impairment. The study consists of approximately 90 subjects who will be randomized in a 2:1 ratio to active treatment (approximately 60 subjects) or placebo (approximately 30 subjects). Subjects will receive one infusion per day of active or placebo treatment for 5 consecutive days during week 1 and week 13. The study duration for the subjects will be approximately 7 months. Each infusion will have a duration of approximately [redacted] with a maximum of [redacted]. The infusion 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, trial partners, study coordinators, physicians, and cognitive/motor test administrators to treatment allocation; use of blinded Outcomes Assessors and unblinded Infusion Nurses; and measures to block view of the infusion setup to avoid unblinding. All subjects will undergo a screening visit, including a magnetic resonance imaging (MRI) scan, baseline visit, two treatment periods, follow-up visits, and an end-of-study/early-termination visit. During each 5-day treatment period, administration of GRF6021/placebo can occur in an inpatient/hospital setting or in outpatient infusion centers or equivalent facilities with appropriate medical personnel. All infusions must be performed by adequately trained personnel under the supervision of the investigator. Safety and tolerability assessments will occur at every visit. Neurocognitive and motor assessments will be performed at baseline and at periodic visits following dosing. Subjects who provide explicit consent to undergo a second, optional MRI scan will have an additional MRI scan at Visit 16 to assess for changes from screening.
Objectives:	The primary objective of the study is to assess the safety and tolerability of an infusion dosing regimen of GRF6021 in subjects with PD and cognitive impairment. As a secondary objective, the study will assess the potential effects of GRF6021 on cognition and motor function as well as changes from baseline in clinical laboratory parameters, vital signs, body weight, and the Sheehan-Suicidality Tracking Scale (S-STS). The exploratory objectives include serial compositional analysis of plasma to identify

specific biomarkers associated with cognitive and motor function and/or indicators of disease progression, and changes on MRI (in consenting subjects).

Endpoints:

Primary Endpoint:

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) identified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and grouped by MedDRA System Organ Class (SOC).

Secondary Efficacy Endpoints:

- Change from baseline in the Montreal Cognitive Assessment (MoCA).
- Change from baseline in Continuity and Power of Attention, Working Memory, and Episodic Memory on the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB).
- Change from baseline in Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency.
- Change from baseline in the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 1, 2, 3, and total score.
- Change from baseline in the Schwab and England Activities of Daily Living (SE-ADL) Scale.
- Change from baseline in the Clinical Impression of Severity Index – PD (CISI-PD).
- Change from baseline in the PD Quality of Life Questionnaire-39 (PDQ-39).
- Change from baseline in the Geriatric Depression Scale-15 (GDS-15).
- Change from baseline in the digital clock drawing test (dCDT).

Secondary Safety Endpoints:

- Change from baseline in clinical laboratory parameters.
- Change from baseline in vital sign measurements.
- Change from baseline in body weight.
- Change from baseline in the S-STS.

Exploratory Endpoints:

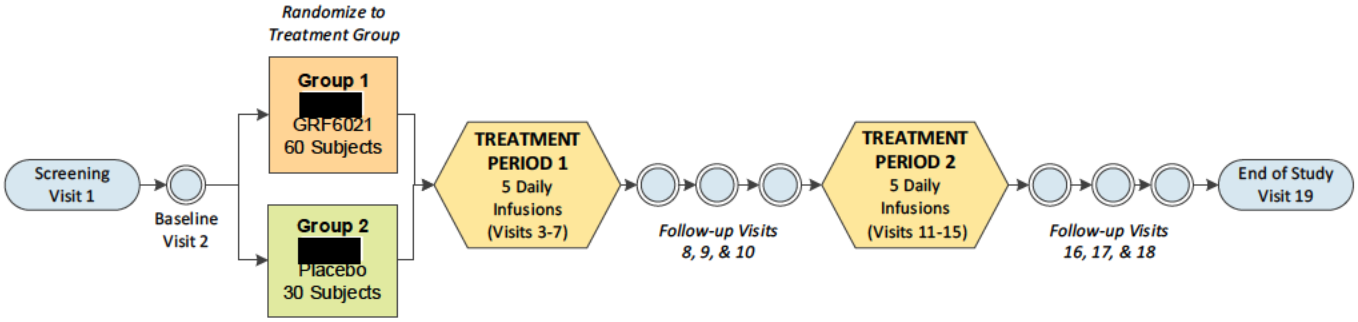
- Proteomic assessment of plasma for investigation of study-related biomarkers.
- Change from baseline in various MRI assessments (in consenting subjects).

Population:

Approximately 90 subjects between 40 and 85 years of age with a diagnosis of either PD with mild cognitive impairment (PD-MCI) or PD with dementia (PDD). Assuming a drop-out rate of 25%, enrollment at this level

	will yield approximately 68 evaluable subjects.
Phase:	2
Number of Sites:	Up to 40 sites in the US and ex-US
Description of Study Agent:	GRF6021: A [redacted] human [redacted] fraction for IV infusion
Description of Placebo Control Agent:	0.9% sodium chloride injection (saline)
Study Duration:	Approximately 24 months
Subject Duration:	Approximately 7 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

[redacted]
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 IECs and IRBs, as applicable) will be maintained by the Sponsor, or their designee, and provided to the investigator.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

The first description of PD was published just over 200 years ago by James Parkinson in *Essay on the Shaking Palsy* (Parkinson 1817). Since its original description, the clinical diagnosis of PD has centered on its cardinal motor deficits including bradykinesia, rigidity, and rest tremor (Postuma 2015, Savica 2018). Loss of dopamine-secreting neurons within the substantia nigra and presence of Lewy bodies are the major pathological findings in PD (Connolly 2014). Early in the disease course, dopamine deficiency is the predominant neurochemical abnormality, but as PD progresses, both nonmotor and motor symptoms emerge that are unresponsive to dopaminergic medication (Connolly 2014). Nonmotor manifestations, including cognitive impairment, have a detrimental impact on quality of life and function (Goldman 2011, Svenningsson 2012). In addition, it has become increasingly apparent that PD patients at all stages of the disease can develop cognitive dysfunction (Schneider 2015, Litvan 2011) ranging from mild cognitive impairment to severe dementia.

PD is the second most common neurodegenerative disease behind Alzheimer's disease (AD), with an average age at onset of approximately 60 years (Olanow 2009). An estimated 6.2 million people throughout the world have PD (Dorsey 2018), with 1 million individuals each in the US and Europe (Olanow 2009). Because the incidence of PD increases sharply with age, and the world population is aging, the number of individuals affected is poised for exponential growth; projections indicate the number of people with PD worldwide will double from 6.9 million to 14.2 million in 2040 (Dorsey 2018). In the US, projections indicate that the number of persons living with PD of all types will increase significantly from approximately 866,000 persons in 2015 to 1.96 million by 2060 (Savica 2018). In that time, it is projected that the number of persons living with PDD will increase from 312,000 persons in 2015 to 810,000 by 2060 (Savica 2018).

PD-MCI, defined as subjective and objective cognitive decline that is not normal for age but with no detectable functional impairments, is found in approximately 26.7% of non-demented PD patients and increases with age and duration/severity of PD (Litvan 2011). The majority of PD-MCI cases will convert to PDD over a period of several years, demonstrating that PD-MCI is a risk factor for development of PDD (Janvin 2006, Litvan 2011). The clinical features of PDD include progressive cognitive impairments in attention, executive, and visuospatial functions as well as memory loss (Emre 2007). Hallucinations, delusions, apathy, and mood changes are also frequently associated behavioral features (Emre 2007). Specific criteria for PDD and PD-MCI have been developed by the Movement Disorder Society (MDS) to allow differentiation between MCI and dementia in patients with PD (Emre 2007, Litvan 2012). The defining feature of PDD is that dementia develops in the context of established PD (Emre 2007).

Given its progression and complex, multifaceted disability, the greatest unmet therapeutic need in PD, PD-MCI, and PDD is identification of effective neuroprotective and disease-modifying agents (AlDakheel 2014). Current barriers include limited knowledge of the basic mechanisms of PD, PD-MCI and PDD, and a multitude of challenges in assessment of disease progression and therapeutic efficacy (AlDakheel 2014).

In 2011, data in parabiotic animal models demonstrated that factors found in circulation could affect the aging brain, and that rejuvenating factors from young animals may ameliorate the effects of aging (Villeda 2011). Following these findings, studies were performed to explore the therapeutic effects of systemic exposure of aged mice to young mouse plasma by direct injection (Villeda 2014). Systemic administration of young mouse plasma in aged mice improved age-related impairments in cognition. In addition, the data demonstrated that exposure of aged mice to young mouse 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 human plasma developed from the plasma of donors aged 18-23 years (Young Plasma) may have beneficial effects on cognitive functions in diseases such as Alzheimer's disease and PD (PD-MCI and PDD).

Although fresh frozen plasma from young donors can be tested as a treatment in humans, safer products have been developed based on pooling the plasma from highly selected donations, fractionating them into clearly defined components, and providing additional processing steps to reduce the potential for pathogen transmission. GRF6021 is a [redacted] human [redacted] fraction, manufactured by Grifols Therapeutics, Inc., [redacted] that serves as a viable source of infusible plasma proteins from healthy male and female donors (PI).

Multiple nonclinical studies conducted by Alkahest (see Section 2.2, Rationale) have demonstrated the beneficial effects of GRF6021 in age-related cognitive/motor decline and histopathological endpoints in mouse models.

These studies complemented the findings from the initial studies conducting by Villeda et al (Villeda 2011, Villeda 2014) and confirmed that factors present in human plasma protect against brain aging and ameliorate age-related cognitive and motor impairments in mice, laying the foundation for testing this [redacted] fraction in humans experiencing cognitive decline from age-related neurodegenerative diseases.

2.2 RATIONALE

Protocol ALK6021-201 will evaluate GRF6021 administered via IV infusion. Nonclinical studies conducted by Alkahest have demonstrated that both Young Plasma and GRF6021 confer beneficial outcomes in cognitive decline, motor function, neuroinflammation, synaptic density, and neurogenesis in mouse models (ALK-2015-R002, VIV-2016-R003, VIV-2016-R009, VIV-2016-R014, VIV-2016-R020, VIV-2016-R021, VIV-2016-R024, VIV-2017-R025, VIV-2017-R036, VIV-2017-R038, VIV-2018-R069, 2018-CET01, 2018-CRL03, 2018-QPS01).

Initial Alkahest nonclinical studies were performed to test whether the positive effects observed with young mouse plasma could be replicated using Young Plasma. Treatment of aged NODscid (non-obese diabetic severe combined immunodeficiency) mice with Young 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 (ALK-2015-R002). These cognitive changes were further supported by electrophysiological and histological correlates of enhanced memory. Together, these results provided support for the hypothesis that young human plasma infusions may have functional clinical benefits, potentially ameliorating or halting the progression of age-related cognitive decline.

Subsequent nonclinical studies at Alkahest were performed to test the effects of GRF6021 using various dosing paradigms in NODscid, NSG (NODscid Gamma), C57BL/6J, and Line 61 α-Synuclein (α-Syn) transgenic mice. Initially, mice were dosed with 150 µL of Young Plasma, GRF6021, or saline (control) via IV infusions 2 times per week for 5 weeks (VIV-2016-R003). 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 (VIV-2016-R014). Following these studies, a novel dosing regimen for GRF6021 that consisted of one 150 µL dose every day for 7 consecutive days (referred to as "pulsed dosing") was assessed, both alone and compared to other intermittent weekly dosing regimens (VIV-2016-R009, VIV-2016-R021, VIV-2016-R024, VIV-2017-R025, 2018-CET-01, 2018-CRL03, 2018-QPS01). Additional studies examined dosing of 150 µL for 5 consecutive days (VIV-2017-R038) as well as subsequent booster dosing for 5 consecutive days (VIV-2017-R036) which is the pulsed-dosing regimen chosen for ALK6021-201.

These studies demonstrated that pulsed dosing with GRF6021 led to significant improvements in cognitive performance, motor function, and histological correlates. Furthermore, the beneficial effects lasted up to 3 months after the end of dosing, suggesting that continuous repeat dosing may not be required (VIV-2017-R036, VIV-2017-R038). After pulsed dosing with GRF6021 in old mice, there is a well-defined timecourse of effects on the brain. Within hours of the end of dosing, C-fos expression increases, demonstrating that GRF6021 administered intravenously results in neuronal activation (2018-CET01). Over the course of a few days to a few weeks, there is a reduction in age-related neuroinflammation, and an improvement in age-related deficits in cognition and locomotion (2018-CET-01, 2018-CRL03, 2018-QPS01). Lastly, there is an increase in synaptic density and hippocampal neurogenesis; the latter lasts for up to 11 weeks after the end of dosing (VIV-2017-R038). Together, these studies indicate that 5 consecutive days of dosing ("pulsed dosing") of GRF6021 and cognitive and other testing for a period of 11 weeks thereafter, followed by a second "booster" dosing period is a reasonable study design in human subjects (VIV-2017-R036).

A randomized, double-blind, placebo-controlled study design has been selected to reduce bias in the interpretation of both safety signals and cognitive and motor endpoints. Since this is primarily a safety and tolerability study, a 2:1 randomization ratio was chosen to increase the number of subjects exposed to active GRF6021 and thus provide additional safety data, while at the same time acquiring data on the potential benefits of GRF6021 in individuals with PD and cognitive impairment. Within-subject and between-group cognitive and motor changes associated with the use of GRF6021 will be evaluated.

While the primary objective of this study is safety and tolerability, and the study is not statistically powered to test specific hypotheses regarding changes in cognitive and motor function, the results are expected to provide initial data on the magnitude and variability of beneficial effects on cognitive and motor endpoints and lay the foundation for larger trials designed and statistically powered to characterize the potential benefits of GRF6021 in PD-MCI, PDD, and other neurodegenerative disorders typified by cognitive and motor dysfunction.

The population of individuals with PD-MCI and mild-to-moderate PDD was chosen for this clinical study as they have identifiable deficits in cognitive function with limited treatment options, making them a population for whom the balance of risk to potential benefit of treatment with GRF6021 is reasonable.

The human dose level for this study was selected based on the known safety profile of GRF6021 and scaling from efficacious doses in nonclinical studies. No safety concerns were observed in nonclinical studies using repeated doses of 150 µL in mice.

GRF6021 is a [redacted] fraction consisting of multiple proteins with a total concentration of [redacted]100 mL. Dosing of GRF6021 is by IV 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 GRF6021 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 [redacted] GRF6021, which is below the equivalent human dose of 413 mL.

Table 1 Isometric Scaling Based on Blood Volume

	Mouse	Human Equivalent Dose (70 kg person)	Human Proposed Dose
GRF6021 Protein Content	[redacted]	[redacted]	[redacted]
Dose Volume	150 µL	413 mL	[redacted]
Protein per Dose	[redacted] mg	[redacted] g	[redacted] g
Blood Volume	2 mL	5,500 mL	5,500 mL
Protein per Dose per mL of Blood	[redacted] mg/mL	[redacted] mg/mL	[redacted] mg/mL

Given the [redacted] with GRF6021 during which doses of [redacted] have been well tolerated, the investigational dose of [redacted] of GRF6021 per day for five days represents a reasonable and appropriate dosing regimen for evaluation in this clinical context ([redacted], [redacted]

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Human plasma is used as a therapeutic product (Burnouf 2007) and serves as the source material for manufacturing plasma-derived therapeutic products via fractionation, including GRF6021. GRF6021 is a [redacted] human [redacted] fraction [redacted] and serves as a viable source of soluble, infusible plasma proteins from healthy male and female donors. It has been [redacted]

GRF6021 has two Important Identified Risks (Hypersensitivity reactions including anaphylaxis and Hypotension and allergic reactions) and one Important Potential Risk (transmission of pathogens).

The overall reporting frequency for hypersensitivity reactions was 0.001% (PSUR). Several steps have been implemented in this study to minimize this risk, including dosing under medical supervision in facilities with adequately trained personnel, access to subcutaneous epinephrine, frequent vital sign measurements during and after each infusion, a 4-hour safety-monitoring period after the end of each infusion, and the exclusion of subjects with a history of allergic reactions to any blood product or IV infusions. In addition, because monitoring beyond the 4-hour period may be required in some cases, all participating study sites will have inpatient facilities available for overnight observation or the ability to transfer the subject to such a facility.

The overall reporting frequency for hypotensive events was 0.002% (PSUR). Several steps have been implemented to minimize this risk, including a slow infusion rate with stepwise increase in rate that can be adjusted to tolerability; frequent monitoring of blood pressure during and after each infusion, guidance on what action to take based on observed changes in blood pressure, and exclusion of subjects with symptomatic orthostatic hypotension. Hypotension is most likely to occur following rapid infusion or intraarterial administration to patients on cardiopulmonary bypass. GRF6021 is contraindicated for use in patients on cardiopulmonary bypass as severe hypotension has been reported [redacted] and these subjects are excluded in this study. In the instance of a hypotensive episode, the blood pressure may normalize spontaneously after the slowing or discontinuation of the infusion. If necessary, vasopressors can also be used to correct the hypotension (PI).

Since GRF6021 is made from human plasma, there is a risk that it may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Since 2006, the total number of infusions administered has been estimated at 466,772, and a total of eleven (11) Individual Case Safety Reports (ICSRs) related to pathogens have been reported; the cumulative risk of pathogen transmission was estimated at 0.002% (PSUR). Several steps have been implemented to minimize the risk that GRF6021 can transmit an infectious agent, including screening plasma donors for prior exposure, testing the donated plasma, and including manufacturing steps, including heat inactivation (heating to 60ºC for 10 hours), with the capacity to inactivate and/or remove pathogens.

The capacity of the GRF6021 manufacturing process to inactivate and/or remove viruses was evaluated in viral validation studies designed in accordance with the quality standards established by the European Committee for Medicinal Products for Human Use (CHMP) and the US FDA. Studies were performed using relevant viruses or models of human viruses that represent a wide range of physicochemical properties. Human immunodeficiency virus (HIV) type 1 was used as a relevant bloodborne pathogen, bovine viral diarrhea virus was used to model hepatitis C virus (HCV), and pseudorabies virus was used as a surrogate for large, enveloped deoxyribonucleic acid (DNA) viruses to model hepatitis B virus (HBV) for which there is not practicable assay system. Reovirus type 3 was used to model non-enveloped viruses, hepatitis A virus was used as a relevant non-enveloped virus, and porcine parvovirus was used as a surrogate for human parvovirus B19. The clearance capacities for all individual processing steps that achieved at least 1 log10 were combined to determine the overall clearance capacities, which demonstrate that the manufacturing process for GRF6021 has the capacity to remove and/or inactivate a diverse variety of enveloped and non-enveloped virus challenges and thereby provides assurance that the process yields a margin of safety from the risk of transmission of infectious viruses.

GRF6021 is contraindicated in patients with severe anemia, congestive heart failure, or increased blood volume (PI) and these are exclusion criteria in this study. GRF6021 is depleted of the majority of immunogenic proteins during the manufacturing process, and thus is not expected to alter the blood typing characteristics of the recipient and should not sensitize humans to its subsequent administration [redacted]. ABO antigen typing is not required prior to administration. GRF6021 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 [redacted]

Based on the cumulative review [redacted] (PSUR), the production steps taken to increase the safety margin and avoid virus transmissions, and the multiple safety minimization steps implemented in this study, the benefit-risk balance for GRF6021 as an investigative product in PD-MCI and PDD is favorable.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no known reported benefit of administering GRF6021 to patients with PD-MCI or PDD.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to assess the safety and tolerability of GRF6021, a [redacted] human [redacted] fraction administered by IV infusion, in subjects with PD and cognitive impairment. Secondarily, this study aims to assess the effects of GRF6021 on subjects' cognitive and motor function. Exploratory objectives include blood and plasma collection to identify specific biomarkers associated with cognitive and motor changes and/or indicators of PD-MCI and PDD progression. In addition, MRI of the brain will be conducted after the second treatment period in consenting subjects to identify potential therapeutic effects of GRF6021.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This will be a randomized, double-blind, placebo-controlled study conducted at up to 40 sites in the US and ex-

US.

During the screening period (Day -35 through Day -8), subjects will undergo all screening assessments, including a screening MRI and an echocardiogram, and complete two training sessions on the Continuity and Power of Attention, Working Memory, and Episodic Memory on the CDR-CCB. During the Baseline Visit (Day -7 through Day -1), subjects will complete cognitive and motor testing. Subjects will then be randomized in a 2:1 ratio to GRF6021 (Group 1) or placebo (Group 2).

There will be two (2) dosing periods. Each dosing period (Treatment 1, starting at Week 1; and Treatment 2, starting at Week 13) consists of 5 consecutive days ("pulsed dosing") of IV infusions of [redacted] of either GRF6021 or placebo. During each 5-day treatment period, the administration of GRF6021/placebo will occur in a setting with appropriate medical monitoring by adequately trained personnel. The infusions can occur in the inpatient/hospital setting or in an outpatient infusion center or equivalent medical facility. Following a 4-hour post-infusion monitoring period, the subject may return home if medically stable based on the investigator's clinical judgement. Should further monitoring be required, subjects may need to remain at and/or be transferred to an appropriate facility for extended outpatient monitoring and/or inpatient observation.

Safety and tolerability assessments will occur at every visit. Cognitive and motor testing will be performed at Baseline and at periodic interim visits following dosing. Cognitive and motor testing may take up to approximately 2.5 hours. It is preferred that the sequence of tests administered should be consistent for all subjects. Subjects (and/or their trial partners, if applicable) may take breaks between assessments as needed.

In the event of early termination of a subject who has received at least one infusion, the end of study procedures will be performed unless the subject has withdrawn consent. A comprehensive efficacy and safety assessment of all data *in toto* will be conducted at the end of the study.

Subjects will also be invited to participate in an additional MRI obtained at Visit 16 to detect potential changes in brain atrophy, cortical thinning, functional connectivity, and cerebral blood flow after treatment. The MRI procedure, as well as the potential risks and benefits, will be explained to all study participants. Participation in the Visit 16 MRI scan is optional and not required for inclusion in the study.

The overall duration of the study/recruitment period is approximately 24 months from study initiation (i.e., following consent of first subject) to study completion (i.e., last subject, last visit). The subject participation period is approximately 7 months from Screening through End of Study, unless prematurely discontinued.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Primary Endpoint:

- Incidence of TEAEs and SAEs identified by MedDRA PT and grouped by MedDRA SOC.

4.2.2 SECONDARY ENDPOINTS

This study is not powered to detect statistically significant differences in cognitive or motor 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 Efficacy Endpoints:

- Change from baseline in the MoCA (Nasreddine 2005)(Appendix 1).
- Change from baseline in Continuity and Power of Attention, Working Memory, and Episodic Memory on the CDR-CCB (Wesnes 1977, Wesnes 2000).
- Change from baseline in D-KEFS Verbal Fluency (Delis 2001, Delis 2004, Emre 2004).
- Change from baseline in the MDS-UPDRS 1, 2, 3, and total score (Fahn 1987, Movement Disorders Task Force 2003)(Appendix 2).
- Change from baseline in the SE-ADL Scale (Schwab 1968)(Appendix 3).
- Change from baseline in the CISI-PD (Martinez-Martin 2006)(Appendix 4).
- Change from baseline in the PDQ-39 (Peto 1998)(Appendix 5).
- Change from baseline in the GDS-15 (Yesavage 1983)(Appendix 6).
- Change from baseline in the dCDT (Müller 2017).

Secondary Safety Endpoints:

- Change from baseline in clinical laboratory parameters.
- Change from baseline in vital sign measurements.
- Change from baseline in body weight.
- Change from baseline in the S-STS (Sheehan 2014)(Appendix 7).

4.2.3 EXPLORATORY ENDPOINTS

The exploratory endpoints include assessment of changes in composition and distribution of blood-based biomarkers and changes in MRI assessments (in consenting subjects).

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 disease progression. DNA will be extracted from blood samples to explore epigenetic changes.

In addition, brain imaging (MRI) will be conducted in consenting subjects to identify potential therapeutic effects of GRF6021. The following changes from baseline may be evaluated:

- Brain morphometry as measured by MRI.
- Functional connectivity as measured by task-free functional MRI (tf-fMRI), where available.
- Cerebral blood flow assessments as measured by arterial-spin labeling (ASL) MRI, where available.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

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

1. Aged 40-85 years at time of enrollment, inclusive.
2. Diagnosis of clinically established or clinically probable PD according to MDS-PD criteria (Postuma 2015)(Appendix 8) with at least 1 year of PD symptoms.
3. Diagnosis of PD-MCI (Level I, i.e. impairment on a scale of global cognitive abilities validated for

use in PD) or probable or possible PDD according to MDS criteria (Litvan 2012, Emre 2007)(Appendix 9).
4. Score on the MoCA of 13-25, inclusive (Nasreddine 2005)(Appendix 1).
5. Hoehn and Yahr Stages 1-4.
6. If on dopaminergic therapy (e.g., levodopa, dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors, amantadine), must be on stable dosage at least 4 weeks prior to baseline.
7. If on medications for cognition (e.g., rivastigmine, galantamine, donepezil, memantine), must be on stable dosage for at least 8 weeks prior to baseline.
8. If on antidepressant medications, must be on stable dosage for at least 8 weeks prior to baseline.
9. If on clozapine, quetiapine, or pimavanserin, must be on stable dosage for 8 weeks prior to baseline.
10. Renal function as defined by estimated glomerular filtration rate (eGFR) $\geq$ 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 $\geq$ 55% on trans-thoracic echocardiogram.
12. Modified Hachinski Ischemic Scale (MHIS) score of 4 or less (Rosen 1980).
13. Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening (Visit 1), Visit 3 (prior to study treatment), and Visit 11 (prior to study treatment). WOCBP must agree to use highly effective contraception prior to study entry (Clinical Trial Facilitation Group 2014). A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately.
14. Have a dedicated, reliable, and competent trial partner (e.g., caregiver or family member) who has frequent contact with the subject (defined as approximately 10 hours per week) who is willing to provide support to the subject to ensure compliance with study requirements.
15. The subject (with support of a trial partner) must be able to follow the study procedures, receive the treatment in the established timeframe, and continue during the follow-up interval.
16. The subject and trial partner must be able to understand the procedures and agree to complete the required assessments.
17. Provide a signed and dated informed consent form (either the subject or the subject's legal representative) in accordance with local regulations and/or IRB/IEC guidelines.

5.2 EXCLUSION CRITERIA

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

1. History of blood coagulation disorders or hypercoagulability.
2. Current use of anticoagulant therapy (e.g., heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors). Use of antiplatelet drugs (e.g., aspirin or clopidogrel) is acceptable.
3. Prior hypersensitivity reaction to any human blood product or any IV infusion; any clinically significant known drug allergy.
4. Treatment with any human blood product, including transfusions and IV immunoglobulin, during the 6 months prior to screening.
5. History of immunoglobulin A (IgA) or haptoglobin deficiency, stroke, anaphylaxis, or thromboembolic complications of IV immunoglobulins.
6. Heart disease, as evidenced by myocardial infarction, unstable, new onset or severe angina, or congestive heart failure (New York Heart Association Class II, III, or IV) in the 6 months prior to

dosing.

7. Presence of signs and/or symptoms of hypervolemia or volume overload, including but not limited to pulmonary edema and/or clinically significant peripheral edema.
8. Patients with recent or planned surgery sensitive to blood volume changes including cardiopulmonary bypass technique.
9. Poorly controlled high blood pressure (BP) (systolic BP of 160 mmHg or higher and/or diastolic BP of 100 mmHg or higher) despite treatment during the 3 months prior to dosing, or treatment refractory high BP, defined as treatment requiring 3 or more antihypertensives from different classes.
10. Supine hypertension (systolic BP of 160 mmHg or higher and/or diastolic BP of > 90 mmHg when in a supine position).
11. Symptomatic orthostatic hypotension (drop in systolic BP of 20 mmHg or higher, or 30 mmHg in the presence of essential hypertension, and/or a drop in diastolic BP of 10 mmHg or higher, after 3 minutes of standing despite adequate hydration); symptoms can include, but are not limited to, lightheadedness, visual blurring, dizziness, and/or syncope.
12. History of Torsades de Pointes dysrhythmia.
13. Clinically significant abnormalities on screening electrocardiogram (ECG) including QTc intervals (using Fridericia's correction formula) of ≥ 450 ms in men and ≥ 470 ms in women.
14. Clinically significant abnormalities on echocardiogram.
15. Hypocalcemia of any kind, including secondary to absorption syndromes related to gastric bypass surgery.
16. Current, active liver disease or known hepatic or biliary abnormalities.
17. Uncontrolled diabetes defined as hemoglobin A1c (HbA1c) > 7.5%.
18. Clinically significant abnormalities in complete blood count, complete metabolic panel, serum albumin, serum lipids, coagulation, or levels of thiamine, pyridoxine, cobalamin, and thyroid stimulating hormone.
19. Positive urine drug screen. The presence of opioids, benzodiazepines, and/or amphetamines in the urine drug screen may be allowed if these are prescribed and the dose stable for at least 8 weeks prior to screening.
20. Hemoglobin < 10 g/dL in women and < 11 g/dL in men.
21. Urine protein-to-creatinine ratio (UPCR) of > 1.5 grams of protein per gram of creatinine.
22. Inadequate venous access to allow IV drug delivery or multiple blood draws.
23. 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.
24. If on deep brain stimulation (DBS), DBS surgery within 12 months of screening and/or a change in DBS settings within 12 weeks of screening. DBS settings must not be changed at any point during the subject's participation in the trial.
25. Presence of a pacemaker or any other implant that would be an MRI contraindication, including DBS if not MRI compatible.
26. More than 2 lacunar strokes or other clinically-relevant imaging abnormality on screening MRI.
27. Any other condition and/or situation that the investigator believes may interfere with the safety of the subject, study conduct, 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 90 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).

The expected length of participation in the study of approximately 7 months is not expected to be challenging to subjects or their trial partners. During the study, financial support for meal and miscellaneous expenses will be available, 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 both the subject and their trial partner in maintaining study visit compliance. A description of the study will be included in local clinical trial databases, as required.

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 adverse event (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 or the subject's legally authorized representative (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.
- Pregnancy.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

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

Approximately 90 subjects (GRF6021: 60; placebo: 30) will be enrolled in the study with the intent of obtaining ~68 evaluable subjects. Subjects who discontinue or are unblinded prior to 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 4-6 weeks of their last visit. The primary reason for study discontinuation will be documented on the case report form (CRF).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor and/or their representatives arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. 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 as assessed by the Sponsor's Program Physician.
- 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 AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

GRF6021 is manufactured by Grifols Therapeutics, Inc. (Clayton, North Carolina, US). The placebo control agent will be 0.9% sodium chloride injection (saline). The study agent and placebo will be supplied to the sites directly from a depot.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

GRF6021 is prepared from large pools of human source plasma [redacted]. GRF6021 is iso-oncotic with normal human plasma and isotonic. Each 100 mL of GRF6021 contains [redacted] selected plasma proteins buffered [redacted]. The plasma proteins consist of approximately [redacted] The approximate concentrations of the main electrolytes in GRF6021 are: sodium [redacted]

Both GRF6021 and saline placebo will be supplied in [redacted] glass vials. Both GRF6021 and the placebo will be labeled for investigational use according to the local regulatory requirements for clinical studies.

6.1.3 PRODUCT STORAGE AND STABILITY

The study agent and placebo should be stored at room temperature not exceeding [redacted] 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. Vials that are cracked or have been previously entered or

damaged should not be used, as this may have allowed the entry of microorganisms. Neither the study agent nor the placebo contain preservatives.

6.1.4 PREPARATION

All vials/containers of study agent/placebo should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GRF6021 should not be mixed with protein hydrolysates or solutions containing alcohol. The study agent and placebo should be prepared in accordance with the Infusion Administration Manual (Appendix 11).

6.1.5 DOSING AND ADMINISTRATION

The study agent/placebo will be infused in accordance with the Infusion Administration Manual (Appendix 11). The purpose of the Infusion Administration Manual is to promote safe administration of the study agent/placebo; maintain appropriate blinding of staff and study subjects; and provide guidance on the management of potential risks, including but not limited to hypersensitivity reactions. The Manual includes provisions for masking the study agent/placebo and concealing the IV setup from view of blinded staff and study subjects.

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.

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

A physician or physician-designated equivalent (e.g., physician assistant, nurse practitioner) should be available (i.e., on site or in the immediate vicinity) during the entire infusion and ~ 4-hour post infusion monitoring period. S/he should be qualified by training and/or experience in acute cardiac life support, or equivalent. Each site must have appropriate equipment and/or medications to treat emergencies (e.g., a crash cart or equivalent, epinephrine).

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 GRF6021 (Group 1: active dosing in both treatment periods) or placebo (Group 2: placebo dosing in both treatment periods). Subjects will receive one infusion of [redacted] per day for 5 consecutive days at Weeks 1 and 13.

6.1.8 DURATION OF THERAPY

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

All subjects will receive 5 consecutive days of therapy at the beginning of Weeks 1 and 13. Thus, the cumulative duration of therapy for all subjects will be 10 exposure days. The duration of therapy for a subject to be considered evaluable is 5 exposure days (see Section 10.3 Analysis Datasets).

6.2 STUDY AGENT ACCOUNTABILITY

Under the supervision of the Principal Investigator, the unblinded study pharmacist or other qualified personnel is responsible for ensuring adequate accountability of all used and unused study agent and placebo control agent. This includes acknowledgment of receipt of each shipment of study agent/placebo (quantity and condition) within the interactive response technology (IRT) system, 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 unblinded Infusion Nurse administering the study agent/placebo. Drug accountability will be monitored by an unblinded Clinical Research Associate (CRA).

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

All unused, partially used, and used study agent/placebo should be kept securely at the site until otherwise instructed. All unused, partially used, and used containers of study agent/placebo at the site should not be returned or destroyed without prior written approval from the Sponsor and must be performed in accordance with the site's drug disposal/destruction policy, or equivalent. The clinical study monitor will evaluate the site's procedure(s) for study drug disposal/destruction in order to ensure that it complies with study requirements. A copy of the site's drug disposal policy should be maintained or referenced in the investigator's study file.

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:

- S-STS
- Assessment of PD, including Hoehn and Yahr
- MHIS
- MoCA
- Medical history
- Demographics
- Review of medications
- Vital signs (including seated, supine, and standing BP)

- Physical examination
- 12-Lead ECG
- Screening Safety Lab Panel and pregnancy test for WOCBP
- Echocardiogram*
- Screening MRI*

***Note**: it is recommended, but not required, that the echocardiogram and screening MRI be performed after all other screening procedures have been completed, and the subject meets all criteria for inclusion into the study. The echocardiogram and screening MRI may be completed in any order.

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

7.1.1.1.1 Sheehan-Suicidality Tracking Scale

The S-STS was developed to provide a brief but efficient instrument for use in assessing change in suicidal ideation and behavior while providing a comprehensive description of suicidal ideation and behavior. The primary goals in the design of the S-STS were for the scale to be: 1) short and inexpensive; 2) simple, clear, and easy to administer or self-rate; 3) highly sensitive (i.e., able to detect a high proportion of patients who are suicidal); 4) specific (i.e., able to screen out those who are not suicidal); 5) sensitive to change in suicidal ideation and behavior; 6) compatible with the regulatory categories of assessment for suicidal ideation and behavior; 7) useful in clinical as well as research settings; 8) useful in detecting an efficacy signal for anti-suicidal medications; and 9) capable of use in pediatric and geriatric settings (Sheehan 2014). The standard version of the S-STS (Appendix 7) is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0-4) ranging from "not at all" (0) to "extremely" (4). It also assesses the frequency of key phenomena and the overall time spent in suicidality.

7.1.1.1.2 Assessment of Parkinson's Disease and Cognitive Impairment

The diagnosis of PD will be verified using MDS-PD criteria (Postuma 2015)(Appendix 8). The prerequisite to apply the MDS-PD criteria is the presence of parkinsonism, defined as bradykinesia, in combination with either rest tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors (Postuma 2015). The stage of the disease will be classified using the Hoehn and Yahr scale.

Subjects will also be evaluated for PD-MCI (Level I) and PDD based on MDS criteria (Litvan 2012, Emre 2007). PD-MCI is a syndrome defined by clinical, cognitive, and functional deficits (Litvan 2012)(Appendix 9). The MDS criteria for MCI were developed to address issues relatively specific to PD. The criteria were also designed to be consistent with the MDS proposed PDD criteria (Emre 2007)(Appendix 10) and thereby allow differentiation between MCI and dementia in patients with PD.

Global cognition (a requisite for the diagnosis of PD-MCI Level I) will be assessed using the MoCA (Nasreddine 2005)(Appendix 1)(see Section 7.1.1.3.1). The score range for PD-MCI is 19-25.2, and for PDD it is 11.4-21. While the score ranges overlap, differentiation between the conditions is dependent upon associated functional impairment (Doerflinger 2012). Per the inclusion criteria for this study, subjects must have a MoCA score of 13-25, inclusive (see Section 5.1 Inclusion Criteria).

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 (an example of the full assessment for this study can be downloaded using the following link: Modified Hachinski Ischemia Scale). The scale is completed by the physician based on clinical information obtained from diagnostic testing 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 this trial.

7.1.1.1.4 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject and the subject's trial partner during screening. The medical history should focus on recent history, with an emphasis on the history of cognitive and motor symptoms related to PD. 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 PD, AD, or other dementias or neurological disorders
- Social history (e.g. exercise, smoking, alcohol, illegal substances) and current living situation
- Cause of parental death (if not living)
- Prior imaging, CSF assessments, or other relevant diagnostic test results, including genetics

7.1.1.1.5 Demographics

Demographic information such as the subject's education level, ethnicity, and race will be collected by interview with the subject and the subject's trial partner at screening.

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 and any dose changes in the last 3 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 BP (mmHg), heart rate (beats per minute [bpm]), respiration rate (breaths per minute), and body temperature. Vital signs will be measured after the subject has been seated for 5 minutes.

In addition, at screening and at every visit during both treatment periods (including follow-up Visits 8 and 16), orthostatic (supine and standing) BP will also be measured. Orthostatics are collected as follows:

- After a 10-minute rest in a supine position, supine BP should be measured while the subject is lying down.

- The subject should then stand for 3 minutes, if physically able or can be held in standing position with assistance, and the BP is taken again.

At Visits 3-7 and Visits 11-15, seated, supine, and standing BP should be measured prior to infusion start and at the end of each infusion (~[redacted] post infusion start). Refer to the Infusion Administration Manual for further guidance (Appendix 11).

7.1.1.1.8 Physical Examination

A full physical examination will be performed to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic and lymphatic systems. The neurological exam will include cranial nerves (visual fields, fundoscopic exam, pupillary light reflex, extraocular muscles, facial sensation and symmetry, palate and tongue, and head turning and shoulder shrug); motor function including muscle strength, tone, bulk, and abnormal movements; reflexes (biceps, triceps, knees, ankles, and plantar); coordination (finger-to-nose, heel-knee-shin); sensory function (light touch and pinprick); and gait. Height will be measured at screening and weight will be monitored during the trial.

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, or abnormal and clinically significant. 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 percentage is ≥ 55% (Gebhard 2012).

7.1.1.1.11 Screening Safety Lab Panel

Biological samples will be analyzed at screening. Samples that remain after study screening is complete may be stored at the central lab in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. Blood will be drawn by a qualified medical provider, and urine specimens will also be collected. The timing and frequency for specimen collection and laboratory evaluations to be performed are further described in Section 15 Schedule of Events.

The labs that will be tested at screening include:

- Serum pregnancy test in WOCBP only
- Hematology: complete blood count (CBC), neutrophils, total lymphocytes, monocytes, eosinophils, basophils, iron, vitamin B12 (cobalamin)
- Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, eGFR, protein (total), albumin, IgA, bilirubin [total, indirect, direct], aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), amylase, lipase, lactate dehydrogenase (LDH), creatinine kinase (CK), glucose, HbA1C, phosphate,

magnesium, cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein [LDL], haptoglobin)
- Coagulation: (prothrombin Time INR, prothrombin time (PTT), activated partial thromboplastin time (APTT)
- Immunochemistry: thyroid-stimulating hormone (TSH ultrasensitive), hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), Human immunodeficiency virus antibody (HIV Ab, HIV-1/HIV-2), brain natriuretic peptide (BNP)
- Urinalysis: specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, hemoglobin, leucocyte esterase, nitrite, white blood cells (WBC), red blood cells (RBC), hyaline casts, granular casts, waxy casts, WBC casts, epithelial cells, bacteria, color, sample aspect
- Urine chemistry: protein, microalbumin, creatinine, sodium, potassium, microalbumin/creatinine, protein/creatinine ratio, sodium/creatinine ratio, potassium/creatinine ratio
- Urine drug screen: cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, opiates, phencyclidine, propoxyphene, methadone
- Other testing: direct antiglobulin test, ionized calcium, vitamin B6 (pyridoxine), vitamin B1 (thiamine), and C1 inhibitor*

*Note: Results of the C1 inhibitor test are not required for eligibility, and thus need not be available prior to randomization and dosing.

7.1.1.1.12 Magnetic Resonance Imaging

The screening MRI is required and will assess for lacunar strokes and other abnormalities (see Section 5.2 Exclusion Criteria).

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
- Weight
- S-STS
- 12-Lead ECGs
- Targeted physical exams
- End of Study (or Early Termination) physical exam
- Blood draw and urine collection for laboratory evaluations

7.1.1.2.1 Review of Adverse Events

AEs will be reviewed, documented, and reported as required at each visit, beginning at Screening. 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 (see the Schedule of Events) with additional measurements during each treatment period. During infusions, vital signs will be collected according to the Infusion Administration Manual (Appendix 11) by the blinded Outcomes Assessor.

7.1.1.2.4 Sheehan-Suicidality Tracking Scale

Refer to Section 7.1.1.1.1 for a description of the S-STS.

7.1.1.2.5 12-Lead ECG

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

7.1.1.2.6 Targeted Physical Exams

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 in Section 7.3.

7.1.1.2.7 Physical Exam

Refer to Section 7.1.1.1.8 for a description of the Physical Exam. The physical exam, including measurements of height and weight, will be performed at screening. The physical exam and weight measurement will be repeated at End of Study (or early termination).

7.1.1.2.8 Blood and Urine Collection for Laboratory Evaluations

Subjects will have blood and urine specimens collected for clinical evaluation and safety monitoring. Samples that remain may be stored at the central lab in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. The timing and frequency of labs for clinical evaluation and safety monitoring are provided below and specified in Section 15 Schedule of Events.

7.1.1.2.8.1 Pregnancy Testing

For WOCBP, serum and/or urine pregnancy testing should be conducted at Visits 3 and 11 with results available prior to infusion start.

7.1.1.2.8.2 Pre-infusion Safety Labs

Pre-infusion Safety Labs will be performed at each site's local laboratory or via an i-STAT Handheld Blood Analyzer. When sending samples to the local laboratory, samples for the Pre-Infusion Safety Labs should be collected prior to infusion start on Visits 3, 4, 6, 11, 12, and 14. This is to allow sufficient turn-around time for local laboratories to receive, process, and report results prior to the subject's next infusion. 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 4, 5, 7, 12, 13, and 15.

Pre-infusion Safety Labs include:

- Sodium
- Potassium
- Ionized calcium
- BUN
- Creatinine
- Hematocrit
- Hemoglobin
- Platelets*

*Please note that the i-STAT Chem 8+ test cartridges can perform all Pre-Infusion Safety Labs with the exception of the platelet count. The platelets lab will need to be obtained and assessed via the site's local laboratory prior to the next day's infusion.

7.1.1.2.8.3 Comprehensive Labs

Samples for Comprehensive Labs will be collected prior to infusion start on Visits 6 and 14 as well as during follow-up on Visits 8, 9, 16, and 17. These include:

- Hematology: CBC, neutrophils, total lymphocytes, monocytes, eosinophils, basophils, and iron
- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, eGFR, protein (total), albumin, IgA, bilirubin (total, indirect, direct), AST, ALT, GGT, alkaline phosphatase, amylase, lipase, LDH, CK, glucose, phosphate, magnesium, cholesterol, triglycerides, HDL, LDL
- Coagulation: prothrombin time/international normalized ratio PT/INR, PTT, APTT
- Urinalysis: specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, hemoglobin, leucocyte esterase, nitrite, WBC, RBC, hyaline casts, granular casts, waxy casts, WBC casts, epithelial cells, bacteria, color, sample aspect
- Urine chemistry: microalbumin, creatinine, sodium, potassium, microalbumin/creatinine, sodium/creatinine ratio, potassium/creatinine ratio
- Ionized calcium

7.1.1.2.8.4 Exit Safety Lab Panel

The labs that will be tested as part of the Exit Safety Lab Panel include:

- Hematology: CBC, neutrophils, total lymphocytes, monocytes, eosinophils, basophils, and iron
- Chemistry: sodium, potassium, chloride, bicarbonate, BUN [urea], creatinine, eGFR, protein (total), albumin, IgA, bilirubin (total, indirect, direct), AST, ALT, GGT, alkaline phosphatase, amylase, lipase, LDH, CK, glucose, phosphate, magnesium, cholesterol, triglycerides, HDL, LDL
- Coagulation: PT/INR, PTT, APTT)
- Immunochemistry: HBsAg, HCV Ab, HIV Ab (HIV-1/HIV-2)
- Urinalysis: specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, hemoglobin, leucocyte esterase, nitrite, WBC, RBC, hyaline casts, granular casts, waxy casts, WBC casts, epithelial cells, bacteria, color, sample aspect
- Urine chemistry: microalbumin, creatinine, sodium, potassium, microalbumin/creatinine, sodium/creatinine ratio, potassium/creatinine ratio
- Other testing: direct antiglobulin test, ionized calcium

7.1.1.3 Procedures to Assess Efficacy

Procedures to assess efficacy include cognitive and motor function testing. Information regarding the timing and frequency of these procedures is provided in Section 15 Schedule of Events.

Cognitive and motor function will be assessed using validated instruments including computer-based assessments and devices. All testing will be performed by qualified evaluators who have undergone standardized rater training and certification, as appropriate. The same evaluator should be used for the duration of each subject's participation unless a change in rater is unavoidable. When possible, all cognitive and motor testing should be performed when the subject is in the "ON" state and at approximately the same time after the last dose of each subject's PD medication(s). The preferred order of behavioral and cognitive testing during visits with multiple assessments is as follows:

1. MoCA
2. CDR-CCB
3. D-KEFS
4. dCDT
5. MDS-UPDRS 1/2/3
6. SE-ADL
7. CISI-PD
8. PDQ-39
9. GDS-15

Descriptions of each neuropsychological and motor function assessment are provided below.

7.1.1.3.1 Montreal Cognitive Assessment

The MoCA (Nasreddine 2005)(Appendix 1) is a commonly used screening test easily administered by nonspecialist staff. It assesses the domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points with a score of 26 or more considered normal.

7.1.1.3.2 Cognitive Drug Research Computerized Cognition Battery

The CDR-CCB is the most widely used automated cognitive function assessment system in clinical research worldwide (Wesnes 1977, Wesnes 2000, Wesnes 2013). It was developed to assess both enhancement and impairment of human cognitive function. There are several core tests available. The core tests have remained constant over the last three decades while being steadily supplemented with others as required. In this study, the following will be measured using the CDR-CCB system: Continuity and Power of Attention, Working Memory, and Episodic Memory. Subjects will have two CDR-CCB training sessions during the screening period to ensure adequate performance at the Baseline Visit (Visit 2).

7.1.1.3.3 Delis-Kaplan Executive Function Verbal Fluency

The D-KEFS Verbal Fluency test is used for assessment of executive function, which is one of the main cognitive domains impaired in PD (Delis 2001, Delis 2004, Emre 2004) (an example of the full assessment for this study can be downloaded using the following link: Delis-Kaplan Executive Function Verbal Fluency). The D-KEFS Verbal Fluency Test has three conditions: Letter Fluency, Category Fluency, and Category Switching. In the Letter Fluency condition, subjects are asked to say as many words that start with a particular letter (e.g., F, A, S) as possible over three trials of 60 seconds. The Category Fluency condition requires subjects to say as many words belonging to a particular semantic category (e.g., animals, tools) as they can in two trials of 60 seconds. In the final condition, subjects are asked to switch between words belonging to two different semantic categories in one trial of 60 seconds (e.g., fruits and furniture). The test requires subjects to exercise mental flexibility, avoid perseverative responses, and engage in an effective and

quick mental search. Importantly, this test provides auxiliary information regarding verbal fluency to the CDR-CCB, which does not include assessments in this critical cognitive domain.

7.1.1.3.4 Digital Clock Drawing Test

The conventional clock drawing test is a rapid and inexpensive screening tool for detection of moderate and severe dementia. Modern digitizing devices offer the opportunity to measure subtle changes of visuo-constructive demands and executive functions that may be used as a fast and easy-to-perform screening instrument for the early detection of cognitive impairment (Müller 2017). The pen-like dCDT device gathers the x-y coordinates that describe the movement of the stylus as it changes its position during the assessment. It also assesses when the stylus or writing device is not exerting pressure on the writing surface (i.e., in-air movements performed by the hand while transitioning from one stroke to the next), making it a more sensitive tool than the conventional clock test with increased diagnostic accuracy (Müller 2017).

7.1.1.3.5 Movement Disorder Society's Unified Parkinson's Disease Rating Scale

The MDS-UPDRS (Fahn 1987, Movement Disorder Society Task Force 2003)(Appendix 2) was developed in an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The MDS-UPDRS has four components (Part 1, Mentation, Behavior, and Mood; Part 2, Activities of Daily Living; Part 3, Motor; Part 4, Complications). Parts 2 and 3 are the most widely used for both clinical and research purposes. One of the core advantages of the UPDRS is that it was developed as a compound scale to capture multiple aspects of PD. It assesses both motor disability (Part 2) and motor impairment (Part 3). In addition, Part 1 addresses mental dysfunction and mood. The rating for each item is from 0 (normal) to 4 (severe). The total score for each Part is obtained from the sum of the corresponding item scores. For this study, Parts 1-3 will be completed, and the estimated time for completion is 20-30 minutes.

7.1.1.3.6 Schwab and England Activities of Daily Living Scale

The SE-ADL evaluates patients' perceptions of global functional capacity and dependence (Schwab 1968)(Appendix 3). Scoring is expressed in terms of percentage, in 10 steps from 100 to 0 (100%, normal status; 0%, bedridden with vegetative dysfunction), so that the lower the score, the worse the functional status. The rating is made by a trained clinician.

7.1.1.3.7 Clinical Impression of Severity Index – Parkinson's Disease

The CISI-PD is a severity index formed by four items (motor signs, disability, motor complications, and cognitive status), rated 0 (not at all) to 6 (very severe or completely disabled) (Martinez-Martin 2006)(Appendix 4). A total score is calculated by summing the item scores. The scale is completed by a clinician. It only takes a few minutes to complete once the state of the subject is known.

7.1.1.3.8 Parkinson's Disease Quality of Life Questionnaire-39

The PDQ-39 is a self-administered questionnaire of 39 questions relating to 8 key areas of health and daily activities, including both motor and non-motor symptoms (Peto 1998)(Appendix 5). The eight dimensions include: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. It is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms.

7.1.1.3.9 Geriatric Depression Scale-15

The GDS-15 is a site-administered questionnaire of depression in older adults that will be read to the subject, and the answers will be recorded by the rater. The GDS-15 is a shortened form of a 30-item questionnaire in which participants are asked to respond by answering yes or no in reference to how they felt over the past week (Yesavage 1983)(Appendix 6). Questions from the long form GDS which had the highest correlation with depressive symptoms in validation studies were selected for the short version which is more easily used by mildly to moderately demented patients who have short attention spans and/or feel easily fatigued. Of the 15 items, 10 indicate the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, 13) indicate depression when answered negatively. It takes about 5 to 7 minutes to complete.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g. whole blood, serum, urine) will be collected for laboratory evaluations in accordance with Section 7.1.1.1.11 Screening Safety Lab Panel, Section 7.1.1.2.8 Blood and Urine Collection for Lab Evaluations, and the Schedule of Events. . Clinical sample processing and laboratory evaluations will be conducted by a central lab's registered and certified Clinical Laboratory Improvement Amendments (CLIA) facilities. Pre-infusion laboratory evaluations will be conducted at the clinical site. Refer to the study's laboratory manual for complete information regarding all laboratory evaluations to be performed, sample collection procedures, and related requirements.

The investigator is responsible for determining and documenting whether out of range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the CRF and followed until determined to be stable or resolved, unless the subject is lost to follow up. Once resolved, the appropriate CRF page(s) will be updated.

7.2.2 OTHER TESTS OR PROCEDURES

7.2.2.1 Apolipoprotein E (ApoE) Genotype Testing

ApoE genotype is a known risk factor for neurodegeneration and dementia 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, neuroimaging, and other exploratory measures. DNA for ApoE analysis will be obtained from a blood serum sample collected during Visit 3 prior to the subject's first infusion.

7.2.2.2 Magnetic Resonance Imaging

MRI will be used to evaluate subjects' eligibility for inclusion in the study at screening. Structural images will be interpreted by a central reader at screening and any exclusionary findings will be reported. Where available, functional imaging will also be acquired to assess for functional connectivity as measured by tf-fMRI and cerebral blood flow as measured by ASL MRI. In consenting subjects, an additional MRI at Visit 16 will assess for changes in brain atrophy as measured by MRI, functional connectivity as measured by tf-fMRI, and cerebral blood flow as measured ASL MRI. During the MRI, the subject will be asked to lie on a narrow bed in a large tunnel while images are captured by the MRI machine. Participation in the screening

MRI is required, while participation in the additional MRI at Visit 16 is optional and not required for inclusion in the study.

7.2.2.3 Proteomic and Genetic Biobanking

Blood samples will be collected for biobanking during Visits 3 and 11 (prior to infusion), all follow-up visits (Visits 8-10, 16-18), and End of Study (Visit 19) or Early Termination Visit. For more 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 GRF6021 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, it is hoped that key proteins that are drivers of cognitive function and/or indicators of disease progression can be identified. Blood samples will be collected for analysis of emergent genetic markers of disease. By understanding the composition and function of plasma samples from the trial, the goal is to identify the biomarkers relevant to further optimizing treatment in PD, PD-MCI, and PDD. 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

To ensure follow-up visits occur at approximately the same intervals following both treatment periods, visit windows should be calculated as follows:

- Visit windows for Visits 1-10 should be calculated relative to Day 1.
- Visit windows for Visits 11-19 should be calculated relative to Day 85 ±7 (i.e., first day of dosing for Treatment Period 2).

Study visit procedures are listed in the recommended order in which they should be completed.

7.3.1 SCREENING

Visit 1, Screening Visit (Day -35 to -8)

- □ Informed consent of subject (or the subject's legally authorized representative) as documented by a signed and dated informed consent form must be obtained prior to any study-related assessments.
- □ Administer the S-STS.
- □ Administer the MoCA.
- □ Administer the MHIS.
- □ Verify diagnosis of PD according to MDS criteria, including Hoehn and Yahr stage.
- □ Verify diagnosis of PD-MCI or PDD according to the consensus criteria.
- □ Obtain medical history, including medical records and test results to support PD, PD-MCI, or PDD diagnosis if available.

- □ Collect demographic information.
- □ Review subject's current and prior medications.
- □ Review and provide the subject (and subject's trial partner) with a list of permitted and prohibited medications.
- □ Collect vital signs (including sitting, supine, and standing BP), height, and weight.
- □ Perform a complete physical and neurological exam.
- □ Perform 12-lead ECG.
- □ Collect blood and urine samples required for the Screening Safety Lab Panel.
- □ Perform transthoracic echocardiogram.
- □ Complete screening MRI scan.
- □ Verify that the subject fulfills all of the inclusion criteria and none of the exclusion criteria.

During the screening period, subjects should complete two training sessions with the CDR-CCB system prior to baseline testing at Visit 2. The two training sessions may be scheduled at any time during the screening window.

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

7.3.2 RANDOMIZATION

Subjects will be randomized after eligibility has been confirmed (including MRI and echocardiography results).

7.3.3 BASELINE

Visit 2, Baseline (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 commencing cognitive and motor testing and that the subject is in the ON state. PD medications should be taken at the standard intervals for each subject and testing should be scheduled to facilitate the subject being in the ON state.
- □ It is preferred that cognitive and motor function testing is performed in the following order (breaks are permitted between assessments as needed):
    1. CDR-CCB
    2. D-KEFS
    3. dCDT
    4. MDS-UPDRS 1/2/3
    5. SE-ADL
    6. CISI-PD
    7. PDQ-39
    8. GDS-15

7.3.4 TREATMENT

There are two treatment periods scheduled during the trial. During each treatment period, subjects will receive a total of 5 infusions of their assigned treatment (i.e., either GRF6021 or placebo). It is anticipated that sites will infuse subjects with 5 doses over 5 consecutive days. A "grace day" is allowed in the event of unanticipated safety or health concerns during each treatment period.

Visits 3-7 (Days 1-5) and 11-15 (Day 85*-89):
*Day 85 has a ± 7-day window

- □ Perform the following procedures prior to administering study treatment:
  - Review AEs and concomitant medications.
  - Obtain blood and urine samples for Comprehensive Labs (**Visits 6 and 14 Only**); fasting samples preferred.
  - Obtain samples for proteomics/epigenetics/biobanking; fasting samples preferred (**Visits 3 and 11 Only**).
  - Obtain sample for ApoE testing (**Visit 3 Only**).
  - For WOCBP Only: perform pregnancy testing and review results (**Visits 3 and 11 Only**).
  - Obtain Pre-infusion Safety Lab samples and assess results **prior to the next day's infusion** (**Visits 3, 4, 6, 11, 12, and 14 Only**). When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion (Visits 4, 5, 7, 12, 13, and 15).
  - Perform targeted physical exam (i.e. auscultation of heart and lungs and assessment of peripheral edema) (**Visits 3, 5, 7, 11, 13, and 15 Only**).
  - Measure body weight in kilograms.
  - Perform 12-lead ECG (**Visit 7, 11, and 15 Only**).
  - Administer the S-STS (**Visit 3 Only**).
  - Collect vital signs (including sitting, supine, and standing BP).
- □ Administer study treatment and perform safety assessments per the Infusion Administration Manual (Appendix 11).
- □ Administer the S-STS after the subject's final infusion (**Visit 7 Only**).

7.3.5 FOLLOW-UP

Visits 8 and 16 (Day 6 + 3 Days and Day 90 + 7 Days):

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs (including sitting, supine, and standing BP) and subject's weight in kilograms.
  - Blood and urine samples for Comprehensive Labs (fasting samples preferred).
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to commencing cognitive and motor testing and that the subject is in the ON state. PD medications should be taken at the standard intervals for each subject and testing should be scheduled to facilitate the subject being in the ON state.
- □ It is preferred that cognitive and motor function testing is performed in the following order (breaks are permitted between assessments as needed):
  1. CDR-CCB
  2. D-KEFS
  3. dCDT
  4. MDS-UPDRS 1/2/3
- □ Consenting subjects will undergo an additional MRI scan (**Visit 16 + 7 days Only**).

Note: Visit 16 (Day 90) may be split to allow for sufficient time to complete all required procedures. Review AEs and concomitant medications during split visits, as applicable.

Visit 9 (Days 28 ± 7 Days) and Visit 17 (Day 112 ± 7 Days):

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs.
  - Blood and urine samples for Comprehensive Labs (fasting samples preferred).
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to commencing cognitive and motor testing and that the subject is in the ON state. PD medications should be taken at the standard intervals for each subject and testing should be scheduled to facilitate the subject being in the ON state.
- □ It is preferred that cognitive and motor function testing is performed in the following order(breaks are permitted between assessments as needed):
  1. MoCA
  2. CDR-CCB
  3. MDS-UPDRS 1/2/3
  4. PDQ-39 (**Visit 9 Only**)

Visit 10 (Day 56 ± 7 Days) and Visit 18 (Day 140 ± 7 Days):

- □ Review AEs and concomitant medications.
- □ Collect the following:
  - Vital signs.
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to commencing cognitive and motor testing and that the subject is in the ON state. PD medications should be taken at the standard intervals for each subject and testing should be scheduled to facilitate the subject being in the ON state.
- □ It is preferred that cognitive and motor function testing be performed in the following order (breaks are permitted between assessments as needed):
  1. CDR-CCB
  2. D-KEFS
  3. dCDT
  4. MDS-UPDRS 1/2/3
  5. SE-ADL (**Visit 10 Only**)
  6. CISI-PD (**Visit 10 Only**)
  7. PDQ-39
  8. GDS-15

7.3.6 FINAL STUDY VISIT

Visit 19, End of Study (Day 168 ± 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 Lab Panel (fasting samples preferred).
  - Samples for proteomics/epigenetics/biobanking (fasting samples preferred).
- □ Perform the physical exam.
- □ Ensure the subject has had an opportunity to eat a meal or snack prior to commencing cognitive and motor testing and that the subject is in the ON state. PD medications should be taken at the standard intervals for each subject and testing should be scheduled to facilitate the subject being in the ON state.
- □ It is preferred that cognitive and motor function testing be performed in the following order (breaks are permitted between assessments as needed):
  1. CDR-CCB
  2. MDS-UPDRS 1/2/3
  3. SE-ADL
  4. CISI-PD
  5. PDQ-39

7.3.7 EARLY TERMINATION

If a subject has received at least one infusion but is terminated or terminates from the study early, the site should try to perform all assessments scheduled at the End of Study Visit. In addition, if a subject withdraws from the study early but is willing to undergo the additional MRI scan, this can be obtained as long as the subject received at least two infusions of GRF6021/placebo.

7.3.8 SCHEDULE OF EVENTS TABLE

A tabular summary of all procedures that will be accomplished at each study visit can be found in Section 15 Schedule of Events.

7.4 CONCOMITANT MEDICATIONS

All concomitant prescription medications taken during study participation will be recorded on the CRFs. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following concomitant medications, treatments, and procedures 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.
- If on DBS, a change in DBS settings at any point during the subject's participation in the trial.

8 ASSESSMENT OF SAFETY

Assessment of safety will be conducted by blinded study personnel except in extraordinary circumstances where knowledge of whether GRF6021 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 pharmaceutical (investigational) product even if the event does not necessarily have a

causal relationship with this treatment.

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

An AE does include any:

- Exacerbation of a pre-existing illness.
- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study (unless it can be demonstrated by medical record review that the onset of the event preceded the date/time of Informed Consent).
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Symptoms associated with disease not previously reported by the subject.
- 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 PD, PD-MCI, and PDD 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)

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.

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; hospitalization for participating in this study is not considered an AE.
   - Complications that occur during hospitalization are AEs; if a complication prolongs hospitalization, the event is an SAE.
   - "Inpatient" hospitalization means the subject has been formally admitted to a hospital for medical reasons that may or may not be overnight; it does not include presentation at a casualty or emergency room unless the event meets the definition of an Important Medical Event (in the opinion of the Investigator or Sponsor).

d. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
   - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions; this definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Results in a congenital anomaly in the offspring of a subject who received drug.

f. Results in an Important Medical Event. Important Medical Events are events that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition; examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
   - Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

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

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

8.2.2 RELATIONSHIP TO STUDY AGENT

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

- Unrelated: another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the study agent; or a causal relationship is considered biologically implausible.
- Possibly Related: There is a clinically plausible time sequence between onset of the adverse event and administration of the study agent, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the study agent is one or several biologically plausible adverse event causes.
- Definitely Related: The adverse event is clearly related to use of the study agent.

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

8.2.3 EXPECTEDNESS

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

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically

mentioned as occurring with the particular drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the Investigator's Brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes (FDA 2012).

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

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

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

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

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

8.3.1 POST-STUDY 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 AE, each AE will be encoded according to the MedDRA.

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

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

8.4.2.1 Timeframes for Reporting SAEs

The Sponsor will notify the FDA as well as the competent authority of each participating country, including the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Therapeutic Goods Administration (TGA), 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 eCRF 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/IEC should submit all applicable events, unanticipated problems, and safety reports to the site's local IRB/IEC, if applicable. All safety reporting deviations should also be submitted to their local IRB/IEC, if applicable.

8.4.3 ADVERSE EVENTS OF SPECIAL INTEREST

Please note that for an event to be classified as an AE of special interest (AESI), the event should meet the definition of an Adverse Event per Section 8.1.1. Thus, if the investigator considers the event to be an AE, and it meets one or more of the criteria listed below, then the event should be classified as an AESI and

reported according to the timeframe specified.

The following will be considered AEs of special interest (AESI) if they qualify as AEs per the preceding paragraph:

- Clinically significant peripheral edema or pulmonary edema.
- Clinically significant systolic BP >160 but <170 mmHg over consecutive timepoints spanning 30 or more minutes.
- Clinically significant systolic BP <90 or >170 mmHg at a single timepoint.
- Clinically significant diastolic BP >100 but <110 mmHg over consecutive timepoints spanning 30 or more minutes.
- Clinically significant diastolic BP <60 or >110 at a single timepoint.
- A change of >25% from baseline in systolic and/or diastolic BP.
- Reduced kidney function (eGFR < 45 mL/min/1.73 m^2).
- Suspected transmission of blood-borne infectious agents.

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

Note: Blood pressures meeting the parameters above that are not considered adverse events need not be reported within the 48-hour window. Rather, these will be considered "blood pressures of special interest" and analyzed separately.

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

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

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (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, FDA, ANSM, and TGA 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(s) 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(s), and available active investigators participating in the trial. Such a meeting may also include external consultants with expertise relevant to the specific safety signal(s) detected. 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(s) in concert with the site investigators. There will be no formal Data Safety Monitoring Board (DSMB) established.

GRF6021 is [redacted] the primary objective of this study is to determine the safety and tolerability of GRF6021 in individuals with Parkinson's disease, ongoing monitoring of cumulative safety data will be conducted in a systematic manner to ensure that any safety signals that may impact the overall benefit/risk ratio in this specific population will be detected, assessed, and any necessary action taken. Cumulative safety data (e.g., AE listings, vital sign plots, safety laboratory values, ECGs, physical exam results) will be reviewed by the CRO's Medical Monitor(s) and by the Sponsor's Program Physician throughout the study. If either physician detects any safety trends of concern, a Safety Evaluation Meeting will be convened as described in Section 8.5 to assess the new safety signal(s).

The Sponsor's Program Physician or designee is the final authority for safety oversight in the study.

9 CLINICAL MONITORING

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

- Monitoring for this study will be performed by the study CRO in accordance with the Clinical Monitoring Plan (CMP).
- A mix of on-site and centralized monitoring will be performed to ensure the safety of clinical subjects and the accuracy and completeness of study data.
- The Sponsor will be provided with copies of monitoring reports per the timelines specified within the CMP.
- Details of clinical site monitoring 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 in accordance with a quality oversight plan or equivalent to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL 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, the study 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 any amount of the study agent.
- **Evaluable Dataset:** all subjects who receive at least 5 of the 10 planned doses, have a diagnosis of PD and cognitive impairment per the inclusion criteria, and complete through Visit 8.
  - **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.

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

- For endpoints that are continuous in nature:
  - Number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive summary
  - For inferential statistics:
    - If the Normality assumption is met, Paired t-test, or Analysis of Covariance (ANCOVA) using the baseline value as a covariate will be used
    - If the Normality assumption is not met, a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used
- For endpoints that are categorical in nature:
  - Frequency counts and percentages will be presented as descriptive summary
  - Chi-square test or Logit model will be used for inferential statistics

Subject disposition (e.g., the number of subjects randomized, completed, and discontinued) will be summarized, and medical history data will be listed. Prior and concomitant medications taken from screening and during the study will be categorized by World Health Organization 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 the reported adverse events will be presented by group after the verbatim terms have been coded to PTs and SOCs using the MedDRA Version 21.0 coding dictionary. The summaries will include severity and attribution to the study agent. Multiple reports of the same AE by the same subject will be counted only once at the highest severity and strongest attribution to the study agent.

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

Additional details are presented in Section 10.4.4.

10.4.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

The study is not powered to detect significant changes in cognition, motor function, activities of daily living, 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. Appropriate paired sample tests (paired t-test or Wilcoxon Signed Rank tests) may be conducted to evaluate within-subject changes from baseline, using a two-tailed α-level of 0.05. Between-group differences may be assessed by One-way ANCOVA or its nonparametric equivalent test.

10.4.4 ANALYSIS OF THE SECONDARY SAFETY ENDPOINTS

Actual values and changes from baseline in clinical laboratory measurements, vital signs, body weight, and S-STS scores will also 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 BP, heart rate, respiratory rate, body temperature, body weight, S-STS score) 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 the study visit schedule, visit procedures, infusions and subject retention will be assessed. Subject adherence may vary across the different groups offering another feasibility measurement as would a comparison of the number of subjects who complete two series of 5 pulsed doses to subjects who complete only the first series. Reasons for study discontinuation will be compared across groups and across other subgroups of subjects, as appropriate.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

See Section 10.4.1.

10.4.7 PLANNED INTERIM ANALYSES

An unblinded interim analysis of the safety endpoints, including the primary endpoint and secondary safety endpoints, was conducted when approximately 20 subjects completed Visit 8 (end of first dosing period). The requirement that subjects remain on an inpatient unit during each treatment period was included in the

protocol to enable safety monitoring during dosing. The Sponsor reviewed the safety data from this interim analysis to assess whether the need for inpatient stays during dosing should remain a requirement. The unblinded safety analysis was performed following a data-cut on 09JUN2019 and included 32 subjects. Based on the results of the interim safety analysis and feedback from FDA, the inpatient requirement is no longer required as reflected in this version of the Protocol.

An unblinded interim analysis of the MoCA, CDR-CCB, and MDS-UPDRS3 secondary efficacy endpoints is planned when approximately 40 subjects have completed Visit 8 (end of first dosing period). As the study is not powered for efficacy and no decisions will be made regarding stopping the trial, statistical testing will be performed at the 0.05 level using two-tailed tests on both the Evaluable and Per Protocol datasets. To minimize potential bias of the remaining efficacy and safety data, only aggregated summary tables will be provided.

Safety will be monitored on an ongoing basis. If a Safety Evaluation Meeting is triggered (see Section 8.5), an ad hoc interim safety analysis will be performed. If such an ad hoc safety interim analysis is conducted, the 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

A total of approximately 90 subjects will be randomized in a 2:1 ratio to active treatment (approximately 60 subjects) or placebo (approximately 30 subjects), with the intent of obtaining ~68 evaluable subjects who have received at least 5 doses and completed the study through Visit 8. Subjects who discontinue prior to completing Visit 8 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced.

The study is not statistically powered to detect differences in measures of clinical efficacy or biomarker endpoints. To evaluate potential safety signals, the statistical approximation described by Hanley (aka the “Rule of Threes” in which the upper bound of the 95% confidence interval for the frequency of an unreported AE is at most 3/n % where n represents the number of subjects who received active GRF6021 in the study) will be used. In a sample of 60 subjects, the upper bound of the 95% confidence interval for the frequency of an unobserved

AE is approximately 5%. In addition, the proposed sample size may be sufficient to identify trends in efficacy endpoints that will be used to determine the appropriate sample size for subsequent studies.

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 in a 2:1 ratio (active: placebo), with a mixed block size. In addition to mixed block size, to reduce the potential impact of sex on study outcomes, the randomization will be stratified by sex; this is to assure a balanced distribution of evaluable male and female subjects in both treatment groups. The randomization will be web-based and centralized. The randomization codes will be generated by a statistician that 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, vials containing [redacted] of the study agent or vials containing 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 study agent or placebo. To ensure that Outcomes Assessors, raters, and other study personnel, as well as subjects and trial partners 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. These measures include, but are not limited to, covering the vial and drip chamber with an opaque black bag or equivalent; using a curtain, drape, or equivalent to shield the infusion administration setup as applicable; concealing vials/containers of study agent/placebo during transport; and returning used containers of the study agent/placebo to the unblinded pharmacist, or other qualified site personnel responsible for drug accountability, promptly at the end of the Infusion Period.

Communication between the blinded Outcomes Assessor and the unblinded Infusion Nurse will be restricted 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.

Finally, to avoid potential unblinding based on subject [redacted] levels, [redacted] lab results (aside from those tested at screening) will remain blinded until the conclusion of the study. Unblinding of [redacted] lab results would only occur for emergent safety reasons.

Aside from designated personnel whose sole responsibility necessitates access to unblinding information (e.g., the unblinded CRA whose sole responsibility is to ensure study agent/placebo accountability, the unblinded clinical supply manager, etc.), the Sponsor and their representatives will be blinded with respect to subjects' treatment allocation through database lock unless breaking the blind is required for safety reasons (see 10.6.3 Breaking the Study Blind/Subject Code). The unblinded interim analyses will be performed by unblinded statisticians who are not members of the protocol study team. The data will be provided in aggregate fashion so the difference between study agent and placebo is compared but individual treatment allocation remains blinded.

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, their trial partners, or study personnel (e.g. investigators, medical providers, cognitive/motor 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 can be broken for safety reasons if the information is required for the management of SAEs or severe AEs. Only the Investigator can obtain the treatment allocation for their subject through the IRT. Before breaking the blind, every attempt should be made to discuss the need with the Sponsor's Program Physician, or designee. When some degree of unblinding must occur, this should be limited to the fewest number of people on a need-to-know basis.

Any noted intentional or unintentional breaking of the blind should be documented and reported to the Sponsor's Study Team Lead. If unintentional unblinding occurs during the study, root cause analysis will be evaluated, and corrective actions implemented.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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/ ETHICS COMMITTEE

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

All changes to the consent form will be IRB/IEC 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/IEC for approval prior to implementation.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT FORMS

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject or healthcare power of attorney or equivalent legal representative, and written documentation of informed consent is required prior to 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 undertaking any study-related procedures.

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

The investigator or designee must utilize an IRB/IEC-approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and/or their legally authorized representative and the person obtaining consent. A copy of the signed consent form 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 subjects who provide consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to the study subject. Once a number is assigned to a subject, that number will remain with that study subject and will not be reused.

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

12.4 PARTICIPANT AND 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 data will be released to any unauthorized third party without prior written approval of the Sponsor.

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

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations. Study subjects' research data, which is for purposes of statistical analysis and scientific reporting, that is transmitted to the Sponsor, CRO, and/or IRB/IEC will not include contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study number. This unique study number should be recorded on non-local lab samples, requisitions, and any documents submitted to the CRO, Sponsor, and/or IRB/IEC. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected.

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 IRB/IECs, 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 specimens with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects may choose whether the Sponsor can store and use samples for further research.

An individual subject can choose to withdraw consent to have biological specimens stored for future research. Samples from subjects who provide consent for future research purposes are collected, stored, and code-linked to the subject until the end of the study at which time the samples are deidentified and may no longer be connected to the individual subject. Throughout the study, at any time, the subject and/or the subject's LAR is able to withdraw consent, and the individual samples can be retrieved and destroyed. However, after the samples have

been deidentified, this may not be possible.

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

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site 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 eCRFs 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 enrolled in the study, the eCRF must be completed in a timely manner. The investigator will review and approve the eCRF for each study subject after all data have been entered, the eCRFs 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 eCRF. 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/IEC), 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, eCRF, IRB/IEC 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

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

These practices are consistent with ICH E6:

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

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

Major Protocol Deviation: a departure 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.
Examples of Major Protocol Deviations include, but are not limited to:

- Failure to obtain informed consent (i.e., no evidence of informed consent)
- Enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population
- A drug dispensing or dosing error that could have affected the safety of the subject
- Failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial

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. Observations categorized as Major may include those situations where there is a pattern of deviation, numerous Minor observations, or other significant deviation.

Minor Protocol Deviation: a departure 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. Examples of Minor Protocol Deviations include, but are not limited to:

- A protocol visit date outside of a visit window
- An isolated case of a missed or incomplete study procedure (e.g., laboratory test)
- An isolated incident of a missed or incomplete study evaluation (e.g., examination)

Minor Protocol deviations would not generally preclude subject data from the *per protocol* analysis population. Observations categorized as Minor may become Major if not corrected.

All deviations will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will serve 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/IEC per their guidelines. The site PI/study staff are responsible for knowing and adhering to their IRB/IEC 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 (including patent protection), 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[b]					Follow-up			Treatment[b,c]					Follow-up			End of Study/Early Termination Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Infusion Number			1	2	3	4	5				6	7	8	9	10				
Day	Day -35 to -8	Day -7 to -1	1	2	3	4	5	6 + 3 days	28 ± 7 days	56 ± 7 days	85 ± 7 days	86	87	88	89	90 + 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days
Week			1						4	8	13						16	20	24
Informed Consent/Optional MRI Consent	X																		
Medical History	X																		
Demographics	X																		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X																		X
Height	X																		
Weight	X		X[1]	X[1]	X[1]	X[1]	X[1]	X			X[1]	X[1]	X[1]	X[1]	X[1]	X			X
Supine and Standing Blood Pressure[d]	X		X[1,3]	X[1,3]	X[1,3]	X[1,3]	X[1,3]	X			X[1,3]	X[1,3]	X[1,3]	X[1,3]	X[1,3]	X			
12-lead ECG	X						X[1]				X[1]				X[1]				
Echocardiogram	X*																		
MRI	X*															X[j]			
Randomization		X[4]																	
Targeted Physical Exam			X[1]		X[1]		X[1]				X[1]		X[1]		X[1]				
Concomitant Medication Review	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X

	Screening[a]	Baseline Visit	Treatment[b]					Follow-up			Treatment[b,c]					Follow-up			End of Study/Early Termination Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Infusion Number			1	2	3	4	5				6	7	8	9	10				
Day	Day -35 to -8	Day -7 to -1	1	2	3	4	5	6 + 3 days	28 ± 7 days	56 ± 7 days	85 ± 7 days	86	87	88	89	90 + 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days
Week			1						4	8	13						16	20	24
Adverse Event Review		X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X
GRF6021/Placebo Infusion			**X**	**X**	**X**	**X**	**X**				**X**	**X**	**X**	**X**	**X**				
Blood/Urine Sampling																			
Screening Safety Lab Panel[e]	X																		
Exit Safety Lab Panel[f]																			X
Pre-Infusion Safety Labs (performed onsite)[g]			X[1]	X[1]		X[1]					X[1]	X[1]		X[1]					
Pregnancy Testing[h]	X		X[1]								X[1]								
Comprehensive Labs[i]						X[1]		X	X					X[1]		X	X		
Proteomics/Epigenetics/ Biobanking			X[1]					X	X	X	X[1]					X	X	X	X
ApoE Genotype Testing			X[1]																
Cognitive and Motor Testing																			
MHIS	X																		
S-STS	X		X[1]				X[2]												
MoCA	X								X								X		
Hoehn and Yahr	X																		
CDR-CCB	X[k]	X						X	X	X						X	X	X	X
D-KEFS		X						X		X						X		X	

	Screening[a]	Baseline Visit	Treatment[b]					Follow-up			Treatment[b,c]					Follow-up			End of Study/Early Termination Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Infusion Number			1	2	3	4	5				6	7	8	9	10				
Day	Day -35 to -8	Day -7 to -1	1	2	3	4	5	6 + 3 days	28 ± 7 days	56 ± 7 days	85 ± 7 days	86	87	88	89	90 + 7 days	112 ± 7 days	140 ± 7 days	168 ± 7 days
Week			1						4	8	13						16	20	24
dCDT		X						X		X						X		X	
MDS-UPDRS 1/2/3		X						X	X	X						X	X	X	X
SE-ADL		X								X									X
CISI-PD		X								X									X
PDQ-39		X							X	X								X	X
GDS-15		X								X								X	

Notes:

*It is recommended, but not required, that the echocardiogram and screening MRI be performed after all other screening criteria have been met. The echocardiogram and screening MRI may be performed in any order.

X^1: To be performed prior to infusion start.

X^2: To be performed after infusion.

X^3: To be performed post-infusion (approximately [redacted] after infusion start).

X^4: If shipping of study agent to the study site will be required, subjects should be randomized at least 5 days prior to treatment start to ensure study agent availability.

a: The Screening Visit may be split to allow for sufficient time to complete all procedures. AEs and concomitant medications should be reviewed during split visits, as applicable.

b: The treatment window is 6 days in the event of a "grace" day.

c: The visit window for Visit 11 is Day 85 ±7 days. Visits 12-15 should follow consecutively. The windows for Visits 16, 17, 18, and 19 should be calculated relative to the day of the subject's first infusion during Treatment Period 2 (i.e., Day 85 ±7 days).

d: Blood pressure (BP) should be taken after the subject has been lying down for at least 10 minutes (supine). The subject should then stand for 3 minutes, and the BP should be taken again.

e: Screening labs are listed in Section 7.1.1.1.11.

	f: Exit Safety labs are listed in Section 7.1.1.2.8.4.
	g: Samples for local pre-infusion labs should be collected and results interpreted PRIOR to the following day's infusion start. When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion for assessment prior to infusion start. Required pre-infusion labs are listed in Section 7.1.1.2.8.2.
	h: Serum pregnancy test required at screening. Serum and/or urine pregnancy test may be used at subsequent timepoints. Results from pregnancy tests conducted at Visits 3 and 11 must be available prior to dosing.
	i: Comprehensive labs are listed in Section 7.1.1.2.8.3.
	j: The second, additional MRI will be performed in consenting subjects only. Task-free functional MRI and arterial-spin labeling MRI will be performed only at a subset of sites. Visit 16 may be split to allow for sufficient time to complete all of the procedures. AEs and concomitant medications should be reviewed during split visits, as applicable.
	k: The CDR-CCB will require 2 training sessions prior to the baseline assessment. These training sessions can be performed at any time during the screening period.

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VIV-2016-R014. Young plasma and [redacted] effects on behavior and survival in aging NODScid mice.

VIV-2016-R020. Effects of [redacted] on cognition.

VIV-2016-R021. Effects of young and aged human plasma and [redacted] on histopathological endpoints in aged NSG mice.

VIV-2016-R024. Effects of human plasma and [redacted] on cognition, behavior and histopathologic endpoints in aged NSG mice.

VIV-2017-R025. Effects of [redacted] on cognition in aged NSG mice (2).

VIV-2017-R036. Effects of [redacted] on histopathological endpoints in aged NSG mice.

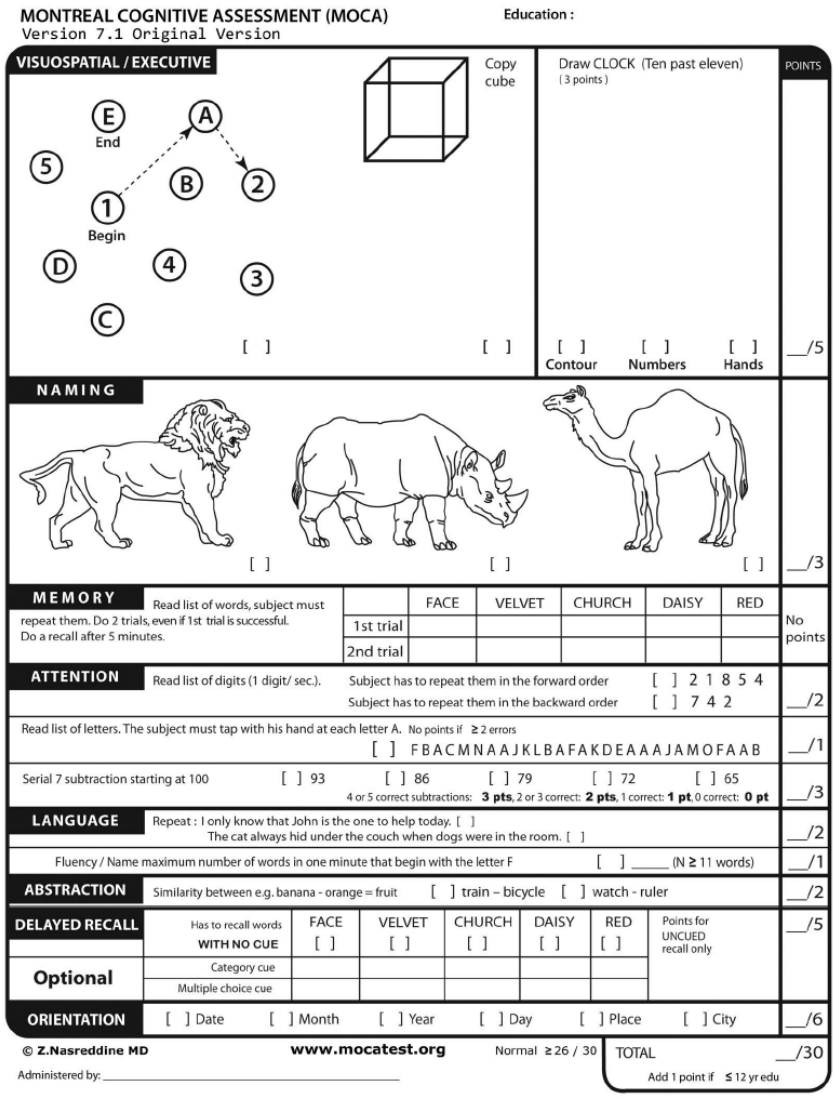
VIV-2017-R038. Effects of [redacted] on cognition, behavior and histopathological endpoints in aged C57BL/6J mice.

VIV-2018-R069. Effects of [redacted] on cognition and neurogenesis in aged, C57BL/6J mice.

17 APPENDICES

Appendix 1. Montreal Cognitive Assessment

The MoCA (Nasreddine 2005) is a commonly used screening test easily administered by nonspecialist staff. It assesses the domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points with a score of 26 or more considered normal. For additional information, the assessment can be downloaded using the following link: Montreal Cognitive Assessment (V7.1).



Appendix 2. Movement Disorder Society's Unified Parkinson's Disease Rating Scale

The MDS-UPDRS (Fahn 1987, Movement Disorder Society Task Force 2003) was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The MDS-UPDRS has four components (Part 1, Mentation, Behavior, and Mood; Part 2, Activities of Daily Living; Part 3, Motor; Part IV, Complications). For the current study, only Parts 1, 2, 3 and total score will be utilized. The rating for each item is from 0 (normal) to 4 (severe). The total score for each Part is obtained from the sum of the corresponding item scores. The estimated time for completion of Parts 1-3 is 20-30 minutes. For additional information, the full assessment can be downloaded using the following link: MDS-UPDRS.

MDS-UPDRS

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,
Consultant: Stephanie Shaftman, Nancy LaPelle

Contact person: Christopher G. Goetz, MD
Rush University Medical Center
1725 W. Harrison Street, Suite 755
Chicago, IL USA 60612

Telephone 312-942-8016
Email: cgoetz@rush.edu

July 1, 2008

Appendix 3. Schwab and England Activities of Daily Living

The SE-ADL evaluates patients' perception of global functional capacity and dependence (Schwab 1968). Scoring is expressed in terms of percentage, in 10 steps from 100 to 0 (100%, normal status; 0%, bedridden with vegetative dysfunction), so that the lower the score, the worse the functional status. The rating is made by an observer/professional. For additional information, the full assessment can be downloaded using the following link: Schwab and England Activities of Daily Living Scale.

Schwab & England Activities of Daily Living scale

100%	Completely independent. Able to do all chores w/o slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. May take twice as long. Beginning to be aware of difficulty.
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowing.
70%	Not completely independent. More difficulty with some chores. X 3-4 as long in some. May spend a large part of the day with chores.
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors, some impossible.
50%	More dependent. Help with 1/2 of chores. Difficulty with everything.
40%	Very dependant. Can assist with all chores but few alone.
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.
20%	Nothing alone. Can do some slight help with some chores. Severe invalid.
10%	Totally dependant, helpless. Complete invalid.
0%	Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Appendix 4. Clinical Impression of Severity Index – Parkinson's Disease

The CISI-PD (V2) is a severity index formed by four items (motor signs, disability, motor complications and cognitive status), rated 0 (not at all) to six (very severe or severely disabled). A total score is calculated by summing the item scores. The scale is completed by a clinician at the time of assessment. It takes a few seconds to complete once the state of the patient is known (Martinez-Martin 2006). For additional information, the full assessment can be downloaded using the following link: Clinical Impression of Severity Index: Parkinson's Disease (V2).

Clinical Impression of Severity Index (CISI-PD). Version 2*

Motor Signs

0. Normal
1. Very mild
2. Mild
3. Mild to moderate
4. Moderate
5. Severe
6. Very severe

Disability

0. Not at all
1. Minimal slowness and/ or clumsiness
2. Slowness and/ or clumsiness. No limitations
3. Limitation for demanding activities
   Does not need help, or rarely, for basic activities of daily living (ADL)
4. Limitation to perform basic ADL Help is required for some basic ADL
5. Great limitation to perform basic ADL Help is required for most or all basic ADL
6. Severely disabled; helpless
   Complete assistance needed

Motor Complications (dyskinesia and fluctuations)

0. Not at all
1. Very mild
2. Mild
3. Mild to moderate
4. Moderate
5. Severe
6. Very severe

Cognitive Status

0. Normal
1. Minimal cognitive problems
2. Mild cognitive problems. No limitations
3. Mild to moderate cognitive problems. Limitations for demanding activities. Does not need help, or rarely, for basic activities
4. Moderate cognitive problems. Limitations for basic activities. Help is needed for some basic activities
5. Severe cognitive problems. Many limitations for basic activities. Help is needed for most or all basic ADL
6. Severely disabled; helpless. Complete and continued assistance needed

Rater Initials: _____ _____ _____ Date: _____

Appendix 5. Parkinson's Disease Quality of Life Questionnaire-39

The PDQ-39 is a self-administered questionnaire of 39 questions relating to 8 key areas of health and daily activities, including both motor and non-motor symptoms (Peto 1998). The eight dimensions include: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. It is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms. For additional information, the full assessment can be downloaded using the following link: Parkinson's Disease Quality of Life Questionnaire-39.

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Due to having Parkinson's disease, how often during the last month have you... Please check one box for each question

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	had difficulty doing the leisure activities you would like to do?	☐	☐	☐	☐	☐
2.	had difficulty looking after your home, for example, housework, cooking or yardwork?	☐	☐	☐	☐	☐
3.	had difficulty carrying grocery bags?	☐	☐	☐	☐	☐
4.	had problems walking half a mile?	☐	☐	☐	☐	☐
5.	had problems walking 100 yards (approximately 1 block)?	☐	☐	☐	☐	☐
6.	had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	had difficulty getting around in public places?	☐	☐	☐	☐	☐
8.	needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please verify that you have *checked one box for each question* before going on to the next page.

Appendix 6. Geriatric Depression Scale-15

The GDS-15 is shortened form of a 30-item questionnaire in which participants are asked to respond by answering yes or no in reference to how they felt over the past week (Yesavage 1983). The GDS-S should be given orally. A clear YES or NO answer is required for each question. If necessary, repeat the question but do not accept a qualified answer from the test-taker. Cross off either yes or no for each question. Depressive answers (errors) are circled on the form and are bolded below. Count up 1 for each depressive answer (error). The final score is the tally of the number of depressive answers with the following scores indicating depression: 0-4 No depression, 5-10 Suggestive of a mild depression, and 11 + Suggestive of severe depression. For additional information, the full assessment can be downloaded using the following link: Geriatric Depression Scale-15.

Geriatric Depression Scale – 15-Item Short Form

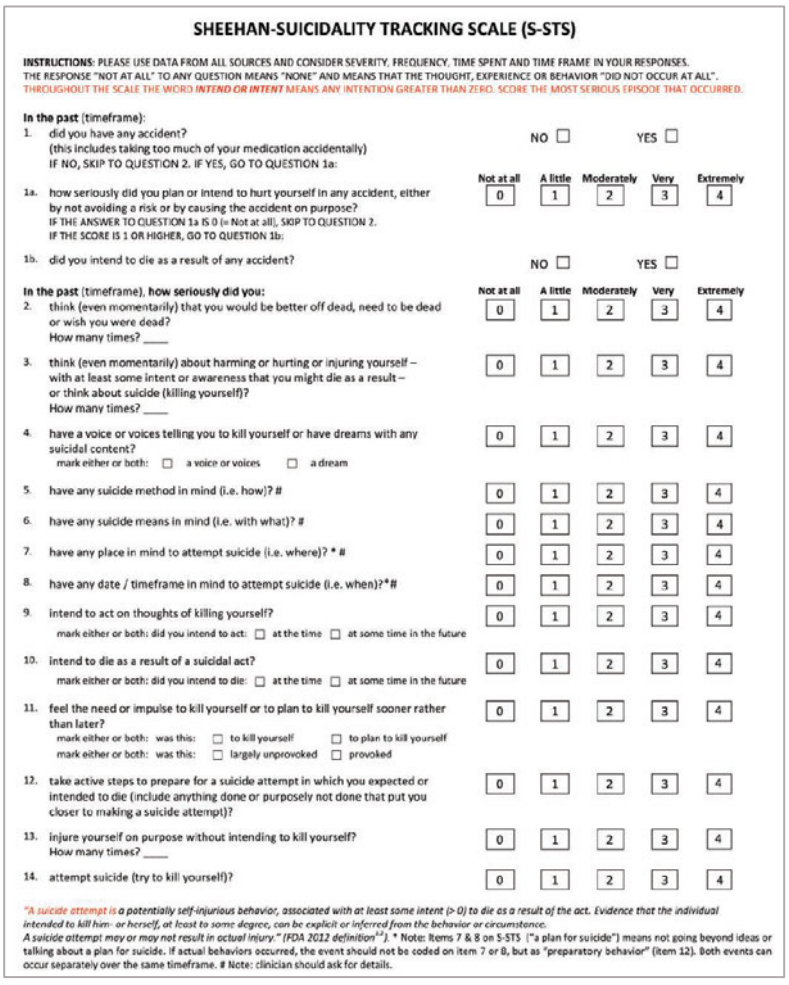
Choose the best answer for how you have felt over the past week:

1.	Are you basically satisfied with your life?	YES	**NO**
2.	Have you dropped many of your activities and interests?	**YES**	NO
3.	Do you feel that your life is empty?	**YES**	NO
4.	Do you often get bored?	**YES**	NO
5.	Are you in good spirits most of the time?	YES	**NO**
6.	Are you afraid that something bad is going to happen to you?	**YES**	NO
7.	Do you feel happy most of the time?	YES	**NO**
8.	Do you often feel helpless?	**YES**	NO
9.	Do you prefer to stay at home, rather than going out and doing new things?	**YES**	NO
10.	Do you feel that you have more problems with memory than most?	**YES**	NO
11.	Do you think it is wonderful to be alive now?	YES	**NO**
12.	Do you feel pretty worthless the way you are now?	**YES**	NO
13.	Do you feel full of energy?	YES	**NO**
14.	Do you feel that your situation is hopeless?	**YES**	NO
15.	Do you think that most people are better off than you are?	**YES**	NO

Geriatric Depression Scale Total Score (number of bold answers circled) ☐

Appendix 7. Sheehan Suicidality Tracking Scale

The S-STS was developed to provide a brief but efficient instrument for use in assessing change in suicidal ideation and behavior while providing a comprehensive description of suicidal ideation and behavior (Sheehan 2014). The primary goals in the design of the S-STS were for the scale to be: 1) short and inexpensive; 2) simple, clear, and easy to administer or self-rate; 3) highly sensitive (i.e., able to detect a high proportion of patients who are suicidal); 4) specific (i.e., able to screen out those who are not suicidal); 5) sensitive to change in suicidal ideation and behavior; 6) compatible with the regulatory categories of assessment for suicidal ideation and behavior; 7) useful in clinical as well as research settings; 8) useful in detecting an efficacy signal for anti-suicidal medications; and 9) capable of use in pediatric and geriatric settings. The standard version of the S-STS is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0-4) ranging from "not at all" (0) to "extremely" (4). It also assesses the frequency of key phenomena and the overall time spent in suicidality. For additional information, the full assessment can be downloaded using the following link: Sheehan Suicidality Tracking Scale.



SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS)

INSTRUCTIONS: PLEASE USE DATA FROM ALL SOURCES AND CONSIDER SEVERITY, FREQUENCY, TIME SPENT AND TIME FRAME IN YOUR RESPONSES. THE RESPONSE "NOT AT ALL" TO ANY QUESTION MEANS "NONE" AND MEANS THAT THE THOUGHT, EXPERIENCE OR BEHAVIOR "DID NOT OCCUR AT ALL". THROUGHOUT THE SCALE THE WORD ***INTEND OR INTENT*** MEANS ANY INTENTION GREATER THAN ZERO. SCORE THE MOST SERIOUS EPISODE THAT OCCURRED.

In the past (timeframe):

1. did you have any accident? (this includes taking too much of your medication accidentally) IF NO, SKIP TO QUESTION 2. IF YES, GO TO QUESTION 1a: NO ☐ YES ☐

	Not at all	A little	Moderately	Very	Extremely
1a. how seriously did you plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose? IF THE ANSWER TO QUESTION 1a IS 0 (= Not at all), SKIP TO QUESTION 2. IF THE SCORE IS 1 OR HIGHER, GO TO QUESTION 1b:	0	1	2	3	4

1b. did you intend to die as a result of any accident? NO ☐ YES ☐

In the past (timeframe), **how seriously did you:**	Not at all	A little	Moderately	Very	Extremely
2. think (even momentarily) that you would be better off dead, need to be dead or wish you were dead? How many times? ___	0	1	2	3	4
3. think (even momentarily) about harming or hurting or injuring yourself – with at least some intent or awareness that you might die as a result – or think about suicide (killing yourself)? How many times? ___	0	1	2	3	4
4. have a voice or voices telling you to kill yourself or have dreams with any suicidal content? mark either or both: ☐ a voice or voices ☐ a dream	0	1	2	3	4
5. have any suicide method in mind (i.e. how)? #	0	1	2	3	4
6. have any suicide means in mind (i.e. with what)? #	0	1	2	3	4
7. have any place in mind to attempt suicide (i.e. where)? * #	0	1	2	3	4
8. have any date / timeframe in mind to attempt suicide (i.e. when)?*#	0	1	2	3	4
9. intend to act on thoughts of killing yourself? mark either or both: did you intend to act: ☐ at the time ☐ at some time in the future	0	1	2	3	4
10. intend to die as a result of a suicidal act? mark either or both: did you intend to die: ☐ at the time ☐ at some time in the future	0	1	2	3	4
11. feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? mark either or both: was this: ☐ to kill yourself ☐ to plan to kill yourself mark either or both: was this: ☐ largely unprovoked ☐ provoked	0	1	2	3	4
12. take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)?	0	1	2	3	4
13. injure yourself on purpose without intending to kill yourself? How many times? ___	0	1	2	3	4
14. attempt suicide (try to kill yourself)?	0	1	2	3	4

"A suicide attempt is a potentially self-injurious behavior, associated with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury." (FDA 2012 definition[1,2]). * Note: Items 7 & 8 on S-STS ("a plan for suicide") means not going beyond ideas or talking about a plan for suicide. If actual behaviors occurred, the event should not be coded on item 7 or 8, but as "preparatory behavior" (item 12). Both events can occur separately over the same timeframe. # Note: clinician should ask for details.

Appendix 8. Movement Disorder Society's Parkinson's Disease Criteria

MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established** PD requires:
1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable** PD requires:
1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
☐ 2. Presence of levodopa-induced dyskinesia
☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:
☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags
☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
☐ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*	Yes ☐	No ☐
2. Are any absolute exclusion criteria present? If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*	Yes ☐	No ☐
3. Number of red flags present ____		
4. Number of supportive criteria present ____		
5. Are there at least 2 supportive criteria *and* no red flags? If yes, patient meets criteira for **clinically established PD**. *If no:*	Yes ☐	No ☐
6. Are there more than 2 red flags? If "yes," probable PD *cannot* be diagnosed. *If no:*	Yes ☐	No ☐
7. Is the number of red flags equal to, or less than, the number of supportive criteria? If yes, patient meets criteria for **probable PD**	Yes ☐	No ☐

Provided for use in clinical trial documentation in Postuma 2015.

Appendix 9. Criteria for Parkinson's Disease with Mild Cognitive Impairment

Criteria for the Diagnosis of PD-MCI

I. Inclusion criteria

- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria[20]
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, *or* observed by the clinician
- Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III)
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria

- Diagnosis of PD dementia based on MDS Task Force proposed criteria[18]
- Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III. Specific guidelines for PD-MCI level I and level II categories

A. Level I (abbreviated assessment)

- Impairment on a scale of global cognitive abilities validated for use in PD[a] *or*
- Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)

B. Level II (comprehensive assessment)

- Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)[b]
- Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
- Impairment on neuropsychological tests may be demonstrated by:
  - Performance approximately 1 to 2 SDs below appropriate norms *or*
  - Significant decline demonstrated on serial cognitive testing *or*
  - Significant decline from estimated premorbid levels

IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)[c]

- PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired *or*
- PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

[a] See Table 2. Examples of scales of global cognitive abilities validated in PD.

[b] See Table 3. Examples of neuropsychological tests for the five cognitive domains.

[c] Subtype classifications are applicable only to those PD-MCI who have had at least two tests within each of the five cognitive domains administered.

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Appendix 10. Parkinson's Disease with Dementia Criteria

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  Acute confusion due to
  a. Systemic diseases or abnormalities
  b. Drug intoxication
  Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Criteria for the diagnosis of probable and possible PD-D

Probable PD-D

A. Core features: Both must be present
B. Associated clinical features:
   - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
   - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis
C. None of the group III features present
D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present
B. Associated clinical features:
   - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
   - Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present
D. None of the group IV features present

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Appendix 11. Infusion Administration Manual

1. PURPOSE

The purpose of this Infusion Administration Manual is to guide site staff in administering study drug (GRF6021 or placebo) and maintaining blinding of staff and study subjects. As applicable, sites should follow their own standard operating procedures (SOPs) and processes for intravenous (IV) infusions and the insertion, management, and removal of IV catheters that will be used for the administration of study drug while at the same time adhering to study-specific requirements pertaining to the administration of the study drug.

2. STUDY DRUG

The active study drug is GRF6021, a purified [redacted] fraction prepared from large pools of human sourced plasma meeting all specifications [redacted]. Each 100 mL of GRF6021 contains [redacted] of selected plasma proteins [redacted]. The plasma proteins consist of approximately [redacted]. The solution is iso-oncotic and isotonic with normal human plasma. The approximate concentrations of significant electrolytes are: [redacted]. GRF6021 is clear and [redacted] and must be administered intravenously. [redacted]

The placebo control agent will be 0.9% sodium chloride injection (saline).

Both active and placebo (hereafter referred to as the "study drug") are supplied in [redacted] glass vials, and a volume of [redacted] will be administered on each infusion day.

3. GENERAL INFORMATION

- GRF6021 is contraindicated in subjects with anemia, increased blood volume, or congestive heart failure, and in subjects on cardiopulmonary bypass. Note: ejection fraction as measured with echocardiography should be performed at screening to determine eligibility before dosing occurs.
- During the dosing periods, Pre-infusion Safety Labs will be drawn locally before the infusion starts. These labs must be reviewed before dosing the follow day. The following blood labs must be documented as within normal limits: sodium, potassium, ionized calcium, blood urea nitrogen, creatinine, hematocrit, hemoglobin, and platelets. Pregnancy testing will be required prior to dosing on Visits 3 and 11 in women of childbearing potential (WOCBP).
- The use of a volumetric infusion pump is the preferred method of administration of study drug. The study drug may be infused by gravity with a rate controlling device if a pump is not available or is not operational. The PI or designee must approve this infusion methodology for each individual subject. If a rate-controlling device is used, it must be continuously monitored by the unblinded Infusion Nurse.
- Study drug administration should be performed in a controlled clinical setting such as a physician's office, Phase 1 unit, or Ambulatory Infusion Center (AIC).

- An appropriately qualified blinded Outcomes Assessor will monitor the subject throughout the infusion and for approximately 4 hours after the infusion has been completed. This person's qualifications must enable them to identify AEs, monitor vital signs, and take the appropriate course of action when an AE or clinically-significant vital sign change occurs.
- Sites must identify and follow procedures that ensure adequate blinding of blinded study personnel, subjects, and trial partners before, during, and after the Infusion Period. This may include the use of study drug container covers and/or the use of drapes to separate the unblinded Infusion Nurse and infusion apparatus from the blinded Outcomes Assessor, PI, subject, and trial partner.
- The unblinded pharmacist, or other qualified site personnel responsible for drug accountability, must retain all used vials/containers for drug accountability, unless otherwise agreed to with the Sponsor. These should be kept in a secure location with limited access to minimize the risk of unblinding blinded study staff. Partially-used vials/containers may not be re-used.

4. INSTRUCTIONS FOR THE UNBLINDED INFUSION NURSE

4.1. Equipment and Supplies

The following equipment and supplies will be needed for each infusion:

Infusion Supplies (Provided by Sponsor)

- GRF6021 or placebo
- Hangers for [redacted] IV vials (for blinding)
- Black IV Cover Bags [redacted] (for blinding)

Infusion Supplies (Not provided)

- Volumetric infusion pump
- IV spike set (vented)
- Pump-compatible IV tubing (without inline filter)
- IV Start Kit or equivalent supplies
- 18-20 gauge peripheral IV catheter
- Piggyback setup if saline bags will be used to flush the IV line post infusion
- 0.9% saline for injection (50 mL bags or 10 mL syringes) for post IV line or peripheral IV flush
- Gloves
- Alcohol pads
- IV pole
- Injectable cap and luer-lock connector (if applicable)
- Epinephrine Pen/Epi Kit
- Heparin Lock and syringe (if used)
- Sharps container
- Privacy screen/blinding setup during infusion

General Study Supplies

- Infusion source notes for the unblinded Infusion Nurse
- Study Drug Infusion Rate Table (See **Table 1. Study Drug Infusion Rates)**

If the site is unable to source needed infusion supplies, the Sponsor will assist in provisioning the required materials.

4.2. Blinding

Each site is required to ensure an appropriate blinding setup is prepared before each infusion and must document the setup employed. This may include any or all of the following:

- A privacy screen (or similar) to shield subject, subject's trial partner, and all blinded study personnel from the infusion setup
- Opaque bag or similar, to mask the content of the glass vial/container
- Other masking devices

4.3. Prior to Infusion

The unblinded Infusion Nurse will take care to ensure the appropriate blinding of the study drug at all times. Prior to infusion:

a. Verify subject identity.
b. Verify randomization assignment/ kit number.
c. Visually inspect the study drug vial for particulate matter or cracks in the vial. Do not use the solution if the vial is cracked or if the solution contains discrete foreign particulate matter. Do not shake. Do not use if the vial has been frozen. Study drug should be stored and infused at room temperature.
d. Obtain the study drug vial from the pharmacy and ensure that it is not visible when being transported to the infusion room or while setting up the IV apparatus.
e. Follow site procedures for peripheral IV catheter insertion, IV setup, and locking (if applicable).
f. The study drug vial should be spiked no more than 4 hours before infusion start.

It is recommended to prime the line using the study drug (either GRF6021 or placebo), while being careful to limit the amount of study drug that is lost (no more than 2-3 mL is ideal). The amount of study drug lost during priming should be noted in the infusion source record, without disclosing any information that could be potentially unblinding.

4.3.1. Considerations if Using a Heparin or Saline Lock

If the peripheral IV site will be locked with saline or heparin, the following steps should be considered:

- Locked peripheral IV sites should be assessed prior to and after each use to inspect for swelling, redness, pain, warmth, and phlebitis.

- Non-infusing peripheral IV catheters should be locked every 8 hours, or as otherwise indicated per site standard operating procedures (SOPs), by flushing first with saline and then heparin (if applicable) to maintain patency of the IV catheter.
- In general, it is recommended to follow the SASH method when flushing the IV catheter:
  1. Saline Flush
  2. Administer Study Drug
  3. Saline Flush
  4. Heparin Flush (if applicable)
- If drawing blood from the catheter, be sure to follow site procedures and use best practices for sample collection. The following are **examples** of best practices for sample collection from the catheter, but should not take the place of site SOPs:
  - Flush the line with saline and sterilize the connector, or equivalent, prior to performing the blood draw.
  - Use a discard tube to draw off a small amount of blood prior to collecting any lab samples to remove the saline or heparin that was in the catheter.

4.4. Administering the Infusion

To ensure subjects receive the study drug over the approximate [redacted] infusion period, refer to **Table 1. Study Drug Infusion Rates** below. The unblinded Infusion Nurse should start at a rate of 30 mL/hour. Thereafter, the rate may be increased by 30 mL/hour every [redacted] (± 5 minutes) to a maximum of 240 mL/hour. Each infusion will last approximately [redacted] or longer*.

Table 1. Study Drug Infusion Rates

Time	Flow Rate
Start (T-0:00)	30 mL/hour
[redacted]	60 mL/hour
	90 mL/hour
	120 mL/hour
	150 mL/hour
	180 mL/hour
	210 mL/hour
	240 mL/hour
	0 mL/hour*

**Infusion time may take longer if the infusion is interrupted or slowed. Total infusion time should not exceed [redacted]. If the subject has not received the full dose after [redacted] has passed, the unblinded Infusion Nurse should stop the infusion and record the actual dose administered on the infusion source record.*

During the infusion, the blinded Outcomes Assessor is responsible for taking all vital signs and monitoring the subject for AEs. If the subject is not tolerating an infusion well, the blinded Outcomes Assessor will instruct the unblinded Infusion Nurse to stop the infusion and will inform the PI or physician designee that the infusion has been stopped (**Section 5.3 During the Infusion [Safety Monitoring and Vital Signs]**).

Any communication between blinded and unblinded staff should be done with extreme care taken to not unblind the subject, the PI, or any other blinded staff. If accidental unblinding occurs, immediately contact your site's unblinded CRA for further instruction.

4.5. Post-Infusion

a. Depending on your infusion line's loading volume, sufficient saline should be used to flush the IV line to ensure [redacted] of study drug was infused into the subject.
b. When the infusion is complete, flush the peripheral IV catheter as ordered if it will remain in place (see **Section 4.3.1**) or discontinue it as appropriate.
c. The unblinded Infusion Nurse will document the following information on the subject's infusion source record:
   - Subject ID
   - Date and time of infusion start and stop
   - Infusion vial label checked for accuracy; record unique vial ID number
   - Actual volume infused (if less than [redacted])
   - What infusion method or pump that was used
   - Titration steps (e.g. changes in flow rate and time of change)
   - Vascular access device and status (including all flushes)
d. Following the infusion, the infusion source record should be maintained with the subject's records.
e. The unblinded Infusion Nurse should return the used vial to the unblinded pharmacist, or other qualified personnel responsible for drug accountability. During transport, ensure the vial/container is concealed from view.

5. INSTRUCTIONS FOR THE BLINDED OUTCOMES ASSESSOR AND INVESTIGATOR

5.1. Equipment and Supplies

The Outcomes Assessor will need the following equipment and supplies for each infusion:

- Source notes for the blinded Outcomes Assessor
- Sphygmomanometer, or equivalent device for measuring BP and heart rate
- Pulse oximeter (optional)
- Thermometer
- Body weight scale

5.2. Prior to Infusion

The blinded Outcomes Assessor will check the following information prior to infusion start:

a. Subject identification to ensure it is the correct subject.
b. Verify eligibility criteria (e.g. subject's history and diagnosis, including allergies and previous reactions to blood or blood products).
c. Review AEs and concomitant medications.
d. Baseline vital signs (temperature, seated BP, orthostatic BP, heart rate, respiratory rate, and weight) within 1 hour of the start of the infusion and record data on source document.

e. Ensure Pre-Infusion Safety Lab and Comprehensive Lab samples are obtained when applicable per the Schedule of Events. The results of the Pre-Infusion Safety Labs should be available and interpreted prior to the following day's infusion.
f. The PI or physician designee should perform a targeted physical exam when applicable per the Schedule of Events.
g. Review and interpret Pre-Infusion Safety Lab results. Refer to **Table 2. Signs or Symptoms Associated with Abnormal Lab Values**.
h. Confirm with PI that the subject is cleared to begin the infusion.

Table 2. Signs or Symptoms Associated with Abnormal Lab Values

Lab abnormality	Signs and Symptoms	Additional Testing*
Hyponatremia	Lethargy, confusion, nausea, vomiting, muscle cramps or weakness	n/a
Hypokalemia	Weakness, fatigue, muscle cramps or heart palpitations	ECG: Increased amplitude and width of P wave, longer PR interval, T wave flattening, ST depression, prominent U waves
Hypocalcemia	paresthesia, circumoral numbness, laryngospasm, muscle spasms or muscle cramps	ECG: Narrowing QRS, shortening PR interval, T wave flattening, QT prolongation, prominent U-wave, ST depression
Hypoglycemia	Palpitations, dyspnea, confusion, fatigue, shakiness, sweating, irritability, tingling around the mouth, blurred vision, dizziness, sleepiness	n/a
Kidney failure (serum creatinine)	Decreased urine output, edema, drowsiness, fatigue, confusion, nausea, dyspnea	Urinalysis: proteinuria or albuminuria
Anemia (Hct or Hgb)	Dizziness, weakness, headache, cold extremities, numbness, low body temperature, pallor	n/a

*Additional testing may be performed as needed in the event that recent results aren't available for review.

5.3. During the Infusion (Safety Monitoring and Vital Signs)

During the infusion, the blinded Outcomes Assessor's primary role is to observe the subject for AEs (refer to **Section 6: Monitoring for Adverse Reactions**) and to monitor vital signs (the unblinded Infusion Nurse is responsible for the administration of all infusions). If the subject is not tolerating an infusion well, the blinded Outcomes Assessor will instruct the unblinded Infusion Nurse to stop the infusion and will inform the PI or physician designee that the infusion has been stopped. **This should be done with care taken to not unblind the Outcomes Assessor, the PI, or his/her designee.** For example, if the subject is not tolerating the infusion well and the Blinded Outcomes Assessor asks the Unblinded Infusion Nurse to stop

the infusion, if the subject is receiving placebo, the Unblinded Infusion Nurse must be careful not to unintentionally convey this (e.g. acting surprised that the subject is not tolerating placebo).

The blinded Outcomes Assessor should follow the guidelines below for ALL INFUSIONS:

a. Monitor and record baseline vital signs not more than one hour prior to infusion start.
b. Once the infusion is started, record vital signs (seated BP, heart rate (HR), respiration rate (RR), temperature) every 15 minutes (± 5 minutes) for the first hour and then every 30 minutes (± 5 minutes) thereafter for as long as the infusion continues (up to [redacted]). Vital signs can also be recorded ad hoc if the subject is experiencing symptoms that indicate a change in vital signs.

5.4. Post-Infusion

a. Upon completion of the infusion (~[redacted] post infusion start), monitor vital signs as follows:
    1. Collect seated BP, HR, RR, temp.
    2. Collect orthostatic BP: ask the subject to lie down; after 10 minutes, collect supine BP. Then, ask the subject to stand (provide assistance if needed); after 3 minutes, collect standing BP.
    3. Subject may return to a seated position.
    4. Approximately 17 minutes after collecting the subject's standing BP, next vitals (seated BP, HR, RR, temp.) should be recorded.
    5. Continue to monitor vital signs (seated BP, HR, RR, temp.) every 30 minutes (± 5 minutes) for 3.5 hours, such that vital signs are monitored every 30 minutes (± 5 minutes) for 4 hours after the end of infusion.
    6. After 4 hours post infusion, the subject may be discharged at the investigator's discretion.
b. Educate the subject and the subject's trial partner regarding signs and symptoms to report to RN/Rx/MD such as: headache, nausea, fatigue, chills, myalgia, fever, shortness of breath, chest pain, back pain, hives, red or itchy skin, or itchy throat.
c. The blinded Outcomes Assessor will ensure that the following information is documented in the subject's source record:
    - Any required labs are performed, reviewed by PI or physician designee; any abnormal values; and interpretation/decision.
    - All vital signs, including body weight, and orthostatic BP.
    - Any adverse reactions to the infusion and actions taken (refer to **Section 6: Monitoring for Adverse Reactions**).
d. The PI or his/her designee will confirm the next infusion date with the subject and relay the request to the blinded Outcomes Assessor, unblinded Infusion Nurse, unblinded pharmacist, and other personnel as needed.

6. MONITORING FOR ADVERSE REACTIONS

Throughout the infusion, the blinded Outcomes Assessor or designee should continuously assess the subject for signs of AEs.

In the event of an AE, the PI or designee physician should be notified, and the event should be recorded for later transcription into the CRF. The PI should assess immediately whether an AE is an AE of special interest and/or an SAE and report it accordingly, as per the protocol.

Table 3. Recommended AE Actions for PI or Physician Designee

Mild Events	
• Body temperature >38.0°C (>100.4°F) but <39.0°C (<102.2° F) • Chills • Dizziness • Fatigue • Flushing • Mild-to-moderate itching • Redness of skin or rash • Urticaria (hives) in the absence of any other sign of symptom • Nausea / Vomiting	Stop the infusion, recheck vital signs, and notify the PI or physician designee. After assessment by a physician and consideration of treatment of fever with acetaminophen (if applicable), the unblinded Infusion Nurse may restart the infusion rate at half the rate at the onset of the infusion event and maintain the reduced rate for at least 30 minutes. If this rate is tolerated, the unblinded Infusion Nurse may increase the rate as tolerated by 30 mL per hour (0.5 mL/min) every 30 minutes (± 5 minutes) as tolerated.
Moderate to Severe Events	
• Bronchospasm (wheezing, coughing) • Hoarseness or other signs of laryngeal edema • Throat or mouth pain or irritation • Chest pain/back pain • Shortness of breath • Fever ≥39 °C (102.2° F) • Rigors • Hemoglobinuria • Oliguria • Sustained hypertension (systolic BP (SBP) >170 and/or diastolic BP (DBP) >100 not present before the first infusion) • Sustained hypotension (SBP <90 and/or DBP <50 not present before the first infusion) • Tachycardia (HR>100 bpm) • Signs / symptoms of volume overload	Stop the infusion, recheck vital signs, and notify the PI or physician designee. The PI or physician designee should administer appropriate supportive treatment, as necessary. The infusion should not be restarted, and the subject should not be dosed further. Notify the Medical Monitor(s) as soon as possible (preferably by end of business day).
Life-Threatening Events	
• Anaphylaxis	If signs and symptoms of anaphylaxis occur or the event is potentially life-threatening, stop infusion immediately. The PI, physician designee, unblinded Infusion Nurse, or blinded Outcomes Assessor should contact emergency medical services and/or proceed according to the site SOP for such situations. Notify the Medical Monitor(s) as soon as possible (preferably by end of business day).

Remember to report all SAEs and AEs of Special Interest per Section 8 of the protocol.

17.1 IMPORTANT SAFETY CONTACT INFORMATION

Premier-Research Medical Monitors	Sponsor Program Physicians
[redacted]	[redacted]
[redacted]	[redacted]

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 5.0 dated 23SEP2019

Replaces: Protocol Version 4.0 dated 08MAR2019

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V4.0_08MAR2019 ***Now reads:*** V5.0_23SEP2019	Version Control
Throughout	Minor changes for grammar, style, and standardization.	Minor grammar/style updates.
Title Page, Protocol Approval Page, Key Roles, Appendix 11	Revised Sponsor Authorized Representative and Program Physician to Esther Rawner, MD, Medical Director, Clinical Development	Sponsor Program Physician replacement.
Table of Contents	Updated to reflect content changes.	Revised to reflect updated content.
List of Abbreviations, 8.4.2.1, 8.5	Paul Ehrlich Institute (PEI) removed.	We will not have German sites in this trial.
Protocol Summary, 2.3.1, 4.1, 6.1.5, 7.1.1.2.6, 7.3.4, Appendix 11	Administration of GRF6021/placebo will now occur in outpatient infusion centers, or equivalent medical facilities, under medical supervision, rather than an inpatient setting. The post-infusion monitoring period has been extended from 2 to 4 hours. If further monitoring of a subject is required, all participating study sites will have inpatient facilities available for overnight observation or the ability to transfer the subject to such a facility.	Requirement for inpatient stay during administration of GRF6021 amended based on available safety data.
Schematic of Study Design	Updated to display follow-up visits 8 and 16 using the same symbol as other follow-up visits.	Revised for clarity and consistency.
4.1, 7.1.1.3, 7.3.3, 7.3.5, 7.3.6	Modified the requirement to perform cognitive and motor testing in a specific sequence. The specified sequence of performing cognitive and motor tests is preferred, but not required.	Revised to enhance study feasibility for sites, subjects and caregivers.

5.4.2	***Previously read:*** Approximately 90 subjects (GRF6021: 60; placebo: 30) will be enrolled in the study with the intent of obtaining ~68 evaluable subjects who have received at least 5 doses and completed through Visit 8. ***Now reads:*** Approximately 90 subjects (GRF6021: 60; placebo: 30) will be enrolled in the study with the intent of obtaining ~68 evaluable subjects.	Additional detail not required in this section as it is detailed in Section 10 Statistical Considerations.
6.1.2, 10.6.1	Clarified that saline placebo is supplied in [redacted] glass vials.	Revised for clarity.
7.1.1.1.8	Provided additional detail regarding assessment of motor function as part of the neurological exam.	Revised to clarify the motor function portion of the neurological exam.
7.1.1.2.8.2, 7.3.4	Modified to reflect Protocol Clarification Memorandum #2.	Revised to provide additional clarity to sites using an i-STAT handheld device to assess pre-infusion safety labs.
7.2.1	Removed sentence indicating total blood volume collected during the study.	This information is conveyed in the Informed Consent Form and may vary depending on whether unscheduled labs are collected.
7.3	***Previously read:*** Visit windows (when noted) should be benchmarked relative to Visit 3 for a subject, such that subjects complete the entire study by Day 168 (± 7 days). ***Now reads:*** To ensure follow-up visits occur at approximately the same intervals following both treatment periods, visit windows should be calculated as follows: • Visit windows for Visits 1-10 should be calculated relative to Day 1. • Visit windows for Visits 11-19 should be calculated relative to Day 85 ±7 (i.e., first day of dosing for Treatment Period 2).	Revised to ensure follow-up assessments are conducted at consistent intervals post-treatment.

7.3.5	• Visit 16 day interval was changed from "90 + 3 Days" to "90 + 7 Days." • Text added: "Note: Visit 16 (Day 90) may be split to allow for sufficient time to complete all required procedures. Review AEs and concomitant medications during split visits, as applicable."	Revised to enhance study feasibility.
8.4.3	• Modified to reflect Protocol Clarification Memorandum #3. • The qualification of "Clinically significant" was added to measurements of systolic and diastolic blood pressure. • The following note was added: "Note: Blood pressures meeting the parameters above that are not considered adverse events need not be reported within the 48-hour window. Rather, these will be considered "blood pressures of special interest" and analyzed separately."	Revised to provide clarity regarding Adverse Events of Special Interest and reporting requirements.
10.3	• The safety dataset includes all subjects who received any amount of the study agent as opposed to "at least one dose." • In the description of the evaluable dataset, added the following text, "have a diagnosis of PD and cognitive impairment per the inclusion criteria"	Since the IMP is administered by IV infusion, subjects who receive any volume of IMP will be considered part of the safety dataset. Revised to ensure that only subjects who have a diagnosis of PD and cognitive impairment are included in the evaluable dataset.
10.4.7	Updated to include the outcome of the interim safety analysis.	Updated since the planned interim safety analysis was completed in June 2019.
13.1	***Previously read:*** For each subject who receives the study agent, the eCRF must be completed […]	Revised for clarity, as screen failure data is captured in the eCRF.

	Now reads: For each subject enrolled in the study, the eCRF must be completed […]	
13.3	Major and Minor Protocol Deviation content updated.	Updated to reflect revised Alkahest Standard Operating Procedures related to Major and Minor Protocol Deviations.
15.1	• Table modified to Word format (previously embedded Excel image) for ease/tracking of revisions. • Visit 16 day interval was changed from "90 + 3 Days" to "90 + 7 Days." • Note X[4] updated as subjects should be randomized at least 5 days prior to treatment start to ensure study drug availability. • Note b updated as treatment window is 6 days in the event of a "grace" day. • Note c updated with the following content, "The windows for Visits 16,17,18, and 19 should be calculated relative to the day of the subject's first infusion during Treatment Period 2 (i.e., 85 ± 7 days)." • Note e updated to include cross-reference to Section 7.1.1.1.11 and list of labs was removed. • Note f updated to include cross-reference to Section 7.1.1.2.8.4 and list of labs was removed. • Note g updated to include the following, "When using an i-STAT Handheld Blood Analyzer, the blood sample(s) may be obtained on the same day as the infusion for assessment prior to infusion start." In addition, cross-reference to Section 7.1.2.8.2 was added and list of labs was removed. • Note I was updated to include cross-reference to Section 7.1.1.2.8.3 and list of labs was removed. • Note j was updated by removing content related to time period for additional MRI and	Updated ensure follow-up assessments are conducted at consistent intervals post-treatment, to promote study feasibility, and for content standardization.

	the following content was added, "Visit 16 may be split to allow for sufficient time to complete all of the procedures. AEs and concomitant medication should be reviewed during split visits, as applicable."	

Protocol Version 4.0 dated 08MAR2019
Replaces: Protocol Version 3.0 dated 16OCT2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V3.0_16OCT2018 ***Now reads:*** V4.0_08MAR2019	Version Control
Throughout	Minor changes for grammar, style, and standardization.	Minor grammar/style updates.
Table of Contents/ List of Abbreviations	Updated to reflect content changes (multiple abbreviations added).	Revised to reflect updated content.
List of Definitions	• Investigational product updated to "study agent." • ***Sentence previously read:*** "…blinding techniques are used to prevent inadvertent unblinding of study staff and study subjects during and immediately following the Infusion Period." • ***Sentence now reads:*** "…blinding techniques are used to prevent inadvertent unblinding of study staff and study subjects."	Revised for standardization and brevity.
Protocol Summary	• ***Sentence previously read:*** "The following measures will be taken to ensure adequate allocation concealment during infusions: blinding of subjects, trial partners, study coordinators, physicians, and cognitive/motor test administrators to treatment allocation; use of blinded Outcomes Assessors and unblinded Infusion Nurses; and measures to block view of the vial or bag, infusion pump, IV tubing, and catheter throughout the infusion. • ***Sentence now reads:*** "The following measures will	Revised for brevity and description of control agent.

Location	Description	Purpose
	be taken to ensure adequate allocation concealment during infusions: blinding of subjects, trial partners, study coordinators, physicians, and cognitive/motor test administrators to treatment allocation; use of blinded Outcomes Assessors and unblinded Infusion Nurses; and measures to block view of the infusion setup to avoid unblinding.**"** • Added line item for "Description of Placebo Control Agent: 0.9 sodium chloride injection (saline)."	
2.1	Content revised to provide additional detail related to characterization/differentiation of Young Plasma and GRF6021.	Clarification of study agent in early nonclinical research and rationale for use of GRF6021.
2.2	Content revised to provide additional detail related to nonclinical research conducted with GRF6021 assessing cognitive performance, motor function, and histological correlates.	Clarification and additional descriptive content to support rationale for use of GRF6021 in PD-MCI and PDD.
2.3.1	Substantial updates to provide a more detailed overview of the known potential risks of GRF6021; section also updated to reflect revised 2018 PSUR.	Additional descriptive content to further characterize the known potential risks of GRF6021, steps taken to mitigate risk (e.g., viral inactivation steps), and content revisions to reflect 2018 PSUR.
4.1	The following content was added: "Cognitive and motor testing may take up to approximately 2.5 hours. While the sequence of tests administered should be consistent for all subjects, subjects (and/or their trial partners, if applicable) may take breaks between assessments as needed."	Some subjects (and/or their trial partners) may require breaks between assessments to avoid/mitigate fatigue.
5.1	***Amended Inclusion Criteria as follows:*** • ***#5 Previously read***: "Modified Hoehn and Yahr Stages 1-4." • ***#5 Now reads***: "Hoehn and Yahr Stages 1-4." • ***13 Previously read:*** "[…] WOCBP and men must agree to use highly effective contraception […]" • ***13 Now reads***: "[…] WOCBP must agree to	Revised for accuracy of assessment utilized and population that must agree to use effective contraception.

Location	Description	Purpose
	use highly effective contraception [...]"	
5.2	***Amended Exclusion Criteria as follows:*** • ***#5 Previously read***: "History of immunoglobulin A (IgA), haptoglobin, or C1 inhibitory deficiency; …" • ***#5 Now reads***: "History of immunoglobulin A (IgA) or haptoglobin deficiency, …" • ***#7 (Added):*** Presence of signs and/or symptoms of hypervolemia or volume overload, including but not limited to pulmonary edema and/or clinically significant peripheral edema. • ***#8 (Added):*** Patients with recent or planned surgery sensitive to blood volume changes including cardiopulmonary bypass technique. • ***#19 (Added)***: Positive urine drug screen. The presence of opioids, benzodiazepines, and/or amphetamines in the urine drug screen may be allowed if these are prescribed and the dose stable for at least 8 weeks prior to screening. • ***#24 (Added):*** If on deep brain stimulation (DBS), DBS surgery within 12 months of screening and/or a change in DBS settings within 12 weeks of screening. DBS settings must not be changed at any point during the subject's participation in the trial. • ***#25 Previously read:*** "Presence of a pacemaker or any other implant that would be an MRI contraindication." • ***#25 Now reads:*** "Presence of a pacemaker or any other implant that would be an MRI contraindication, including DBS if not MRI compatible."	Exclusion criteria added/modified to reflect potential risks to specified patient populations and eliminate patients who may have characteristics/medical devices that may interfere with study assessments.
6.1.2	The following sentence was removed: "The label will clearly identify if it is the study agent or placebo control agent."	The same study label is used for both the study agent and placebo. The placebo also maintains its primary drug label that specifies its contents.

Location	Description	Purpose
6.1.4	Added: "GRF6021 should not be mixed with protein hydrolysates or solutions containing alcohol."	Prohibited per the PI.
6.1.5	Updated to provide additional guidance regarding staff qualifications and monitoring during and after administration of the study agent/placebo.	To further clarify that appropriately qualified staff will be available during infusions for safety monitoring and clinical management of study subjects.
6.1.8	***Previously read***: "The duration of therapy for a subject to be considered evaluable in the intent to treat population is 4 exposure days […]" ***Now reads***: "The duration of therapy for a subject to be considered evaluable is 5 exposure days […]"	Protocol consistency and clarity.
6.2	Clarified that all unused, partially used, and used study agent/placebo should be kept securely at the site until the Sponsor provides written approval to initiate return or destruction.	Updated to more accurately align with current study processes.
7.1.1.1, 7.1.1.1.10, 7.1.1.1.12	***Previously read:*** "the echocardiogram and screening MRI should be performed after all other screening procedures have been completed […]" ***Now reads:*** "it is recommended, but not required, that the echocardiogram and screening MRI be performed after all other screening procedures have been completed [...]"	Clarification regarding timing of echocardiogram and MRI.
7.1.1.1.3	Added a link to the full assessment.	Protocol clarity and standardization.
7.1.1.1.7	Clarified the procedural steps for collecting orthostatic blood pressure.	Protocol clarity and standardization.
7.1.1.1.11	Updated to list all lab tests performed as part of the Screening Safety Lab Panel.	Protocol clarity.
7.1.1.2.8	Updated to list all lab tests required for clinical evaluation and safety monitoring as well as their timing and frequency.	Protocol clarity.
7.1.1.3.3	Updated to include a link to the full assessment.	Protocol clarity and standardization.
7.2.2	Updated to include the timing and frequency of sample collection for ApoE Genotype Testing and Proteomic and Genetic Biobanking.	Protocol clarity.
7.3.2	Revised the order of subheadings in this section such that "Randomization" follows Section 7.3.1 Screening.	To more clearly reflect the order of procedures

Location	Description	Purpose
		and aid clinical sites in ensuring that study drug is available on site prior to a subject's first treatment period.
7.3.3, 7.3.5, 7.3.6	Added: "…(breaks are permitted between assessments as needed):"	Some subjects (and/or their trial partners) may require breaks between assessments to avoid/mitigate fatigue.
7.3.4	***Previously read:*** "Collect vital signs (including sitting, supine, and standing blood pressure) prior to infusion and [redacted] after dosing. ***Now reads:*** "Collect vital signs (including sitting, supine, and standing BP)."	This bullet point falls under instructions specific to the pre-infusion period; thus, guidance regarding the collection and timing of post-infusion vital sign was removed for clarity.
7.5	Added: "If on DBS, a change in DBS settings at any point during the subject's participation in the trial."	Consistency with updated Exclusion Criterion (#24).
8.4.2.1, 8.5	Updated to list the competent authorities of each participating country.	Updates related to regulatory submissions.
8.4.3	Updated the AESIs to clarify specifications for systolic and diastolic BP.	Additional clarity for AESI BP values.
8.6	• Updated to describe ongoing safety oversight activities, including procedures for detecting safety signals, and provided rationale as to the decision not to establish a formal DSMB. • Updated content to reflect new data from 2018 PSUR.	Clarification of safety oversight procedures and content revisions related to revised 2018 PSUR.
10.3	Updated the definition of the Per Protocol Dataset.	Updated definition for standardization with current Alkahest statistical standards.
10.6.1	Provided additional guidance regarding measures to ensure adequate blinding; clarified that [redacted] lab results obtained post-randomization will remain blinded until conclusion of the study, unless unblinding is required for emergent safety reasons.	Clarification of blinding procedures.

Location	Description	Purpose
10.6.3	Updated to describe the process for an Investigator to obtain the treatment allocation for a subject for the management of an SAE or severe AE, if required.	Clarification of process by which unblinding may occur at the site level.
12.4	Removed mention of labeling samples/data with subject initials. Clarified that study subjects' research data that is transmitted to the Sponsor, CRO, IRB/IEC will not include identifying information; individual subjects and their research data will be identified by a unique study number that will be recorded on non-local lab samples, requisitions, and any documents submitted to the Sponsor, CRO, and/or IRB/IEC.	Updates related to current procedures at Alkahest to protect participant/data confidentiality.
12.5	Updated to provide additional information as to why it may not be possible to destroy a subject's samples if s/he withdraws consent after the study is completed.	Updates related to current procedures at Alkahest.
15	Updated footers to reflect changes made to the body of the protocol; moved the timepoint for Randomization from baseline to screening, as randomization may occur at any point after eligibility has been confirmed, but prior to Visit 3.	
16	Updated the references to include the latest versions of Gahart 2019, PSUR 2018, and PI 2018.	References updated to current versions.
17	• Modified Appendices 1-10 to include links to the study source document for each assessment. • Appended the Infusion Administration Manual.	• Provision of full assessments for regulatory/site review. • Infusion Administration Manual was previously provided as a separate document but will now be included in the protocol for ease of access.

Protocol Version 3.0 dated 16OCT2018
Replaces: Protocol Version 2.1 dated 10AUG2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V2.1_10AUG2018 ***Now reads:*** V3.0_16OCT2018	Version Control
Table of Contents	Updated to reflect new content.	Provide for appropriate navigation of document.
Schematic of Study Design	Modified schematic to include Visit numbers.	Provide clarification of study design.
5.2	• Revised criteria for hypertension to exclude patients with refractory hypertension. • Added criteria to exclude patients with orthostatic hypotension and/or significant supine to upright blood pressure variability (e.g., supine hypertension).	• Patients with refractory hypertension may present a potential safety issue. • PD patients may suffer from orthostatic hypotension and/or supine hypertension which may present a potential safety issue.
7.1.1.1.7	Vitals signs revised to include timing and descriptions of supine and standing blood pressure measurements.	Provide timing and description of increased safety monitoring assessments.
7.1.1.2.3	Additional vital signs measured are noted and cross-referenced to Section 7.1.1.1.7.	Provide clarification of additional standing and supine blood pressure measurements.
7.2.2.3	***Section content previously read:*** • Blood samples will be retained for analysis of emergent genetic markers of disease. ***Now reads:*** • Blood samples will be collected for analysis of emergent genetic markers of disease.	Changed wording to indicate that blood samples will be "collected," and removed the word "retained" as the retention of samples is optional for subjects.
7.3.1	***Collection of vital signs bullet previously read:*** • Collect vital signs, height, and weight. ***Now reads:*** • Collect vital signs (including sitting, supine, and standing blood pressure), height, and weight.	Provide clarification of additional standing and supine blood pressure measurements.
7.3.3	***Section content previously read:*** • Subjects will be randomized at the conclusion of Visit 2 after eligibility has been confirmed (including MRI and echocardiography results). ***Now reads:*** • Subjects will be randomized after eligibility	Subjects may now be randomized as soon as eligibility is confirmed to give applicable study sites adequate time to procure the study agent/placebo for eligible subjects.

Location	Description	Purpose
	has been confirmed (including MRI and echocardiography results).	
7.3.4	***Bullet re: vital sign measurements previously read:*** • Collect pre-infusion vital signs. ***Now reads:*** • Collect vital signs (including sitting, supine, and standing blood pressure) prior to infusion and [redacted] after dosing.	Provide for increased safety monitoring.
7.3.5	***Timing for Visit 8 and Visit 16 previously read:*** • Visits 8 and 16 (Day 6 +1 Day and Day 90 +1 Day – Last Day of Inpatient Stay) ***Now reads:*** • Visits 8 and 16 (Day 6 + 3 Days and Day 90 + 3 Days) ***Bullet re: vital signs and weight measurements previously read:*** • Vital signs and subject's weight in kilograms ***Now reads*** • Vital signs (including sitting, supine, and standing blood pressure) and subject's weight in kilograms.	• Visit 8 and Visit 16 windows extended so a weekend follow-up visit is not required (patient can be discharged, and the visit can occur on a Monday). • Provide for increased safety monitoring.
10.4.5	***First sentence previously read:*** • Subject adherence with the study visit schedule, visit procedures, infusions; subject retention; and an overall trial partner survey will be assessed. ***Now reads:*** • Subject adherence with the study visit schedule, visit procedures, infusions, and subject retention will be assessed.	Requirement for an overall trial partner survey was removed.
10.4.7	Paragraph added (first paragraph) detailing an additional interim (safety) analysis to be conducted after 20 subjects have completed Visit 8 (end of first dosing period). Following review of results, the	If safety data is satisfactory, study may be amended to include outpatient treatment periods.

Location	Description	Purpose
	Sponsor will reassess the need for inpatient stays during dosing.	
15.1	• Modified the schedule for Visit 1. • Modified the schedule for Visit 2: Randomization to include the following notation: "If shipping of study agent to the study site will be required, subjects should be randomized at least 3 days prior to treatment start to ensure study agent availability." • Modified the visit window for Visit 8 and 16 from +1 Day to +3 Days. • Modified the schedule for Visits 3-8 and 11-16 to include supine and standing blood pressure measurements with notations re: timing of measurements.	• Added screening for orthostatic hypotension and supine hypertension. • Added to provide clarification and ensure availability of study agent/placebo at study site for eligible subjects. • Visit windows extended so a weekend follow-up visit is not required (patient can be discharged, and the visit can occur on a Monday). • Increased safety monitoring.

Protocol Version 2.1 dated 10AUG2018
Replaces: Protocol Version 2.0 dated 19JUL2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V2.0_19JUL2018 ***Now reads:*** V2.1_10AUG2018	Version Control
7.3.5	Modified the schedule for Visits 8, 9, 16, and 17 as follows: • MoCA moved from Visits 8 and 16 to Visits 9 and 17.	MoCA testing was shifted to avoid potential data redundancies and complications of administration during the same visit as the D-KEFS and dCDT evaluations.

Location	Description	Purpose
15.1	Modified the schedule for Visits 8, 9, 16, and 17 as follows: • MoCA moved from Visits 8 and 16 to Visits 9 and 17.	MoCA testing was shifted to avoid potential data redundancies and complications of administration during the same visit as the D-KEFS and dCDT evaluations.

Protocol Version 2.0 dated 19JUL2018
Replaces: Protocol Version 1.1 dated 04JUN2018

Location	Description	Purpose
Throughout	***Protocol version previously read:*** V1.1_04JUN2018 ***Now reads:*** V2.0_19JUL2018	Version Control
Throughout	Grammar and style changes	For protocol clarity and standardization
List of Abbreviations	***The following abbreviations have been added:*** • AD: Alzheimer's disease • ASL MRI: Arterial-spin Labeling magnetic resonance imaging • BP: Blood pressure • CRA: Clinical research associate • tf-MRI: Task-free functional magnetic resonance imaging • WOCBP: Women of childbearing potential	Updated the list of abbreviations to reflect abbreviations used in the body of the protocol
List of Definitions Infusion Nurse	***Sentence Previously Read:*** The unblinded study personnel, […] responsible for administering the investigational product. The Infusion Nurse ensures the investigational product is administered at the correct infusion rate and appropriate blinding techniques are used to prevent inadvertent unblinding of study staff and study subjects during and immediately following the infusion period. ***Sentence Now Reads:*** The unblinded study personnel, […] responsible for administering the	Updated for clarity to reflect the placebo-controlled design

Location	Description	Purpose
	investigational product/placebo. The Infusion Nurse ensures that the investigational product (GRF6021)/placebo is allocated appropriately, administered at the correct infusion rate, and appropriate blinding techniques are used to prevent inadvertent unblinding of study staff and study subjects during and immediately following the Infusion Period.	
List of Definitions Infusion Time	***List of Definitions*** Infusion Time is now Infusion Period	For protocol clarity and standardization
Schematic of Study Design	Inpatient Treatment 2 Follow up Visit was incorrectly listed as Day 6. Changed to Day 90 to reflect the Schedule of Events.	Correct typographic error in Schematic of Study Design
2.2, 2.3	Removed "young" as a descriptor of the donor pool for manufacturing GRF6021.	To more accurately reflect the donor pool
3	Modified description of exploratory objectives as follows: ***Sentence previously read:*** In addition, brain imaging (MRI) will be conducted in consenting patients to identify potential indicators of PD MCI and PDD progression, as well as potential therapeutic effects of GRF6021. ***Sentence Now Reads:*** In addition, magnetic resonance imaging (MRI) of the brain will be conducted after the second treatment period in consenting subjects to identify potential therapeutic effects of GRF6021.	For protocol clarity and standardization
4.1	Updated the Description of the Study Design to more accurately reflect the Schedule of Events and clarify the additional, optional MRI.	For protocol clarity and standardization
4.2.3	Added details to the Exploratory Endpoints regarding the endpoints that may be evaluated using the second MRI obtained from consenting subjects.	For protocol clarity
5.1	***Amended Inclusion Criteria as follows:*** • #4: Clarified that the MoCA score required for inclusion is 13-25, **inclusive** • #11: Clarified that the systolic ejection fraction required for inclusion is greater than	#4, 11: For protocol clarity and standardization #13: Removed "serum" pregnancy testing, as urine pregnancy testing may be performed at Visits 3 and 11

Location	Description	Purpose
	or equal to 55% • #13: Removed specification for "serum" pregnancy testing	
5.2	***Amended Exclusion Criteria as follows:*** • #14: Removed "The trial partner should understand the nature of the study and be willing to complete the trial partner scales and functional assessments throughout the study." • #18: Added that concurrent participation in any other therapeutic treatment trial is exclusionary to align with Section 7.5 Prohibited Medications, Treatments, and Procedures	#14: It is not anticipated that the trial It partner will be expected to complete any scales or functional assessments as part of this study. #18: For protocol clarity and standardization
5.4.1, 8.4.1	Clarified the investigator's responsibilities for following Adverse Events (AEs). AEs will be followed until resolution or deemed stable, unless the subject is lost to follow up.	For protocol clarity, standardization, and alignment with the study's safety management plan (in draft)
5.4.2, 7.3.7	Clarified that only subjects **who have received at least one infusion** but are withdrawn or withdraw from the study early will be encouraged to complete the End of Study Visit procedures.	Clarification
7.1.1.1	Added the Hoehn and Yahr scale as part of the assessment of PD to the list of Screening procedures.	For protocol clarity and standardization, as Hoehn and Yahr is required for assessment of eligibility
7.1.1.1.1	Removed schedule for administering the Sheehan-Suicidality Tracking Scale (S-STS), as this information is specified in Section 7.3 Study Schedule and Section 15 Schedule of Events.	For protocol standardization.
7.1.1.1.2, 7.3.1	Added that "The stage of the disease will be classified using the Hoehn and Yahr scale" as part of the assessment of PD and cognitive impairment and other minor edits.	For consistency with Section 5.1 Inclusion Criteria
7.1.1.1.5	***Previously read:*** Information pertaining to the subject's socioeconomic status (e.g. highest level of income achieved, education, longest held occupation), ethnicity, race, marital status, and family size will be collected by interview with the subject and the subject's trial partner at screening. ***Now reads***: Demographic information such as the subject's education level, ethnicity, and race will be	To clarify the types of demographic data that may be collected

Location	Description	Purpose
	collected by interview with the subject and the subject's trial partner at screening.	
7.1.1.8	Added a more detailed description of the neurological exam.	To specify required assessments to be performed as part of the neurological examination
7.1.1.1.10	Removed upper limit of systolic ejection fraction, as this was inconsistent with Section 5.1 Inclusion Criteria.	For protocol clarity and standardization
7.1.1.1.12	Removed description of the Visit 16 MRI from the description of the MRI required for screening.	For protocol clarity and standardization. A detailed description of MRI procedures is provided in Section 7.2.2.2.
7.1.1.2.7	Clarified that only the physical exam and weight measurements (not height) will be repeated at the End of Study Visit.	To align with the updated Schedule of Events
7.1.1.3.2	Added that "Subjects will have two CDR-CCB trainings during the screening period to ensure adequate performance at the Baseline Visit."	For protocol clarity and alignment with the Study Schedule
7.1.1.3.5	Specified that only Parts 1-3 of the MDS-UPDRS will be completed for this study.	Clarification
7.1.1.3.9	Provided further guidance regarding administration of the GDS-15.	For protocol clarity
7.2.2.1	Modified to state that DNA for ApoE analysis will be obtained from a blood serum sample.	Clarification
7.2.2.2	Updated to more accurately reflect the processes for MR image acquisition and interpretation as well as describe the exploratory endpoints that may be assessed using MR images obtained from consenting subjects.	Clarification
7.2.3	Removed reference to laboratory addendum.	An addendum to the lab manual is not required. A lab manual will be developed and distributed to sites that includes instructions for collecting and processing all specimens (standard, non-standard, and specialty).
7.3.2, 7.3.6, 15	Removed option for splitting Baseline and End of Study Visits.	It is expected that all required Baseline and End of Study activities may be completed in a single visit.
7.3.2, 7.3.4, 15	Amended the schedule for collecting samples for proteomics/epigenetics/biobanking and ApoE testing, such that no samples will be collected	The proteomics/ epigenetics/ biobanking samples collected during Visit 3 are sufficient for baseline. The

Location	Description	Purpose
	during the Baseline Visit and the sample for ApoE will be obtained during Visit 3.	Visit for collecting ApoE was changed to reduce the number of required blood draws.
7.3.3	Clarified that subjects will be randomized at the conclusion of Visit 2 after eligibility has been confirmed (including MRI and echocardiography results).	Clarification
7.3.4, 15	Added a ± 7-day visit window for Day 85.	To aid protocol feasibility
7.3.5, 15	Modified the schedule for Follow-up Visits as follows: • PDQ-39 moved from Visit 8 to Visit 9. • Added a ± 7-day visit window for the optional MRI at Visit 16.	To allow for a greater window between collection timepoints for the PDQ-39 Added the MRI visit window to aid protocol feasibility
7.5	***Previously read:*** Concurrent participation in any other therapeutic treatment trial. If there was prior clinical trial participation, then the last dose of the investigational agent for symptomatic therapies must have been at least 30 days for small molecules, 4 months for disease modifying therapies, and 1 year for vaccine or immunotherapy trials prior to screening. ***Now reads:*** 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.	For protocol clarity and alignment with the Inclusion/Exclusion Criteria
8.2.2	Modified to reflect that if either the investigator or the Sponsor considers an AE related, then the event will be considered related for reporting purposes.	To align with the study's safety management plan (in draft) and processes
8.2.3	***Previously read:*** The investigator will be initially responsible for determining whether an AE is expected or unexpected.	To align with the study's safety management plan (in draft) and processes

Location	Description	Purpose
	Now reads: The Sponsor or designee will be responsible for determining whether an AE is expected or unexpected.	
8.4.2.1, 8.4.2.2	Modified the timeframes for reporting SAEs and provided additional instructions for SAE reporting.	For protocol clarity and alignment with safety management processes and procedures.
8.4.3	Provided additional details and guidance on reporting AEs of Special Interest.	Clarification.
8.4.4	Provided additional details and guidance on reporting of pregnancy.	For protocol clarity and alignment with safety management processes and procedures.
8.5	Updated the Study Halting Rules to reflect that dosing ***may*** be temporarily halted if a Safety Evaluation Meeting is triggered. The decision to temporarily halt dosing will be based on the safety observations.	Clarification.
10.4.7	Updated to include additional information regarding the Planned Interim Analysis.	Clarification.
10.6.1	Removed mixed block size specifications.	Information is not relevant to the protocol.
12.5	Added that "Subjects may choose whether the Sponsor can store and use samples for further research."	To align with the informed consent form.
15.1	Updated the Schedule of Events Table to reflect revised Study Schedule and provided additional details/clarification in the footnotes.	For protocol clarity and standardization.

Protocol Version 1.1 dated 04JUN2018
Replaces: Protocol Version 1.0 dated 01MAY2018

In this table, changes from Version 1.0 dated 01MAY2018 are described and their rationale is given.

Location	Description	Purpose
Throughout	Update of study design to 90 subjects who will be randomized in a 2:1 ratio to active treatment (approximately 60 subjects) or placebo (approximately 30 subjects). Subjects will receive one infusion per	Updated study design

Location	Description	Purpose
	day of active or placebo treatment for 5 consecutive days during week 1 and week 13.	
Throughout	***Protocol version previously read:*** V1.0_01MAY2018 ***Now reads:*** V1.1_04JUN2018	Version Control
Throughout	Grammar and style changes	For protocol clarity and standardization
Throughout	Optional cerebrospinal fluid biomarker research was removed.	Removed for safety considerations
Throughout	Secondary endpoint added: Change from baseline in Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency.	Test provides auxiliary information regarding verbal fluency to the CDR-CCB, which does not include assessments in this critical cognitive domain
List of Abbreviations	Removed CSF: Cerebrospinal Fluid and added D-KEFS: Delis-Kaplan Executive Function System.	CSF biomarker was removed and D-KEFS test was added
Schematic of Study Design	Schematic updated to reflect new study design.	Updated study design
Section 2.2	Provided additional content regarding an allometric scaling model for conversion of preclinical to clinical dosing volumes, as well as alternative models, including isometric scaling. Using isometric scaling based on blood volume provides an equivalent human dose of 413 mL. A table (Table 1) with detailed information is included.	Provided clarification of the dosing volume calculations
Section 7.1.1.3.3	***Previously:*** Digital Clock Drawing Test (with accompanying descriptive information). ***Now:*** Delis-Kaplan Executive Function System (with accompanying descriptive information).	Section added for description of D-KEFS test
Sections 7.1.1.3.4-7.1.1.3.9	***Previously:*** Sections 7.1.1.3.3 – 7.1.1.3.8. ***Now:*** Sections 7.1.1.3.4 – 7.1.1.3.9.	Sections renumbered to accommodate new section for D-KEFS test.
7.2.1	Added the following sentence to the first paragraph: "The total blood volume collected for each subject during Visits 1-19 is approximately 465 mL."	Provide clarification regarding total blood volume collected during the study.

Location	Description	Purpose
Section 7.2.2.4	Section for Cerebrospinal Fluid Biomarker Collection was removed.	Removed for safety considerations
Section 7.3.5	MRI Assessment removed from Visit 10 and added to Visit 16.	Due to new study design there will be no crossover (placebo to active), so this timing for MRI investigation is more appropriate
Section 10.5	***Sentence previously read:*** In a sample of 45 subjects, the upper bound of the 95% confidence interval for the frequency of an unobserved AE is approximately 7%. ***Sentence now reads:*** In a sample of 60 subjects, the upper bound of the 95% confidence interval for the frequency of an unobserved AE is approximately 5%.	Correction for new sample size for 2:1 randomization ratio
Section 15.1	Updated Schedule of Events Table: removed CSF/lumbar puncture and added D-KEFS.	Removed CSF biomarker for safety considerations; D-KEFS test added
Section 16.1	Added three new references (Delis 2001, Delis 2004, Emre 2004).	Added in support of D-KEFS test