Rationale and Design of a Prospective, Randomized, Double-Blind, Dose-Comparison Safety and Tolerability Study of GRF6019 in Mild to Moderate Alzheimer's Disease

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Background and Rationale

- Alzheimer's disease (AD) is a degenerative brain disease and the most common cause of dementia; as of 2018, an estimated 5.7 million Americans are living with AD.[1-3]
- Studies by Villeda et al[4,5] have demonstrated benefits of intravenous (IV) administration of plasma from young mice on activity, locomotion, and cognition in aged mice.
- The data also indicated that exposure of aged mice to young plasma was capable of rejuvenating synaptic plasticity late in life.
- Subsequent studies performed at Alkahest extended these results and showed significant improvements in cognitive performance and histological correlates in aged mice following IV infusions of young human plasma and of GRF6019, a proprietary human plasma protein fraction developed and manufactured by Grifols. GRF6019 is produced by pooling source plasma from multiple healthy donors and fractionating into protein fractions.
- The rationale for using a plasma protein fraction rather than whole plasma in human trials was based on the favorable risk profile, feasibility, and scalability.
  - The potential transfer of pathogens is reduced by validated processing steps with viral clearance capacity. The risk of allergic reactions to proteins, such as clotting factors and immunoglobulins, is reduced with removal from this plasma protein fraction.
- Preclinical studies performed at Alkahest with GRF6019 determined that "pulsed dosing" (daily infusions for 5 to 7 consecutive days) was superior to intermittent dosing (2 to 3 times per week for up to 12 weeks) on multiple endpoints, including cognition and neurogenesis and that these effects lasted at least 12 weeks after the end of dosing.
  - A pulsed dosing regimen of 5 consecutive days, with a subsequent booster pulse 12 weeks later, was chosen for the initial human study of GRF6019.

Study Objective

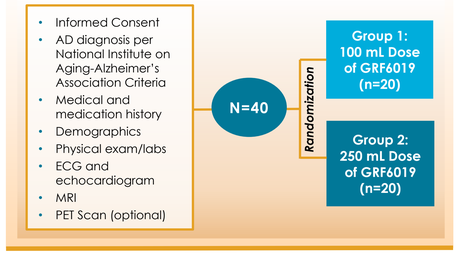
- To evaluate the safety, tolerability, and potential therapeutic effects of a pulsed infusion regimen of GRF6019 in human subjects with mild to moderate AD.

Methods

Study Design

- This study is a randomized, double-blind, dose-comparison trial that is currently being conducted at 8 sites in the United States.
- Following screening procedures, eligible subjects are randomized to receive infusions of GRF6019 of 100 mL (Group 1) or 250 mL (Group 2)(**Figure 1**).

Figure 1: Study Screening/Enrollment



- Following screening, subjects undergo a baseline visit, 2 inpatient treatment periods, each followed by 3 safety visits, and an end of study visit over a period of approximately 7 months (**Figure 2**).
- During each 5-day treatment period, subjects reside in inpatient observation units to facilitate safety evaluation.

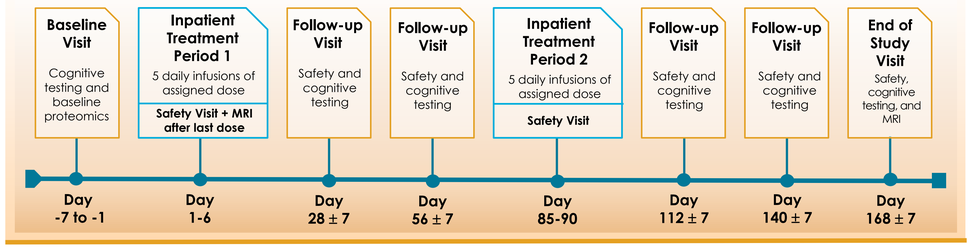
Study Population

- Key eligibility criteria include (**Table 1**):
  - Diagnosis of probable AD based on NIA-AA criteria (MMSE score of 12-24 inclusive).
  - Patients with evidence of clinically relevant neurological disorder(s) other than probably AD are excluded.

Table 1: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age: 60- 90 years. • Diagnosis of probable AD based on National Institute of Aging-Alzheimer's Association (NIA-AA) criteria. • Mini-Mental State Examination (MMSE) score 12-24 inclusive. • Modified Hachinski Ischemia Score (MHIS) of ≤ 4. • eGFR ≥ 45 mL/min/1.73m^2 • Systolic ejection fraction > 55% on trans-thoracic echo. • The subject (with support of a trial partner) must be able to follow the study protocol, receive the treatment in the established timeframe, and continue during the follow-up interval.	• Neurological disorder(s) other than probable AD. • > 2 lacunar strokes on MRI. • History of blood coagulation disorders or hypercoagulability; anticoagulant therapy. • Initiation or change in the dosage of cholinesterase inhibitors within 3 months prior to screening. • Heart disease; uncontrolled high blood pressure. • Prior hypersensitivity reaction to any human blood product or IV infusion; clinically significant drug allergy. • Treatment with any human blood product, including transfusions and IV immunoglobulin, during the 6 months prior to screening. • Hemoglobin <10 g/dL in women; and <11 g/dL in men.

Figure 2: Study Design



Study Assessments

- Primary Endpoints:
  - Incidence of treatment-emergent adverse events (TEAEs) identified by MedDRA preferred term (PT) and grouped by MedDRA System Organ Class.
  - Feasibility and tolerability of each dosing regimen.
- Secondary Efficacy Endpoints:
  - MMSE
  - 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog/11)
  - Grooved Pegboard Test
  - Category Fluency Test (CFT)
  - Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB)
  - Alzheimer's Disease Cooperative Study – Activities of Daily Living$_{23}$ (ADCS-ADL$_{23}$)
  - Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change rating (ADCS-CGIC)
  - Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Savonix™ Neurocognitive Assessments and Digit Span
- Secondary Safety/Feasibility Endpoints:
  - Clinical laboratory parameters.
  - Vital sign measurements.
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Changes on MRI scans designed to assess for Amyloid Related Imaging Abnormalities (ARIA).
  - Subject compliance with study visit schedules, visit procedures, and subject retention; success of blinding.
- Exploratory Endpoints:
  - MRI (vMRI), functional MRI (fMRI), and Arterial Spin Labeling (ASL).
  - Changes in blood-based biomarkers.
  - Changes in CSF biomarkers (in participating subjects).

Results

- The study is currently underway, and 18 subjects (12 women/6 men) have completed the first dosing period; dose allocation remains blinded but approximately 50% of subjects have received 100 mL and 50% have received 250 mL.
- The baseline characteristics of the dosed subjects are presented in **Table 2**.

Table 2: Demographic Data *(as of June, 2018)*

Dosed Subjects (n=18)	Mean	SD
Age (y)	71.8	5.7
Sex (% women)	67%	
Disease duration (y)	7.1	4.4
MMSE score	20.8	3.6

- There were 8 TEAEs in 5 subjects (of 18 dosed).
- All TEAEs were mild, and no subjects have discontinued due to difficulty tolerating the infusions.
- The most common TEAEs were headache (n=3) and hematoma at the IV site (n=3).
- There have been no clinically significant changes in laboratory values, blood pressure, heart rate, respiratory rate, body temperature, body weight, or ECG.

Conclusions

- Alkahest is conducting the first study of the safety, tolerability, and potential therapeutic effects of the plasma fraction GRF6019 in mild to moderate AD.
- GRF6019 dosed at 100 mL and 250 mL every day for 5 consecutive days in subjects with mild to moderate AD and a mean age of 72, to date, is safe and well tolerated.
- Pending additional safety data, Alkahest will evaluate adding a higher dose arm.

References

1. **Alzheimer's Association.** Alzheimer's disease facts and figures. Alzheimers Dement. 2018;14:367-429. 2. **Wilson RS, et al.** The natural history of cognitive decline in Alzheimer's disease. Psychol Aging. 2012;27:1008-1017. 3. **Hebert LE, et al.** Alzheimer disease in the United States (2010-2050) estimated during the 2010 Census. Neurology. 2013;80:1778-83. 4. **Villeda SA, et al.** The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature. 2011;477:90-94. 5. **Villeda SA, et al.** Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nature Med. 2014;20:659-663.

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