Statistical Analysis Plan

premier research

Sponsor	Alkahest, Inc.
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
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Approvals

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Document History

Version	Date	Section	Description of Change/Purpose
1.0	05-Feb-2019	N/A	N/A
2.0	21-May-2019	3.5	Added additional detail about timing of randomization.
2.0	21-May-2019	3.6	Added additional detail about measures to ensure blinding of vial and drip chamber. Stated [redacted] laboratory results will remain blinded until study end except for the screening value. Clarified the personnel who remain blinded and unblinded.
2.0	21-May-2019	3.7	Replaced Schedule of Events table.
2.0	21-May-2019	4.2	Clarified table presentations will be displayed in aggregate at interim analyses and no subject level listings will be provided. Added external consultants to the list of parties that may be involved in the Safety Evaluation Meetings.
2.0	21-May-2019	5	Updated definition of Evaluable Set to reflect 5 planned doses for consistency with the end of first treatment

			period. Listed additional reasons for exclusion from the Per Protocol Set.
2.0	21-May-2019	8.3.1	Clarified the visit in which the blood sample will be obtained for ApoE analysis
2.0	21-May-2019	9.1	Added language describing tabulations of TEAEs, AEs leading to withdrawal, Deaths and SAEs, and AESIs from previous drafts that was erroneously omitted due to subheading formatting.
2.0	21-May-2019	9.1.3	Removed the AESI criteria as these are left to the discretion of the PI. Added text describing new table presenting AEs associated with blood pressure changes by infusion period, SOC, PT, and treatment.
2.0	21-May-2019	9.2	Added descriptions of screening, pre-infusion, and exit safety laboratory evaluations from previous drafts that was erroneously omitted due to subheading formatting. Explicitly stated the visits in which pregnancy test results

			would be listed. Stated shifts from baseline in coagulation and quantitative urinalysis parameters will also be provided.
2.0	21-May-2019	9.3	Clarified the visits in which orthostatic vital signs will be presented pre- and post-infusion. Clarified the position of abnormal vital signs and added criterion of orthostatic hypotension. Included reference to the blood pressures of special interest that will be summarized separately.
2.0	21-May-2019	10	Stated that BPSIs were identified and summarized in the SAP, but are not in the current protocol version.
2.0	21-May-2019	11.1	Clarified the Hoehn and Yahr will be used, not the modified Hoehn and Yahr.
2.0	21-May-2019	11.3	Added a subsection to detail the echocardiogram results that will be listed.
2.0	21-May-2019	13.1	Indicated which demographic and safety TFLs will also be provided at the efficacy IA.

2.0	21-May-2019	14.2	Updated footnotes, titles, and table shell formatting for consistency with text and other shells. Added a table of AEs with terms associated with blood pressure changes. Added summary and shift tables of coagulation and quantitative urinalysisf laboratory parameters. Added a table of blood pressure values of special interest.
2.0	21-May-2019	14.3	Added listings of coagulation, immunology, and serology laboratory parameters. Added a column to the protocol deviations listing to indicate which deviations exclude someone from the Per Protocol analysis Set.
3.0	01-May-2020	8.3.2	Added subsections for Volumetric MRI, Resting fMRI, and ASL MRI describing what tests, locations and laterality will be presented.
3.0	01-May-2020	13.2	Removed the 'X' from ANCOVA tables as they were not provided

			and the interim efficacy analysis
3.0	01-May-2020	14.2	Added table shells for Volumetric MRI and ASL MRI
3.0	01-May-2020	14.3	Added listing shells for Volumetric MRI and ASL MRI
3.0	01-May-2020	14.4	Added figure shells for the individual MDS-UPDRS scores (Part 1, Part 2, and Part 3)
4.0	17-Aug-2020	5	Refined Per Protocol set definition, Added Complete population
4.0	17-Aug-2020	7.1	Added description of subjects who did not complete the study due to COVID-19
4.0	17-Aug-2020	9.1.1	Added derived action taken variable for AEs
4.0	17-Aug-2020	13	Added medical history table by LLT, added efficacy tables in the Complete Set
4.0	17-Aug-2020	14	Added medical history table shell and efficacy table shells for Complete Set Updated footnotes, titles, columns for consistency with text

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Alkahest protocol number ALK6021-201 (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), dated 08MAR2019 V4.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1] All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Alkahest's study ALK6021-201.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to assess the safety and tolerability of GRF6021, a [redacted] human [redacted] fraction administered by intravenous (IV) infusion, in subjects with Parkinson's disease (PD) and cognitive impairment.

2.1.2. Secondary Objectives

As a secondary objective, the study aims to assess the effects of GRF6021 on cognitive and motor function.

2.1.3. Exploratory Objectives

The exploratory objectives include blood and plasma collection to identify specific biomarkers associated with cognitive and motor function and/or indicators of PD with mild cognitive impairment (PD-MCI) and PD with dementia (PDD) progression. In addition, magnetic resonance imaging (MRI) of the brain will be conducted after the second dosing period in consenting subjects to identify potential therapeutic effects of GRF6021.

2.2. Study Endpoints

2.2.1. Safety Endpoints

2.2.1.1. Primary Safety Endpoints

The primary safety endpoints of this study include the following:

- 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).

2.2.1.2. Secondary Safety Endpoints

The secondary safety endpoints include the following:

- 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.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

Not Applicable.

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- 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).

2.2.2.3. Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints of this study include the following:

- Serial compositional analysis of individual subject's plasma to identify specific biomarkers associated with cognitive functional changes and/or indicators of disease progression.
- Epigenetic changes.
- Change from baseline in the following assessments (in consenting subjects):
  - 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.

3. Overall Study Design and Plan

3.1. Overall Design

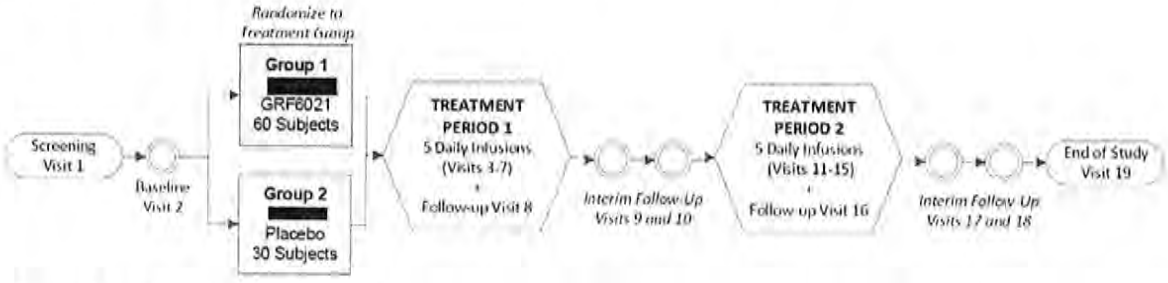
This is a randomized, double-blind, placebo-controlled study to assess the safety and tolerability of GRF6021, a [redacted] human [redacted] fraction, administered by IV infusion to subjects with PD and cognitive impairment.

All subjects will undergo a screening visit, including an MRI scan, baseline visit, 2 dosing periods, follow-up visits, and an end-of-study/early-termination visit. 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 dosing period, subjects will reside in inpatient units and can be discharged after the fifth day of dosing. The subject participation period is approximately 7 months from Screening through End of Study, unless prematurely discontinued.

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.

The overall schema of the study is presented in Figure 1:

Figure 1: Study Schema



3.2. Sample Size and Power

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 before 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 [CI] 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% CI 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.

3.3. Study Population

This study includes male and female subjects, aged 40-85 years old, with a diagnosis of either PD-MCI or PDD.

3.4. Treatments Administered

GRF6021 is a [redacted] human [redacted] fraction made from pooled human plasma product [redacted] that serves as a viable source of soluble, infusible plasma proteins from healthy male and female donors. It is administered by IV infusion of [redacted] to subjects. The placebo control agent will be 0.9% sodium chloride injection, USP (saline). 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. Subjects will receive one infusion of [redacted] per day for 5 consecutive days at Weeks 1 and 13.

3.5. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to GRF6021 (Group 1: active dosing in both dosing periods) or placebo (Group 2: placebo dosing in both dosing periods) in a 2:1 ratio. Randomization will be stratified by sex to ensure a balanced distribution of male and female subjects in both treatment groups. Subjects will be randomized at the conclusion of Visit 2, after eligibility has been confirmed (including MRI and echocardiography results).

3.6. Blinding and Unblinding

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.

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 all study outcome measures will be assessed by a blinded Outcomes Assessor.

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. In addition, the vial and drip chamber will be covered with an opaque black bag or equivalent; a curtain, drape, or equivalent will be used to shield the infusion

administration setup; used vials/containers of the study agent or placebo will be concealed during transport and returned to the pharmacy at the end of the Infusion Period.

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.

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. Except for the designated personnel whose sole responsibility necessitates access to unblinding information (e.g the unblinded CRA whose sole responsibility is to ensure study agent or placebo accountability, the unblinded clinical supply manager, etc.) and the unblinded statistician performing the interim analyses , the study 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. The study blind can be broken for safety reasons if the information is required for the management of SAEs or severe AEs.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	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 ± 3 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[e]	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[4]				X[1]				X[1]				
Echocardiogram	X*																		
MRI	X*															X[2]			
Randomization		X[5]																	
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
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[e]	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[2]	X						X	X	X						X	X	X	X
D-KEFS		X						X		X						X		X	
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 3 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 5 days. Visits 8 and/or 16 may occur 1-3 days later.
c: The visit window for Visit 11 is Day 85 ±7 days. Visits 12-15 should follow consecutively.
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: Includes all comprehensive labs, infectious serology (HIV, HBV, HCV), cobalamin (vitamin B12), pyridoxine (vitamin B6), thiamine (vitamin B1), TSH, direct antiglobulin test, BNP, serum IgA, haptoglobin, and C1 inhibitor (availability of C1 inhibitor lab results not required for evaluation of I/E criteria). Urine drug screen: cannabinoids, benzodiazepine, barbiturates, opiates, cocaine, amphetamines, methadone, phencyclidine, propoxyphene. Urinalysis: UPCR.
f: Includes all comprehensive labs, infectious serology, and direct antiglobulin test.
g: Samples for local pre-infusion labs should be collected and results interpreted PRIOR to the following day's infusion start. The following should be measured: sodium, potassium, ionized calcium, BUN, creatinine, hematocrit, hemoglobin, platelets.
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: ALP, ALT, amylase, AST, bicarbonate, bilirubin (direct, indirect, and total), ionized calcium, chloride, cholesterol, LDL, HDL, CK, creatinine, GGT, glucose (random), iron, lactate dehydrogenase (LDH or LD), lipase, magnesium, phosphate, potassium, protein total, sodium, triglycerides, BUN, albumin, aPTT, PT/INR, CBC with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils). Urinalysis: blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, urobilinogen, urine creatinine, urine albumin, albumin/creatinine ratio, urine sodium, sodium/creatinine ratio, urine potassium, potassium/creatinine ratio, and reflex urine microscopy if indicated.
j: The second, additional MRI will be performed in consenting subjects only and should be performed at Visit 16 + 7 days.

	Task-free functional MRI and arterial-spin labeling MRI will be performed only at a subset of sites.
	k: The CDR-CCB will require two training sessions prior to the baseline assessment. These training sessions can be performed at any time during the screening period.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified. Percentages will not be displayed when the numerator for a cell is 0.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% CIs will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

An unblinded interim analysis of the safety endpoints, including the primary endpoint and secondary safety endpoints, is planned when approximately 20 subjects have completed Visit 8 (end of first dosing period). The requirement that subjects remain in an inpatient unit during each dosing period was included in the protocol to enable safety monitoring during dosing. Once the Sponsor has reviewed the safety data from this interim analysis, the need for inpatient stays during dosing will be reassessed.

An unblinded interim analysis of the MoCA, CDR-CCB, and MDS-UPDRS Part 3 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 sets. To minimize potential bias of the remaining efficacy and safety data, only aggregated summary tables will be provided. The data will be provided in aggregate fashion so the difference between study agent and placebo is compared but individual treatment allocation remains blinded. An independent statistician other than the author of this plan will perform the unblinded analysis.

Safety will be monitored on an ongoing basis. If safety events of potential concern occur during the trial (i.e., 3 related events in the same SOC or a suspicious overall pattern), a Safety Evaluation Meeting will be triggered and an ad hoc interim safety analysis will be performed. Dosing may be temporarily halted based on the observations. The purpose of the meeting is for investigators, the Sponsor, external consultants with expertise relevant to the specific safety signal(s) detected as necessary, and the contract research organization (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.

The results that will be presented for each interim analysis are flagged in the table of contents.

A separate analysis plan will be prepared for the CDR-CCB endpoints.

5. Analysis Sets

The following analysis sets are planned for this study:

- **Safety Set:** The Safety Set includes all subjects all subjects who receive at least 1 dose of the study agent. All safety analyses will be performed using the Safety Set, based on treatment received.
- **Intent-To-Treat Set (ITT):** The ITT Set includes all randomized participants. The presentation of baseline characteristics will be conducted on the ITT Set.
- **Evaluable Set:** The Evaluable Set includes all subjects who receive at least 5 of the 10 planned doses and complete through Visit 8. All efficacy analyses will be performed using the Evaluable Set, based on randomized treatment.
- **Per Protocol Set (PP):** The PP Set is a subset of the Evaluable set comprised of subjects who receive all 10 planned doses, who complete Visit 18 and Visit 19 in window, and who do not have any of the deviations listed below or any other deviation that could potentially affect the assessment of efficacy identified prior to database lock. Visit windows are found in Section 6.1.5. Deviations related to novel coronavirus disease 2019 (COVID-19) will also be evaluated in determining Per Protocol population eligibility prior to database lock. All efficacy analyses will be repeated in the Per Protocol Set, based on randomized treatment.
- **Complete Set:** The Complete Set is a subset of the PP Set comprised of subjects who did not have any changes to any of the following concomitant medications preferred terms reported at any time on study: Dopaminergic agents (e.g. Rotigotine [Neupro Patch], Duopa Pump, Sinemet [Carbidopa, Levodopa], Carbidopa, Rytary), Pregabalin (Lyrica), Amantadine, Antipsychotics (e.g. Pimavanserin Tartate [Nuplazid], Clozapine, Quetiapine Fumarate [Seroquel]), or benzodiazepines (e.g. Alprazolam). This includes those that were stable per protocol prior to first dose and either changed dose or stopped on study as well as those that began on study.

Deviation Type	Deviation	Major/Minor	Excluded from Per Protocol Set	Additional Clarification

Eligibility	I2. 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	Major	Yes	
Eligibility	I3. 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)	Major	Yes	
Eligibility	I4. Score on the MoCA of 13-25, inclusive (Nasreddine 2005)(Appendix 1)	Major	Yes	
Eligibility	I5. Hoehn and Yahr Stages 1-4	Major	Yes	
Eligibility	I6. 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	Major	Yes	only if change in the last 2 weeks
Eligibility	I7. If on medications for cognition (e.g., rivastigmine, galantamine, donepezil, memantine), must be on stable dosage for at least 8 weeks prior to baseline	Major	Yes	only if change in the last 4 weeks
Eligibility	I8. If on antidepressant medications, must be on stable dosage for at least 8 weeks prior to baseline	Major	Yes	only if change in the last 4 weeks

Eligibility	I9. If on clozapine, quetiapine, or pimavanserin, must be on stable dosage for 8 weeks prior to baseline	Major	Yes	only if change in the last 4 weeks
Eligibility	I12. Modified Hachinski Ischemic Scale (MHIS) score of 4 or less (Rosen 1980)	Major	Yes	
Eligibility	E4. Treatment with any human blood product, including transfusions and IV immunoglobulin, during the 6 months prior to screening	Major	Yes	
Eligibility	E19. 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	Major	Yes	
Eligibility	E23. 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	Major	Yes	
Eligibility	E24. 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	Major	Yes	

Eligibility	E26. More than 2 lacunar strokes or other clinically relevant imaging abnormality on screening MRI	Major	Yes	
Eligibility	E27. 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	Major	Yes	Only when interfering with the interpretation of study data
Compliance	Incorrect treatment dispensed and administered to subject	Major	Yes	
Out of Window	Efficacy Procedures performed outside of the protocol window which are a consistent pattern or potential risk to study data outcomes	Major	Yes	
Study Drug Temp Excursion	Study drug temperature excursions when determined to have impacted the quality of the study drug	Major	Yes	
Concomitant meds	Use of prohibited concomitant medications as defined in the protocol that have an effect on cognition	Case by Case		

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded before the first dose will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

If there is a statistical difference among treatment groups with respect to baseline characteristics or values, that variable may be added to the statistical models as covariate to determine the effect on treatment. Baseline scores will be added as a covariate in models to assess efficacy.

6.1.3. Multiple Comparisons

No adjustments will be made for multiple comparisons for any endpoint.

6.1.4. Handling of Dropouts or Missing Data

Subjects who discontinue or are unblinded before Visit 8 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced. Subjects who have received at least 1 dose 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.

Missing data will not be imputed.

6.1.5. Analysis Visit Windows

Visits will be analyzed as scheduled. Unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available and the unscheduled/repeated measurement falls within the analysis visit windows as described below. The windows follow the Schedule of Events in Table 1. Unscheduled/repeated measurements will be listed.

Visit	Target Start Day	Lower Limit	Upper Limit
1		-35	-8
2		-7	-1
3	1	1	1
4	2	2	2
5	3	3	3
6	4	4	4
7	5	5	5
8	6	6	9
9	28	21	35
10	56	49	63
11	85	78	92
12	86	79	93
13	87	80	94
14	88	81	95
15	89	82	96
16	90	83	100
17	112	105	119
18	140	133	147
19	168	161	175

6.1.6. Pooling of Sites

Not Applicable.

6.1.7. Derived Variables

- MoCA Total score = sum of individual item scores, with a range from 0 to 30.

- D-KEFS Letter Fluency Total Correct Score = sum of F+A+S correct responses from 1-15, 16-30, 31-46, and 46-60 seconds.

- D-KEFS Category Fluency Total Correct Score = sum of Animals and Boys' Names correct responses from 1-15, 16-30, 31-46, and 46-60 seconds

- D-KEFS Category Switching Total Correct Score = sum of Fruits/Furniture correct responses from 1-15, 16-30, 31-46, and 46-60 seconds.

- D-KEFS Total Correct Score = sum of D-KEFS Letter Fluency Total Correct Score, Category Fluency Total Correct Score, and D-KEFS Category Switching Total Correct Score.

- MDS-UPDRS Part 1 score = sum of all Part 1 individual item scores. Part 1 consists of 13 items on a scale of 0 (normal) to 4 (severe), so the Part 1 score ranges from 0 to 52. If an individual item is missing, it will be imputed as the average score for that part.

- MDS-UPDRS Part 2 score = sum of all Part 2 individual item scores. Part 2 consists of 13 items on a scale of 0 (normal) to 4 (severe), so the Part 2 score ranges from 0 to 52. If an individual item is missing, it will be imputed as the average score for that part.

- MDS-UPDRS Part 3 score = sum of all Part 3 individual item scores. Part 3 consists of 33 items on a scale of 0 (normal) to 4 (severe), so the Part 3 score ranges from 0 to 132. If an individual item is missing, it will be imputed as the average score for that part.

- MDS-UPDRS Parts 1-3 total score = sum of Part 1, Part 2, and Part 3 scores. If any of the individual part scores are missing, the total score will be set to missing.

- CISI-PD total score = sum of the four individual item scores (motor signs, disability, motor complications, and cognitive status) rated 0 (not at all) to 6 (very severe or disabled), with a range of 0 to 24.

- PDQ-39 Mobility subscore = sum of 10 items in the Mobility domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Activities of Daily Living subscore = sum of 6 items in the Activities of Daily Living domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Emotional Well-Being subscore = sum of 6 items in the Emotional Well-Being domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Stigma subscore = sum of 4 items in the Stigma domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Social Support subscore = sum of 3 items in the Social Support domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Cognitions subscore = sum of 4 items in the Cognitions domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Communication subscore = sum of 3 items in the Communication domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Bodily Discomfort subscore = sum of 3 items in the Bodily Discomfort domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.

- PDQ-39 Total score = mean of all of the PDQ-39 subscores.

- GDS-15 Total score = sum of the 15 item questionnaire, with a range of 0 to 15. Each question is answered "yes" or "no". Question numbers 1, 5, 7, 11, 13 indicate presence of depression when answered positively (yes) while the remaining questions indicate presence of depression when answered negatively (no). One point is counted for each depressive answer. A score of 0-4 indicates no depression, a score of 5-10 is suggestive of a mild depression, and a score of 11 or more is suggestive of severe depression.

- Modified Hachinski Ischemic Scale Total score = sum of the 8 item scores, with a range of 0-8.

- Change from baseline = value at current time point – value at baseline.

- TEAE = any adverse event with an onset date/time after first dose of medication.

- Disease duration (years) = [Enrollment date – PD onset date (as recorded on the Medical History case report form) + 1] / 365.25.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 21.0 thesaurus or higher.

A treatment related AE is any AE with a relationship to the study drug of possibly related or definitely related.

If partial AE or medication dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, then impute as the month and day of the first dose date.
    - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
    - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00;

- if the date is the same as the date of the first dose and

    - only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later;

    - only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later;

- Otherwise if the date is not the same as the date of first dose, the hour assigned is 12 if the hour is missing and the minute assigned is 30 if the minute is missing.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number of subjects randomized into each treatment group, the number of subjects who completed each series of infusions in Dosing Period 1 and Dosing Period 2, the number of subjects completing the study, tabulated reasons for discontinuation from the study, and number of subjects in each analysis dataset. The number of subjects completing each visit will also be presented, as will the number of subjects who did not complete the study per protocol due to COVID-19. A subject is considered to not have completed the study per protocol due to COVID-19 if they had any missing visits that affected treatment administration or collection of end of study efficacy assessments due to COVID-19. If a subject did not complete the study per protocol due to COVID-19, this category will supersede their study status on the study completion CRF page.

This summary will be based on the ITT Set.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, race, ethnicity, height, weight, disease duration, and apolipoprotein E (ApoE) genotype will be presented by treatment group using summary statistics or frequencies, as appropriate. See Section 6.1.7 for derivation of disease duration.

The means of continuous demographic variables will be tested using Wilcoxon rank-sum test and the proportions of categorical demographic variables will be tested using a Chi-square test or Fisher's Exact test, as appropriate, in order to evaluate the effectiveness of the randomization in producing homogeneous pre-treatment groups.

These analyses will be conducted for the ITT Set.

The number and percent of subjects reporting various medical histories grouped by MedDRA system organ class and preferred term, will be tabulated. Medical histories of Parkinson's disease will also be presented by SOC, PT, and lower level term (LLT). Subject and family medical history as well as tobacco smoking, alcohol, and illicit substance use will be listed. Social history and exercise level will also be listed.

7.4. Exposure

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. Exposure days and volume administered will be summarized by treatment group and dosing period. The proportion of subjects who are considered evaluable over both dosing periods will also be displayed.

8. Efficacy Analysis

All secondary endpoints will be summarized using the Evaluable, Per Protocol, and Complete Sets. All efficacy data, regardless of population, will be presented in data listings.

8.1. Primary Efficacy Analysis

Not applicable. The primary analysis for this study is safety.

8.2. Secondary Efficacy Analysis

Normality assumptions will be tested using the Anderson-Darling method. If the *P* value for the normality test is >0.05 the data will be considered normally distributed and will be analyzed as specified in subsequent sections. Otherwise, if the *P* value is ≤0.05 the data will be considered non-normal. If the data are non-normal, the Wilcoxon rank sum test will be used for comparisons between treatments and a non-parametric ANCOVA model will be run on the ranks. If the data is considered non-normal, the Wilcoxon signed rank test will be used to assess the within-subject changes.

8.2.1. Montreal Cognitive Assessment (MoCA)

The MoCA is a 1-page, 30-point test designed as a rapid screening instrument for mild cognitive dysfunction. The questionnaire assesses several different cognitive domains, including attention and concentration, executive functions, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation. Higher scores indicate better cognitive function; the total possible score is 30 and a score of 26 or more is considered normal. Derivation for the MoCA total score is described in Section 6.1.7.

The MoCA will be collected at Screening (Visit 1), Week 4 (Visit 9), and Week 16 (Visit 17).

Change from baseline to study visit in the MoCA total score and individual domains will be summarized by treatment group. Boxplots of the MoCA total score will also be provided by treatment group and visit. A test of hypothesis comparing mean total scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed

rank test, as appropriate. The null hypothesis is that the change from baseline to subsequent visit is 0.

Additionally, the mean change from baseline in MoCA total score will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline MoCA total score, age, and ApoE genotype as covariates.

8.2.2. Cognitive Drug Research Computerized Cognition Battery (CDR-CCB)

The CDR-CCB assesses both enhancement and impairment of human cognitive function. 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). CDR-CCB will also be assessed at Week 1 (Visit 8), Week 4 (Visit 9), Week 8 (Visit 10), Week 13 (Visit 16), Week 16 (Visit 17), Week 20 (Visit 18), and Week 24 (Visit 19).

Please refer to the separate SAP for the analysis of the CDR-CCB.

8.2.3. Delis-Kaplan Executive Function Verbal Fluency (D-KEFS)

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). D-KEFs is measured at Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18).

The number of correct F, A, and S responses from 1-15, 16-30, 31-46, and 46-60 seconds will be presented by treatment group and visit. Change from baseline in total score will be presented by treatment group. Derivation for the D-KEFS Total score is described in Section 6.1.7. Boxplots of the D-KEFSs total score will also be provided by treatment group and visit. A test of hypothesis comparing mean scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed rank test, as appropriate. The null hypothesis is that the mean change from baseline to subsequent visit is 0.

Mean change from Baseline will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline score, age, and ApoE genotype as covariates.

8.2.4. Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS has four components (Part 1, Mentation, Behavior, and Mood; Part 2, Activities of Daily Living; Part 3, Motor; Part 4, Complications). Only Parts 1, 2, 3 and total score will be utilized for this study. Part 1 has 13 items that address mental dysfunction, mood,

and nonmotor aspects of experiences of daily living. Part 2 has 13 items that assess motor disability and aspects of experiences of daily living. Part 3 has 33 items that assess motor impairment and motor examination. The rating for each item is from 0 (normal) to 4 (severe) and the descriptions of each rating are provided in the table below.

Scale for the MDS-UPDRS Rating	Description
0 = normal	No symptoms/signs
1 = slight	Symptoms/signs with sufficiently low frequency or intensity to cause no impact on function
2 = mild	Symptoms/signs of frequency or intensity sufficient to cause a modest impact on function
3 = moderate	Symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function
4 = severe	Symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function

The total score for each part is obtained from the sum of the corresponding item scores. Derivation for the MDS-UPDRS Total score is described in Section 6.1.7.

MDS-UPDRS is measured at Baseline (Visit 2), Week 1 (Visit 8), Week 4 (Visit 9), Week 8 (Visit 10), Week 13 (Visit 16), Week 16 (Visit 17), Week 20 (Visit 18), and Week 24 (Visit 19). Change from baseline to study visit in MDS-UPDRS scores will be summarized by treatment group. A test of hypothesis comparing mean scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed rank test, as appropriate. The null hypothesis is that the mean change from baseline to subsequent visit is 0.

Mean change from baseline in Total score will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline score and age as covariates.

Boxplots of the MDS-UPDRS Part 3 score will also be provided by treatment group and visit.

8.2.5. Schwab and England Activities of Daily Living Scale (SE-ADL)

The SE-ADL evaluates patients' perceptions of global functional capacity and dependence. 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 scoring is as follows:

Scale for the SE-ADL Rating	Description
100%	Completely independent. Able to do all chores without 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 completed independent. More difficulty with some chores. X3-4 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 ½ of chores. Difficulty with everything.
40%	Very dependent. 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 dependent, helpless. Complete invalid
0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

The SE-ADL is measured at Baseline (Visit 2), Week 8 (Visit 10), and Week 24 (Visit 19). The number and percentage of subjects falling in each category at each time point will be displayed by treatment group. A 2-sided Cochran-Mantel-Haenszel (CMH) test will be performed at the 5% significance level to determine whether there is a significant relationship between treatment group and level of independence.

8.2.6. Clinical Impression of Severity Index – Parkinson's Disease (CISI-PD)

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). CISI-PD is measured at Baseline (Visit 2), Week 8 (Visit 10), and Week 24 (Visit 19). Change from baseline to study visit in each item will be summarized by treatment group. A test of hypothesis comparing mean scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed rank test, as appropriate. The null hypothesis is that the mean change from baseline to subsequent visit is 0.

Mean change from baseline in Total score will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline score, age, and ApoE genotype as covariates.

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

The long form of the PDQ has 39 questions, with eight dimensions:

- Mobility (10 items)
- Activities of daily living (6 items)
- Emotional well-being (6 items)
- Stigma (4 items)
- Social support (3 items)
- Cognitions (4 items)
- Communication (3 items)
- Bodily discomfort (3 items)

The frequency of each event is recorded as one of five options, with each option assigned a numeric value as indicated: never (0), occasionally (1), sometimes (2), often (3), or always/cannot do at all (4). It is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms. Derivations for each of the subscores and total score are described in Section 6.1.7.

The PDQ-39 will be collected at Baseline (Visit 2), Week 4 (Visit 9), Week 8 (Visit 10), Week 20 (Visit 18), and Week 24 (Visit 19).

Change from baseline to study visit in the PDQ-39 Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognitions, Communication, and Bodily Discomfort subscores and PDQ-39 Total score will be summarized by treatment group. A test of hypothesis comparing mean scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed rank test, as appropriate. The null hypothesis is that the mean change from baseline to subsequent visit is 0.

Mean change from baseline in Total score will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline score, age, and ApoE genotype as covariates.

8.2.8. Geriatric Depression Scale-15 (GDS-15)

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. 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. Each item is recorded as yes or no which is assigned a numeric value of 1 or 0, respectively. 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
- 11 + Suggestive of severe depression

Derivations for the final score is described in Section 6.1.7. The GDS-15 will be collected at Baseline (Visit 2), Week 8, (Visit 10) and Week 20 (Visit 18). The number and percentages of subject responses will be summarized by treatment group and visit. Change from baseline to study visit in GDS-15 total score will be summarized by treatment group.

8.2.9. Digital Clock Drawing Test (dCDT)

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).

The dCDT will be collected at Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18).

The dCDT score is a number from 0 and 100 that represents a person's overall cognitive function as assessed by DCTclock. The score will be classified as within normal limits, indeterminate, outside normal limits, or unanalyzable based on cut scores and test performance.

Change from baseline to study visit in dCDT score will be summarized by treatment group. A test of hypothesis comparing mean scores between baseline and subsequent study visits will be conducted using a 2-sided paired t-test or Wilcoxon signed rank test, as appropriate. The null hypothesis is that the mean change from baseline to subsequent visit is 0.

Mean change from baseline in dCDT score will be compared between treatment groups using an ANCOVA model with treatment, visit, and treatment by visit interaction as a main effects and baseline score, age, and ApoE genotype as covariates.

The number and percentage of subjects falling in each classification at each time point will be displayed by treatment group.

The cognitive features within the drawing efficiency, simple motor, information processing, and spatial reasoning composite scales will be listed.

8.3. Exploratory Efficacy Analysis

8.3.1. Apolipoprotein E (ApoE) Genotype Testing

DNA for ApoE analysis will be obtained from a blood serum sample collected at Visit 3 to determine ApoE genotype at baseline. ApoE genotype will be listed and summarized as part of demographics and baseline characteristics. See Section 7.3. The number and proportion of subjects with the genotype for each allele will be presented.

8.3.2. Magnetic Resonance Imaging (MRI)

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.

8.3.2.1. Safety MRI

The number and percentage of subjects with presence of screening safety MRI abnormalities along with the type of abnormality and primary location of abnormality reported will be presented by treatment group. Additionally, abnormality sequence, abnormality status, and presence of white matter disease will be tabulated by treatment group. The number and percentage of subjects whose screening safety MRI findings suggest there is a potential alternative diagnosis to PD will also be presented.

Screening safety MRI results will be listed.

8.3.2.2. Volumetric MRI

Volume will be summarized using descriptive statistics for the left, right, and bilateral sides of the following locations:

- Whole brain (bilateral only)
- Lateral ventricles (bilateral only)
- Intracranial (bilateral only)
- Cortical
- Hippocampus
-

Cerebral cortex average thickness will be summarized using descriptive statistics for the left, right, and bilateral sides of the following locations:

- Cortical

- Mayo (bilateral only)
- Prefrontal lobe
- Whole temporal lobe
- Superior temporal lobe
- Medial temporal lobe
- Lateral parietal lobe
- Inferior parietal lobe
- Precuneus
- Isthmus-cingulate
- Entorhinal cortex

Atrophy absolute change and cerebral cortex thickness average change will be summarized using descriptive statistics for the left, right, and bilateral sides of the following locations at follow-up:

- Whole brain (bilateral only)
- Lateral ventricles (bilateral only)
- Cortical
- Hippocampus

Additionally, cerebral cortex thickness average change will be summarized using descriptive statistics for the left, right, and bilateral sides of the following locations at follow-up:

- Cortical
- Hippocampus
- Mayo (bilateral only)
- Prefrontal lobe
- Whole temporal lobe
- Superior temporal lobe
- Medial temporal lobe
- Lateral parietal lobe
- Inferior parietal lobe
- Precuneus
- Isthmus-cingulate
- Entorhinal cortex

Volumetric MRI results will also be listed.

8.3.2.3. Resting fMRI

Since there are 85 correlations between regions, fMRI data will not be summarized or listed due to file size. If summaries or listings are desired, they will be provided on an ad hoc basis.

8.3.2.4. ASL MRI

Cerebral blood flow measurements will be summarized using descriptive statistics for the left, right, and bilateral sides of the following locations:

- Frontal lobe

- Cingulate cortex
- Parietal lobe
- Temporal lobe
- Occipital lobe
- Striatum
- Cerebellum
- Thalamus
- Pallidum
- Substantia nigra
- Hippocampus

ASL MRI results will also be listed.

9. Safety and Tolerability Analysis

The primary endpoint of this study is the incidence of TEAEs and SAEs identified by MedDRA PT and grouped by MedDRA SOC.

The secondary safety endpoints are as follows:

- 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

Safety will also be evaluated from electrocardiogram (ECG) results and physical examination results.

All safety analyses will be performed on the Safety Set.

9.1. Adverse Events

All AEs that occur after the time of treatment with the study agent will be considered TEAEs. Events meeting this definition will be those events that are a change from the subject's baseline conditions, including an increase in frequency or severity (these will be entered as new AEs). For AEs occurring on the date of first dose, if the time of onset is missing, the AE will be assumed to be treatment emergent.

All AEs, TEAEs, and SAEs will be coded using the MedDRA Version 20.1 or higher coding dictionary. The AE analyses will focus on those that are treatment emergent, however any AEs that are reported after consent has been signed and before initial dosing will be considered intercurrent events and flagged in the listings as such.

The causal relationship of the AE to the study drug is determined by the investigator as Unrelated, Possibly Related, or Definitely Related. These can be mapped to Unrelated (*Unrelated*) and Related *(Possibly Related* and *Definitely Related*). Adverse event summaries will be repeated for treatment related TEAEs.

Adverse events severity grades are reported as mild, moderate, or severe.

Summaries of incidence rates (frequencies and percentages) of individual TEAEs will be presented by SOC, PT, and treatment group. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by relationship.

Each subject will be counted only once within each summation level (SOC and PT). If a subject experiences more than 1 TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = definitely related).

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects then alphabetically in case of a tie.

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.1.8.

In the AE data listings, all AEs will be displayed. AEs that are treatment emergent will be flagged.

A test of hypothesis comparing the proportion of subjects reporting a TEAE throughout the study will be conducted using a Chi-square test or Fisher's exact test, as appropriate. The null hypothesis is that there is no difference in proportion between treatment groups, with a two-sided alternative that considers the possibility of a difference in either direction. The number and percentage of subjects reporting a TEAE and the 95% Wilson confidence interval (CI) for the proportion will be presented for each treatment group. In addition, the difference in proportions between the GRF6021 and placebo groups and the 95% Wilson CI will be presented. The same statistics and hypothesis testing will be performed for subjects reporting an SAE throughout the study.

9.1.1. Adverse Events Leading to Withdrawal

A derived action taken variable will be created for subjects who withdrew from the study or study drug due to an AE as noted on the study completion (DS) CRF. If the reason for discontinuation entered on the DS CRF was "Adverse Event" and the AE occurred between the start of the first infusion in Period 1 through the final infusion in Period 2, the derived action taken will be set to "study drug withdrawn" regardless of what action taken was entered on the AE CRF. Since treatment is administered during two distinct periods and not on a continuous basis, if an AE that causes withdrawal occurs between the two infusion periods, action taken may not accurately indicate "study drug withdrawn" unless it was decided that subject would not get a second infusion since the subject will not actively be receiving treatment between the two periods.

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and PT will be prepared for the Safety Dataset. No inferential statistical tests will be performed. These summaries will be based on the derived action taken.

A data listing of AEs leading to withdrawal of study drug will be provided, displaying details of the event(s) captured on the CRF. Both derived and CRF action taken variables will be presented in the listing.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and tabulated by SOC, PT, and treatment group.

9.1.3. Other Significant Adverse Events

AEs of special interest (AESI) are defined in the protocol. These are to be considered as Adverse Events by the PI in order to be recorded:

A summary tabulating these criteria for safety will be presented by SOC, PT, and treatment group. All AESIs will be flagged in the AE listings.

Adverse events with preferred terms associated with blood pressure changes will also be presented by infusion period, SOC, PT, and treatment group. Infusion period will be further categorized by whether the event start date occurred during the infusion period or after the infusion period. Examples of such events can be identified by the following preferred terms: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, blood pressure increased, increased blood pressure, blood pressure diastolic increased, blood pressure systolic increased, hypotension, hypertension, low blood pressure, high blood pressure. This is a non-exhaustive list and a review of AE MedDRA coding will be conducted prior to lock to identify all events associated with blood pressure changes.

9.2. Laboratory Evaluations

The screening safety lab panel includes: all comprehensive labs (hematology, chemistry, coagulation, urinalysis, urine chemistry, ionized calcium), immunochemistry (HIV, hepatitis B, hepatitis C, thyroid-stimulating hormone (TSH), brain natriuretic peptide (BNP)), cobalamin (vitamin B12), pyridoxine (vitamin B6), thiamine (vitamin B1), direct antiglobulin test, IgA, haptoglobin, and C1 inhibitor. The urine drug screen includes cannabinoids, benzodiazepine, barbiturates, opiates, cocaine, amphetamines, methadone, phencyclidine, and propoxyphene.

Pre-infusion safety labs will be performed onsite and should be collected and results interpreted prior to the following day's infusion start. The following should be measured at Visit 3, Visit 4, Visit 6, Visit 11, Visit 12, and Visit 14: sodium (Na), potassium (K), ionized calcium, urea nitrogen (BUN)/urea, creatinine (Crea), hematocrit, hemoglobin, platelets. These results are only available at each site and will therefore not be summarized.

The exit safety lab panel includes all comprehensive labs, immunochemistry, direct antiglobulin test, and ionized calcium.

Comprehensive labs will be performed at screening/Visit 1, Visit 6, Visit 8, Visit 9, Visit 14, Visit 16, Visit 17, and upon exit/Visit 19.

Laboratory test results, excluding the site's pre-infusion safety labs mentioned above, will be summarized descriptively by treatment and visit as both observed values and change from baseline values for each parameter. Categorical urinalysis results will be summarized using frequencies by treatment group and visit.

Shifts from baseline for clinical laboratory values below, within, or above the normal range will be provided for hematology, chemistry, coagulation, and quantitaive urinalysis results by visit and treatment. See Section 6.1.1 for the definition of baseline.

Subjects with significant laboratory abnormalities will be identified in data listings. If any laboratory tests are collected at an unscheduled visit post-baseline, the results will be included in listings.

Pregnancy test results from Screening (Visit 1), Visit 3, and Visit 11 will be listed.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for seated systolic blood pressure, standing systolic blood pressure, and supine systolic blood pressure, seated diastolic blood pressure, standing diastolic blood pressure, and supine diastolic blood pressure, heart rate, respiration rate, and body temperature. These summaries will be presented by visit and treatment group. Vital signs are collected at all study visits. During the infusion periods (Visit 3-Visit 7 and Visit 11- Visit 15), orthostatic vital signs (supine systolic and supine diastolic blood pressure compared to standing systolic and standing diastolic blood pressure) should be measured prior to infusion start and at approximately [redacted] after infusion start. Seated systolic and seated diastolic blood pressure is measured at multiple timepoints during and after each infusion. Abnormal vital sign values will be flagged in the listings. Abnormal vital sign values are as follows:

- Seated systolic blood pressure value < 90 mmHg
- Seated systolic blood pressure value > 180 mmHg
- Seated diastolic blood pressure value < 50 mmHg
- Seated diastolic blood pressure value > 110 mmHg
- Incidence of orthostatic hypotension (a decrease in systolic blood pressure of > 20 mm Hg and/or a decrease in diastolic blood pressure of > 10 mm Hg between supine and standing)
- Heart rate > 100 beats per minute
- Temperature > 37.5°C
- Temperature < 36.5°C
- Respiration rate > 20 breaths per minute
- Respiration rate < 12 breaths per minute

The vital sign measurements that meet the criteria for blood pressures of special interest (listed below) will also be identified from the vital signs source data and summarized separately by study visit, timepoint, and treatment.

- Seated systolic blood pressure >180 mmHg
- Seated systolic blood pressure > 200 mmHg
- Seated systolic blood pressure < 90 mmHg
- Seated diastolic blood pressure > 110 mmHg
- Seated diastolic blood pressure > 120 mmHg
- Seated diastolic blood pressure < 50 mmHg
- A change of ≥ 30% from baseline in seated systolic and/or seated diastolic blood pressure

9.4. Electrocardiograms (ECGs)

12-Lead Electrocardiograms will be obtained at Screening, Week 1 (Visit 7) and Week 13 (Visits 11 and 15).

Descriptive summaries will be presented for ECG measures of QT interval, QTc interval, and HR. Corrected QTc intervals will be calculated using Fridericia's correction formula. These summaries will be presented by treatment group and visit.

The number and percentage of subjects with normal, abnormal but not clinically significant, and abnormal and clinically significant ECG results will be summarized for the Safety Dataset by treatment group and visit.

9.5. Further Safety Evaluations

9.5.1. Physical Examination

A full physical examination will be performed to assess the following organ systems: skin; ears, nose, and throat (ENT); head; eyes; lungs/chest; heart; abdomen; musculoskeletal; extremities; neurologic system; and lymphatic system. 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); muscle strength, tone, and bulk; 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.

While the subject is inpatient, a targeted physical exam, including auscultation of the heart and lungs, an assessment of peripheral edema, and weight, will be performed per the study schedule.

All physical exam results will be listed.

9.5.2. Sheehan-Suicidality Tracking Scale (S-STS)

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. This study is only collecting the total

scale score. S-STS total scores will be summarized descriptively by treatment and visit as both observed values and change from baseline values.

9.6. Concomitant Medication

Prior and concomitant medications, coded using World Health Organization drug dictionary (WHO-DDE) (March 2018), will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and PT (i.e., ATC classification Level 5), if applicable, and by treatment group using counts and percentages. Additionally, the number of subjects with prior medications for PD and cognition will be presented by treatment group. Medications for PD will be identified from the indication field on the CRF as well as those in ATC Classes N04, N04A, and N04B. Medications for cognition will be identified by ATC Class N06D and N06DX. A review of prior and concomitant medications along with their indications will be performed prior to database lock.

Prior medications will be presented separately from concomitant medications. The assignment of medications as prior and/or concomitant will be done as follows:

- **Prior medications:** Medications that started before first dose will be considered prior medications whether or not they were stopped before dose.
- **Concomitant medications:** Any medications continuing or starting after the first dose through the end of study will be considered to be concomitant.

If a medication starts prior to the first dose and continues after the first dose it will be considered both prior and concomitant. Prior and concomitant medications will also be listed.

10. Changes from Planned Analysis

The protocol will be amended such that blood pressure values, in conjunction with signs and symptoms of hypo/hypertension, will be at the discretion of the PI as to whether or not they constitute an AESI. As such, ranges for blood pressures of special interest (BPSI) were identified and will be used for consideration in determining whether events are BPSIs going forward. Separate summaries of these measurements will be presented. See Section 9.3.

11. Other Planned Analysis

11.1. Hoehn and Yahr Scale

The Hoehn and Yahr Scale is used to describe the symptom progression of PD. The scale is as follows:

Stage	Description
0	No signs of disease
1.0	Symptoms are very mild; unilateral involvement only
2	Bilateral involvement without impairment of balance

Stage	Description
3	Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

The Hoehn and Yahr Scale will be assessed at Screening (Visit 1) only and will be listed.

11.2. Modified Hachinski Ischemic Scale (MHIS)

The MHIS 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. 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.

The MHIS will be assessed at Screening (Visit 1) only and the presence of the clinical features will be listed.

11.3. Echocardiogram

During Screening (Visit 1), an echocardiogram will be performed to evaluate the subject's left ventricular (LV) systolic function to ensure the subject's ejection fraction percentage is $\geq 55\%$. Echocardiogram results will be listed.

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (listing number).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number ALK6021-201. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 2: Demographic Data Summary Tables and Figures

Number	Set	Title	Safety IA	Efficacy IA
Table 14.1.1	ITT	Summary of Subject Disposition	X	X
Table 14.1.2.1	ITT	Demographics and Baseline Characteristics	X	X
Table 14.1.3.1	Safety	Summary of Medical History by SOC, PT, and Treatment		
Table 14.1.3.2	Safety	Summary of Parkinson's Disease Medical History by SOC, PT, LLT, and Treatment		
Table 14.1.4	Safety	Summary of Prior Medications by ATC Class Level 4, PT, and Treatment		
Table 14.1.5	Safety	Summary of Exposure by Treatment	X	X

13.2. Efficacy Data Tabulations

Table 3: Efficacy Data

Number	Set	Title	Include in Interim Efficacy Analysis?
Table 14.2.1.1	Evaluable	Summary of Change from Baseline in MoCA Scores by Treatment	X
Table 14.2.1.2	Evaluable	Mean Change from Baseline in MoCA Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.1.3	Per Protocol	Summary of Change from Baseline in MoCA Scores by Treatment	X
Table 14.2.1.4	Per Protocol	Mean Change from Baseline in MoCA Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.1.5	Complete	Summary of Change from Baseline in MoCA Scores by Treatment	
Table 14.2.1.6	Complete	Mean Change from Baseline in MoCA Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.2.1	Evaluable	Summary of Change from Baseline in D-KEFS Total Score by Treatment	
Table 14.2.2.2	Evaluable	Mean Change from Baseline in D-KEFS Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.2.3	Per Protocol	Summary of Change from Baseline in D-KEFS Total Score by Treatment	

Number	Set	Title	Include in Interim Efficacy Analysis?
Table 14.2.2.4	Per Protocol	Mean Change from Baseline in D-KEFS Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.2.5	Complete	Summary of Change from Baseline in D-KEFS Total Score by Treatment	
Table 14.2.2.6	Complete	Mean Change from Baseline in D-KEFS Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.3.1	Evaluable	Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment	X
Table 14.2.3.2	Evaluable	Mean Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.3.3	Per Protocol	Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment	X
Table 14.2.3.4	Per Protocol	Mean Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.3.5	Complete	Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment	
Table 14.2.3.6	Complete	Mean Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.4.1	Evaluable	Summary of SE-ADL by Study Visit and Treatment	
Table 14.2.4.2	Per Protocol	Summary of SE-ADL by Study Visit and Treatment	
Table 14.2.4.3	Complete	Summary of SE-ADL by Study Visit and Treatment	
Table 14.2.5.1	Evaluable	Summary of Change from Baseline in CISI-PD Scores by Treatment	
Table 14.2.5.2	Evaluable	Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.5.3	Per Protocol	Summary of Change from Baseline in CISI-PD Scores by Treatment	
Table 14.2.5.4	Per Protocol	Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	

Number	Set	Title	Include in Interim Efficacy Analysis?
Table 14.2.5.5	Complete	Summary of Change from Baseline in CISI-PD Scores by Treatment	
Table 14.2.5.6	Complete	Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.6.1	Evaluable	Summary of Change from Baseline in PDQ-39 Scores by Treatment	
Table 14.2.6.2	Evaluable	Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.6.3	Per Protocol	Summary of Change from Baseline in PDQ-39 Scores by Treatment	
Table 14.2.6.4	Per Protocol	Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.6.5	Complete	Summary of Change from Baseline in PDQ-39 Scores by Treatment	
Table 14.2.6.6	Complete	Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.7.1	Evaluable	Summary of GDS-15 Categories by Study Visit and Treatment	
Table 14.2.7.2	Evaluable	Summary of Change from Baseline in GDS-15 Score by Treatment	
Table 14.2.7.3	Evaluable	Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.7.4	Per Protocol	Summary of GDS-15 Categories by Study Visit and Treatment	
Table 14.2.7.5	Per Protocol	Summary of Change from Baseline in GDS-15 Score by Treatment	
Table 14.2.7.6	Per Protocol	Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.7.7	Complete	Summary of GDS-15 Categories by Study Visit and Treatment	
Table 14.2.7.8	Complete	Summary of Change from Baseline in GDS-15 Score by Treatment	

Number	Set	Title	Include in Interim Efficacy Analysis?
Table 14.2.7.9	Complete	Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.8.1	Evaluable	Summary of Change from Baseline in dCDT Score by Treatment	
Table 14.2.8.2	Evaluable	Mean Change from Baseline in dCDT Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.8.3	Per Protocol	Summary of Change from Baseline in dCDT Score by Treatment	
Table 14.2.8.4	Per Protocol	Mean Change from Baseline in dCDT Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.8.5	Complete	Summary of Change from Baseline in dCDT Score by Treatment	
Table 14.2.8.6	Complete	Mean Change from Baseline in dCDT Score by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA	
Table 14.2.8.7	Evaluable	Summary of dCDT Classification by Study Visit and Treatment	
Table 14.2.8.8	Per Protocol	Summary of dCDT Classification by Study Visit and Treatment	
Table 14.2.8.9	Complete	Summary of dCDT Classification by Study Visit and Treatment	
Table 14.2.9.1	Evaluable	Summary of Screening Safety MRI Results by Treatment	
Table 14.2.9.2	Per Protocol	Summary of Screening Safety MRI Results by Treatment	
Table 14.2.9.3	Evaluable	Summary of Volumetric MRI Results by Treatment	
Table 14.2.9.4	Evaluable	Summary of ASL MRI Results by Treatment	

13.3. Safety Data

Table 4: Safety Data

Number	Set	Title	Include in Interim Safety Analysis?	Include in Interim Efficacy Analysis?
14.3.1 Displays of Adverse Events				
Table 14.3.1.1	Safety	Summary of Adverse Events by Treatment	X	X
Table 14.3.1.2	Safety	Incidence of Treatment Emergent Adverse Events by SOC, PT, and Treatment	X	X
Table 14.3.1.3	Safety	Incidence of Treatment Emergent Adverse Events by Maximum Severity, SOC, PT, and Treatment	X	
Table 14.3.1.4	Safety	Incidence of Treatment Emergent Adverse Events by Relationship, SOC, PT, and Treatment	X	
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events				
Table 14.3.2.1	Safety	Incidence of Adverse Events Leading to Withdrawal by SOC, PT, and Treatment	X	X
Table 14.3.2.2	Safety	Incidence of Serious Adverse Events by SOC, PT, and Treatment	X	X
Table 14.3.2.3	Safety	Incidence of Adverse Events of Special Interest by SOC, PT, and Treatment	X	X
Table 14.3.2.4	Safety	Incidence of Adverse Events with Terms Associated with Blood Pressure Changes by Infusion Period, SOC, PT, and Treatment	X	X
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events				
Table 14.3.3.1	Safety	Listing of Adverse Events Leading to Study Drug Discontinuation		
Table 14.3.3.2	Safety	Listing of Serious Adverse Events		
Table 14.3.3.3	Safety	Listing of Deaths		
Table 14.3.3.4	Safety	Listing of Adverse Events of Special Interest		
14.3.4 Abnormal Laboratory Value				
NA				
14.3.5 Laboratory Data Summary Tables				

Number	Set	Title	Include in Interim Safety Analysis?	Include in Interim Efficacy Analysis?
Table 14.3.5.1.1	Safety	Summary of Hematology Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.1.2	Safety	Shift from Baseline in Hematology Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.2.1	Safety	Summary of Serum Chemistry Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.2.2	Safety	Shift from Baseline in Serum Chemistry Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.3.1	Safety	Summary of Quantitative Urinalysis Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.3.2	Safety	Shift from Baseline in Quantitative Urinalysis Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.3.3	Safety	Summary of Qualitative Urinalysis Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.4.1	Safety	Summary of Coagulation Laboratory Results by Study Visit and Treatment	X	
Table 14.3.5.4.2	Safety	Shift from Baseline in Coagulation Laboratory Results by Study Visit and Treatment	X	
14.3.6 Other Safety Data Summary Tables				
Table 14.3.6.1.1	Safety	Summary of Vital Signs by Study Visit and Treatment	X	
Table 14.3.6.1.2	Safety	Summary of Blood Pressures of Special Interest by Study Visit and Treatment	X	
Table 14.3.6.2.1	Safety	Summary of 12-Lead Electrocardiogram by Study Visit and Treatment		
Table 14.3.6.2.2	Safety	Summary of 12-Lead Electrocardiogram Interpretation by Study Visit and Treatment		
Table 14.3.6.3	Safety	Summary of Sheehan-Suicidality Tracking Scale (S-STS) by Study Visit and Treatment	X	
Table 14.3.6.4	Safety	Summary of Concomitant Medications by ATC Class Level 4, PT, and Treatment		

13.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number ALK6021-201.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 5: Planned Listings

Number	Dataset	Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Inclusion and Exclusion Criteria Not Met
Listing 16.2.2.2	All Subjects	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses		
Listing 16.2.3	All Subjects	Analysis Sets
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	All Subjects	Demographics and Baseline Characteristics
Listing 16.2.4.2.1	All Subjects	Medical History
Listing 16.2.4.2.2	All Subjects	Family Medical History
Listing 16.2.4.2.3	All Subjects	Social History and Exercise/Activity Level
Listing 16.2.4.3	All Subjects	Alcohol, Tobacco, and Substance Use
Listing 16.2.4.4	All Subjects	Modified Hachinski Ischaemia Scale (MHIS)
Listing 16.2.4.5	All Subjects	Hoehn and Yahr Scale
16.2.5 Compliance and/or Drug Concentration Data		
Listing 16.2.5	All Subjects	Drug Infusion
16.2.6 Individual Efficacy Response Data		
Listing 16.2.6.1	All Subjects	MoCA
Listing 16.2.6.2	All Subjects	D-KEFS Verbal Fluency Test
Listing 16.2.6.3	All Subjects	MDS-UPDRS
Listing 16.2.6.4	All Subjects	SE-ADL Scale

Number	Dataset	Title / Summary
Listing 16.2.6.5	All Subjects	CISI-PD
Listing 16.2.6.6	All Subjects	PDQ-39
Listing 16.2.6.7	All Subjects	GDS-15
Listing 16.2.6.8	All Subjects	dCDT
Listing 16.2.6.9	All Subjects	Patient Questionnaire Status
Listing 16.2.6.10	All Subjects	Safety MRI Results
Listing 16.2.6.11	All Subjects	Volumetric MRI Results
Listing 16.2.6.12	All Subjects	ASL MRI Results
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	All Subjects	Adverse Events
16.2.8 Laboratory Values and Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.8.1.1	All Subjects	Clinical Laboratory Data: Hematology
Listing 16.2.8.1.2	All Subjects	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.1.3	All Subjects	Clinical Laboratory Data: Urinalysis
Listing 16.2.8.1.4	All Subjects	Clinical Laboratory Data: Urine Drug Screen and Pregnancy Tests
Listing 16.2.8.1.5	All Subjects	Clinical Laboratory Data: Coagulation
Listing 16.2.8.1.6	All Subjects	Clinical Laboratory Data: Immunology
Listing 16.2.8.1.7	All Subjects	Clinical Laboratory Data: Serology
Listing 16.2.8.2.1	All Subjects	Vital Signs
Listing 16.2.8.2.2	All Subjects	Blood Pressure
Listing 16.2.8.3	All Subjects	12-Lead Electrocardiogram (ECG) Results
Listing 16.2.8.4	All Subjects	Echocardiogram Results
Listing 16.2.8.5.1	All Subjects	Physical Examination
Listing 16.2.8.5.2	All Subjects	Targeted Physical Examination
Listing 16.2.8.6	All Subjects	S-STS
Listing 16.2.8.7	All Subjects	Prior and Concomitant Medications

13.5. Planned Figure Descriptions

Table 6: Planned Figures

Number	Population	Title	Safety IA	Efficacy IA
Figure 14.2.1.1	Evaluable	Boxplots of MoCA Total Scores by Visit and Treatment		
Figure 14.2.1.2	Per Protocol	Boxplots of MoCA Total Scores by Visit and Treatment		
Figure 14.2.2.1	Evaluable	Boxplots of D-KEFS Total Scores by Visit and Treatment		
Figure 14.2.2.2	Per Protocol	Boxplots of D-KEFS Total Scores by Visit and Treatment		
Figure 14.2.3.1	Evaluable	Boxplots of MDS-UPDRS Parts 1-3 Scores by Visit and Treatment		
Figure 14.2.3.2	Per Protocol	Boxplots of MDS-UPDRS Parts 1-3 Scores by Visit and Treatment		
Figure 14.2.3.3	Evaluable	Boxplots of MDS-UPDRS Part 1 Scores by Visit and Treatment		
Figure 14.2.3.4	Per Protocol	Boxplots of MDS-UPDRS Part 1 Scores by Visit and Treatment		
Figure 14.2.3.5	Evaluable	Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment		
Figure 14.2.3.6	Per Protocol	Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment		
Figure 14.2.3.7	Evaluable	Boxplots of MDS-UPDRS Part 3 Scores by Visit and Treatment		
Figure 14.2.3.8	Per Protocol	Boxplots of MDS-UPDRS Part 3 Scores by Visit and Treatment		
Figure 14.3.1.1	Safety	Hematology Data by Parameter, Visit, and Treatment		
Figure 14.3.1.2	Safety	Serum Chemistry Laboratory Data by Parameter, Visit, and Treatment		
Figure 14.3.1.3	Safety	Quantitative Urinalysis Laboratory Data by Parameter, Visit, and Treatment		
Figure 14.3.2.1	Safety	Hematology: Mean (SD) by Parameter, Visit, and Treatment		
Figure 14.3.2.2	Safety	Serum Chemistry: Mean (SD) by Parameter, Visit, and Treatment		
Figure 14.3.2.3	Safety	Quantitative Urinalysis: Mean (SD) by Parameter, Visit, and Treatment		

Number	Population	Title	Safety IA	Efficacy IA
Figure 14.3.3.1	Safety	Vital Signs Data by Parameter, Visit, and Treatment		
Figure 14.3.3.2	Safety	Vital Signs: Mean (SD) by Parameter, Visit, and Treatment		

14. Tables, Listings, and Figures (TLF) Shells

14.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all TLFs in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Figure 2: Standardized Layout

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Protocol: ALK6021-201 Version

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

<Note: If directly Applicable>

Footnote 1 *<if applicable>* Recommendation is to keep footnotes to a minimum

Footnote 2 *<if applicable>*

Footnote n *<if applicable>*

Footnote n+1 *<pgm path and name>, <date>*

14.2. Planned Table Shells

Table 14.1.1
Summary of Subject Disposition
ITT Set

Status	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Randomized	XX	XX	XX
Completed Dosing Period 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Completed Dosing Period 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Completed Study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Did not complete the study per protocol due to COVID-19	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Prematurely Discontinued from Study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for Discontinuation:			
Adverse Event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lost to Follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Physician Decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pregnancy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Protocol Deviation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Study Terminated by Sponsor	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Withdrawal by Legally Authorized Representative	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Withdrawal by Subject	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Worsening Condition	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Completed Study Visit:			
Visit 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 5	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 6	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviation: COVID-19 = novel coronavirus disease 2019; CRF = case report form;
Note: Percentages are based on the number of subjects randomized. A subject is considered to not have completed the study per protocol due to COVID-19 if they had any missing visits that affected treatment administration or collection of end of study efficacy assessments due to COVID-19. If a subject did not complete the study per protocol due to COVID-19, this category supersedes their study status on the study completion CRF.
[1] The ITT Set consists of all randomized subjects.
[2] The Safety Set consists of all subjects who received at least one dose of the study agent.
[3] The Evaluable Set consists of subjects who receive at least 5 of the 10 planned doses and complete through Visit 8.
[4] The Per Protocol Set is a subset of the Evaluable Set comprised of subjects who receive all 10 planned doses, who complete Visit 18 and Visit 19 in window, and who have no protocol deviations that could affect the assessment of efficacy.
[5] The Complete Set is a subset of the PP Set comprised of subejects who did not have any changes to any of the following concomitant medications preferred terms reported at any time on study: Dopaminergic agents (e.g. Rotigotine [(Neupro Patch]), Duopa Pump, Pimavanserin Tartate (Nuplazid), Quetiapine Fumarate (Seroquel), Sinemet [(Carbidopa, Levodopa]), Carbidopa, Rytary), Pregabalin (Lyrica), Amantadine, Antipsychotics (e.g. Pimavanserin Tartate [Nuplazid], Clozapine, Quetiapine Fumarate [Seroquel]), or benzodiazepines (e.g. Alprazolam). This includes those that startedwere stable per protocol beforeprior to first dose and either changed dose or stopped on study andas well as those that began on study.

Source: Listing 16.2.1

Table 14.1.1 (cont.)
Summary of Subject Disposition
ITT Set

Status	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Completed Study Visit:			
Visit 7	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 8	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 9	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 10	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 11	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 12	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 13	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 14	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 15	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 16	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 17	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 18	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Analysis Sets:			
ITT Set [1]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Safety Set [2]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Evaluable Set [3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Per Protocol Set [4]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Complete Set [5]			

Abbreviation: COVID-19 = novel coronavirus disease 2019.
Note: Percentages are based on the number of subjects randomized. A subject is considered to not have completed the study per protocol due to COVID-19 if they had any missing visits that affected treatment administration or collection of end of study efficacy assessments due to COVID-19.
[1] The ITT Set consists of all randomized subjects.
[2] The Safety Set consists of all subjects who received at least one dose of the study agent.
[3] The Evaluable Set consists of subjects who receive at least 5 of the 10 planned doses and complete through Visit 8.
[4] The Per Protocol Set is a subset of the Evaluable Set comprised of subjects who receive all 10 planned doses, who complete Visit 18 and Visit 19 in window, and who have no protocol deviations that could affect the assessment of efficacy.
[5] The Complete Set is a subset of the PP Set comprised of subjects who did not have any changes to any of the following concomitant medications preferred terms reported at any time on study: Dopaminergic agents (e.g. Rotigotine [Neupro Patch], Duopa Pump, Sinemet [Carbidopa, Levodopa], Carbidopa, Rytary), Pregabalin (Lyrica), Amantadine, Antipsychotics (e.g. Pimavanserin Tartate [Nuplazid], Clozapine, Quetiapine Fumarate [Seroquel]), or benzodiazepines (e.g. Alprazolam). This includes those that were stable per protocol prior to first dose and either changed dose or stopped on study as well as those that began on study.
Source: Listing 16.2.1

Table 14.1.2
Demographics and Baseline Characteristics
ITT Set

Variable Statistic or Category	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Age (years)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
P value [1]		X.XXXX	
Sex			
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX	
Child-Bearing Potential? [3]			
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ethnicity			
Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX	

Abbreviations: ApoE = polopoprotein E; CRF = case report form; PD = Parkinson's Disease.
Note: Percentages are n/Number of subjects in the ITT Set*100. Subjects are summarized by randomized treatment. Disease duration = [Enrollment date – PD onset date (as recorded on the Medical History CRF) + 1] / 365.
[1] P value from Wilcoxon rank-sum test.
[2] P value from Chi-square test.
[3] Only captured for female subjects; percentages are based on the number of female subjects in the ITT Set.
[4] Obtained from Visit 3 blood draw.
Source: Listing 16.2.4.1

Table 14.1.2 (cont.)
Demographics and Baseline Characteristics
ITT Set

Variable Statistic or Category	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Race			
White	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Black or African-American	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Asian	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
American Indian or Alaska Native	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Native Hawaiian or Other Pacific Islander	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
More than One Race	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX	
Height (cm)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
P value [1]		X.XXXX	
Weight (kg)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
P value [1]		X.XXXX	
Body Mass Index (kg/m^2)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
P value [1]		X.XXXX	

Abbreviations: ApoE = polopoprotein E; CRF = case report form; PD = Parkinson's Disease.
Note: Percentages are n/Number of subjects in the ITT Set*100. Subjects are summarized by randomized treatment. Disease duration = [Enrollment date – PD onset date (as recorded on the Medical History CRF) + 1] / 365.
[1] P value from Wilcoxon rank-sum test.
[2] P value from Chi-square test.
[3] Only captured for female subjects; percentages are based on the number of female subjects in the ITT Set.
[4] Obtained from Visit 3 blood draw.
Source: Listing 16.2.4.1

Table 14.1.2 (cont.)
Demographics and Baseline Characteristics
ITT Set

Variable Statistic or Category	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Disease Duration (years)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
P value [1]		X.XXXX	
ApoE Genotype [4]			
2/2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2/3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3/3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4/3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4/4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2/4	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX	

Abbreviations: ApoE = polopoprotein E; CRF = case report form; PD = Parkinson's Disease.
Note: Percentages are n/Number of subjects in the ITT Set*100. Subjects are summarized by randomized treatment. Disease duration = [Enrollment date – PD onset date (as recorded on the Medical History CRF) + 1] / 365.
[1] P value from Wilcoxon rank-sum test.
[2] P value from Chi-square test.
[3] Only captured for female subjects; percentages are based on the number of female subjects in the ITT Set.
[4] Obtained from Visit 3 blood draw.
Source: Listing 16.2.4.1

***Programming Note:** If cell counts are <5, use Fisher's Exact Test and update footnote accordingly.*

Table 14.1.3.1
Summary of Medical History by SOC, PT, and Treatment
Safety Set

System Organ Class Preferred Term	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Subjects with at least 1 Recorded Medical History	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: PT = Preferred Term; SOC = System Organ Class.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. Medical histories were coded using MedDRA version 21.0. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.4.2.1

Programming note: *SOC & PT text should be in proper case in table, as shown in the shell.*

Table 14.1.3.2
Summary of Parkinson's Disease Medical History by SOC, PT, LLT and Treatment
Safety Set

System Organ Class Preferred Term Lower Level Term	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Subjects with at least 1 Recorded Medical History	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower Level Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower Level Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower Level Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lower Level Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: LLT = Lower Level Term; PT = Preferred Term; SOC = System Organ Class.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. Medical histories were coded using MedDRA version 21.0. This table contains histories of Parkinson's Disease-Mild Cognitive Impairment and Parkinson's Disease-Dementia which includes the following LLTs: Parkinson's Disease, cognitive disorder, cognitive impairment, and dementia. Subjects were counted once for each system organ class (SOC), once for each preferred term (PT) and once for each Lower Level Term (LLT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, then LLT within PT, and then alphabetically by LLT.
SOURCE: Listing 16.2.4.2.1

Programming note: *SOC & PT text should be in proper case in table, as shown in the shell.*

Table 14.1.4
Summary of Prior Medications by ATC Class Level 4, PT, and Treatment
Safety Set

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Subjects with at least 1 Prior Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least 1 Prior Medication for PD	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least 1 Prior Medication for Cognition	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; PD = Parkinson's Disease; PT = Preferred Term.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. Medications were coded using WHODrug version March 2018. Medications that started before first dose will be considered prior medications whether or not they were stopped before dose. Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by PT within ATC, and then alphabetically. Subjects were counted only once for each ATC and PT. Medications for PD are identified from the indication field on the CRF as well as those in ATC Classes N04, N04A, and N04B. Medications for cognition are identified by ATC Class N06D and N06DX.
SOURCE: Listing 16.2.8.6

Programming note: *ATC & PT text should be in proper case in table, as shown in the shell. Ensure correct WHODrug version is printed in footnote.*

Table 14.1.5
Summary of Exposure by Treatment
Safety Set

Dosing Period: Overall

Variable / Statistic	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Evaluable Subjects [1]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Total Number of Exposure Days			
n	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Actual Volume Administered			
n	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX

Continue for Dosing Period 1 and Dosing Period 2

Note Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
[1] The duration of therapy for a subject to be considered evaluable is 5 exposure days.
SOURCE: Listing 16.2.5

Table 14.2.1.1
Summary of Change from Baseline in MoCA Scores by Treatment
Evaluable Set

Parameter: Total Score

Study Visit	Placebo (N=XX)			GRF6021 (N=XX)		
Statistic	Observed	CFB	%CFB	Observed	CFB	%CFB
Baseline [1]						
n	XX			XX		
Mean (SD)	XX.X (XX.XX)			XX.X (XX.XX)		
Median	XX.X			XX.X		
Min, Max	XX, XX			XX, XX		
Week 4 (Visit 9)						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
P value [2]					X.XXXX	
Week 16 (Visit 17)						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
P value [2]					X.XXXX	

Repeat for all parameters.

Abbreviations: CFB = change from baseline; MoCA = Montreal Cognitive Assessment.
Note: Higher scores indicate better cognitive function; the total possible score is 30 and a score of 26 or more is considered normal. A positive value of change means an improvement, and a negative value of change means deterioration. Subjects are summarized by randomized treatment.
[1] The baseline value is the MoCA Score from Visit 1 (Screening).
[2] P-value for testing mean change from baseline to subsequent visit is 0 is calculated using a paired t-test.
SOURCE: Listing 16.2.6.1

Programming note: *Check normality per Section 8.2 of the SAP. If the data are non-normal, use the Wilcoxon signed-rank test and update the footnote accordingly. Parameters will be: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, orientation.*

Table 14.2.1.2
Mean Change from Baseline in MoCA Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

Study Visit Statistic [1]	Placebo (N=XX)	GRF6021 (N=XX)
Week 4 (Visit 9)		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Week 16 (Visit 17)		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX

Abbreviations: ANCOVA = analysis of covariance; ApoE = apolopoprotein E; CI = confidence interval; LS = least squares; MoCA = Montreal Cognitive Assessment; SE = standard error.
Note: Higher scores indicate better cognitive function; the total possible score is 30 and a score of 26 or more is considered normal. A positive value of change means an improvement, and a negative value of change means deterioration. Subjects are summarized by randomized treatment.
[1] Estimates for LS means (change from baseline and difference from placebo [ie, change from baseline for GRF6021 minus change from baseline for Placebo]) and accompanying 95% CIs and P values are from an ANCOVA model with treatment, visit, and treatment-by-visit interaction as the main effects, and baseline MoCA total score,age, and ApoE genotype as covariates.
[2] P value for testing mean change from baseline is 0.
[3] P value for testing difference (GRF6021 minus Placebo) in mean change from baseline from is 0.
SOURCE: Listing 16.2.6.1

Table 14.2.1.3
Summary of Change from Baseline in MoCA Total Score by Treatment
Per Protocol Set

(Same Shell as Table 14.2.1.1)

Table 14.2.1.4
Mean Change from Baseline in MoCA Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

(Same Shell as Table 14.2.1.2)

Table 14.2.1.5
Summary of Change from Baseline in MoCA Total Score by Treatment
Complete Set

(Same Shell as Table 14.2.1.1)

Table 14.2.1.6
Mean Change from Baseline in MoCA Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

(Same Shell as Table 14.2.1.2)

Table 14.2.2.1
Summary of Change from Baseline in D-KEFS Scores by Treatment
Evaluable Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Letter Fluency, Category Fluency, and Category Switching. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add D-KEFs to abbreviations. Update footnote to read "*[1] The baseline value is the D-KEFS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.2.*

Table 14.2.2.2
Mean Change from Baseline in D-KEFs Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

Same Shell as Table 14.2.1.2

Programming Note: *Add D-KEFs to abbreviations. SOURCE: Listing 16.2.6.2.*

Table 14.2.2.3
Summary of Change from Baseline in D-KEFs Scores by Treatment
Per Protocol Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Letter Fluency, Category Fluency, and Category Switching. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add D-KEFs to abbreviations. Update footnote to read "*[1] The baseline value is the D-KEFS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.2. Update footnote to reflect Per Protocol Set.*

Table 14.2.2.4
Mean Change from Baseline in D-KEFs Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

Same Shell as Table 14.2.1.2

Programming Note: *Add D-KEFs to abbreviations. SOURCE: Listing 16.2.6.2. Update footnote to reflect Per Protocol Set.*

Table 14.2.2.5
Summary of Change from Baseline in D-KEFs Scores by Treatment
Complete Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Letter Fluency, Category Fluency, and Category Switching. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add D-KEFs to abbreviations. Update footnote to read "*[1] The baseline value is the D-KEFS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.2. Update footnote to reflect Complete Set.*

Table 14.2.2.6
Mean Change from Baseline in D-KEFs Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

Same Shell as Table 14.2.1.2

Programming Note: *Add D-KEFs to abbreviations. SOURCE: Listing 16.2.6.2. Update footnote to reflect Complete Set.*

Table 14.2.3.1
Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment
Evaluable Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Part 1 Score, Part 2 Score and Part 3 Score. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), Week 16 (Visit 17), Week 20 (Vsit 18), and Week 24 (Visit 19). Add MDS-UPDRS to abbreviations. Update footnote to read "*[1] The baseline value is the MDS-UPDRS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.3.*

Table 14.2.3.2
Mean Change from Baseline in MDS-UPDRS Parts 1-3 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

Same Shell as Table 14.2.1.2.

Programming Note: *Add MDS-UPDRS to abbreviations.* Age and baseline score will be the only covariates used in the model, update footnote accordingly. *SOURCE: Listing 16.2.6.3.*

Table 14.2.3.3
Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment
Per Protocol Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Part 1 Score, Part 2 Score and Part 3 Score. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), Week 16 (Visit 17), Week 20 (Vsit 18), and Week 24 (Visit 19). Add MDS-UPDRS to abbreviations. Update footnote to read "*[1] The baseline value is the MDS-UPDRS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.3. Update footnote to reflect Per Protocol Set.*

Table 14.2.3.4
Mean Change from Baseline in MDS-UPDRS Parts 1-3 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set
Same Shell as Table 14.2.1.2

Programming Note: *Add MDS-UPDRS to abbreviations.* Age and baseline score will be the only covariates used in the model, update footnote accordingly. *SOURCE: Listing 16.2.6.3. Update footnote to reflect Per Protocol Set.*

Table 14.2.3.5
Summary of Change from Baseline in MDS-UPDRS Parts 1, 2, and 3 and Parts 1-3 Total Scores by Treatment
Complete Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameters will be Total Score, Part 1 Score, Part 2 Score and Part 3 Score. Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), Week 16 (Visit 17), Week 20 (Vsit 18), and Week 24 (Visit 19). Add MDS-UPDRS to abbreviations. Update footnote to read "*[1] The baseline value is the MDS-UPDRS Score from Visit 2 or before." *SOURCE: Listing 16.2.6.3. Update footnote to reflect Complete Set.*

Table 14.2.3.6
Mean Change from Baseline in MDS-UPDRS Parts 1-3 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

Same Shell as Table 14.2.1.2

Programming Note: *Add MDS-UPDRS to abbreviations.* Age and baseline score will be the only covariates used in the model, update footnote accordingly. *SOURCE: Listing 16.2.6.3. Update footnote to reflect Complete Set.*

Table 14.2.4.1
Summary of SE-ADL by Study Visit and Treatment
Evaluable Set

Study Visit Statistic	Placebo (N=XX)	GRF6021 (N=XX)
Baseline [1]		
100% = Completely independent, ability to do chores essentially normal.	XX (XX.X%)	XX (XX.X%)
90% = Completely independent, chores might take twice as long.	XX (XX.X%)	XX (XX.X%)
80% = Completely independent in most chores, takes twice as long.	XX (XX.X%)	XX (XX.X%)
70% = Not completely independent. Spend a large part of day with chores.	XX (XX.X%)	XX (XX.X%)
60% = Some dependency. Can do most chores, but exceedingly slowly.	XX (XX.X%)	XX (XX.X%)
50% = More dependent. Help with half of chores.	XX (XX.X%)	XX (XX.X%)
40% = Very dependent. Can assist with all chores but few alone.	XX (XX.X%)	XX (XX.X%)
30% = A few chores alone or begins alone. Much help needed.	XX (XX.X%)	XX (XX.X%)
20% = Nothing alone. Severe invalid.	XX (XX.X%)	XX (XX.X%)
10% = Totally dependent, helpless. Complete invalid.	XX (XX.X%)	XX (XX.X%)
0% = Vegetative functions. Bedridden.	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX
Week 8 (Visit 10)		
100% = Completely independent, ability to do chores essentially normal.	XX (XX.X%)	XX (XX.X%)
90% = Completely independent, chores might take twice as long.	XX (XX.X%)	XX (XX.X%)
80% = Completely independent in most chores, takes twice as long.	XX (XX.X%)	XX (XX.X%)
70% = Not completely independent. Spend a large part of day with chores.	XX (XX.X%)	XX (XX.X%)
60% = Some dependency. Can do most chores, but exceedingly slowly.	XX (XX.X%)	XX (XX.X%)
50% = More dependent. Help with half of chores.	XX (XX.X%)	XX (XX.X%)
40% = Very dependent. Can assist with all chores but few alone.	XX (XX.X%)	XX (XX.X%)
30% = A few chores alone or begins alone. Much help needed.	XX (XX.X%)	XX (XX.X%)
20% = Nothing alone. Severe invalid.	XX (XX.X%)	XX (XX.X%)
10% = Totally dependent, helpless. Complete invalid.	XX (XX.X%)	XX (XX.X%)
0% = Vegetative functions. Bedridden.	XX (XX.X%)	XX (XX.X%)
P value [2]		X.XXXX

Continue for Week 24 (Visit 19).

Abbreviations: CMH = Cochran-Mantel-Haenszel; SE-ADL = Schwab and England Activities of Daily Living Scale.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
[1] The baseline value is the SE-ADL Score from Visit 2.
[2] P value from CMH test.
SOURCE: Listing 16.2.6.4

Table 14.2.4.2
Summary of SE-ADL by Study Visit and Treatment
Per Protocol Set

(Same Shell as Table 14.2.4.1)

Programming Note: *Update footnote to reflect Per Protocol Set.*

Table 14.2.4.3
Summary of SE-ADL by Study Visit and Treatment
Complete Set

(Same Shell as Table 14.2.4.1)

Programming Note: *Update footnote to reflect Complete Set.*

Table 14.2.5.1
Summary of Change from Baseline in CISI-PD Scores by Treatment
Evaluable Set

(Same Shell as Table 14.2.1.1)
Programming Note: *Parameters will be Total Score, Motor Signs, Disability, Motor Complications, and Cognitive Status. Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 24 (Visit 19). Add* CISI-PD *to abbreviations. Update footnote to read "*[1] The baseline value is the CISI-PD Score from Visit 2 or before." *SOURCE: Listing 16.2.6.5.*

Table 14.2.5.2
Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Add* CISI-PD *to abbreviations. SOURCE: Listing 16.2.6.5.*

Table 14.2.5.3
Summary of Change from Baseline in CISI-PD Scores by Treatment
Per Protocol Set

(Same Shell as Table 14.2.1.1)
Programming Note: *Parameters will be Total Score, Motor Signs, Disability, Motor Complications, and Cognitive Status. Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 24 (Visit 19). Add* CISI-PD *to abbreviations. Add* CISI-PD *to abbreviations. Update footnote to read "*[1] The baseline value is the CISI-PD Score from Visit 2 or before." *SOURCE: Listing 16.2.6.5. Update footnote to reflect Per Protocol Set.*

Table 14.2.5.4
Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

Same Shell as Table 14.2.1.2
Programming Note: *Add* CISI-PD *to abbreviations. SOURCE: Listing 16.2.6.5. Update footnote to reflect Per Protocol Set.*

Table 14.2.5.5
Summary of Change from Baseline in CISI-PD Scores by Treatment
Complete Set

(Same Shell as Table 14.2.1.1)

Programming Note: *Parameters will be Total Score, Motor Signs, Disability, Motor Complications, and Cognitive Status. Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 24 (Visit 19). Add* CISI-PD *to abbreviations. Add* CISI-PD *to abbreviations. Update footnote to read* "[1] The baseline value is the CISI-PD Score from Visit 2 or before." *SOURCE: Listing 16.2.6.5. Update footnote to reflect Complete Set.*

Table 14.2.5.6
Mean Change from Baseline in CISI-PD Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

Same Shell as Table 14.2.1.2

Programming Note: *Add* CISI-PD *to abbreviations. SOURCE: Listing 16.2.6.5. Update footnote to reflect Complete Set.*

Table 14.2.6.1
Summary of Change from Baseline in PDQ-39 Scores by Treatment
Evaluable Set

(Same Shell as Table 14.2.1.1)

Programming Note: *Parameters will be Total Score, Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognitions, Communication, and Bodily Discomfort. Visits will be Baseline (Visit 2), Week 4 (Visit 9), Week 8 (Visit 10), Week 20 (Visit 18), and Week 24 (Visit 19). Add PDQ-39 to abbreviations. Update footnote to read "Note: PDQ-39 is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms. [1] The baseline value is the PDQ-39 Score from Visit 2 or before." SOURCE: Listing 16.2.6.6.*

Table 14.2.6.2
Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

(Same Shell as Table 14.2.1.2)

Programming Note: *Add PDQ-39 to abbreviations. SOURCE: Listing 16.2.6.6.*

Table 14.2.6.3
Summary of Change from Baseline in PDQ-39 Scores by Treatment
Per Protocol Set

(Same Shell as Table 14.2.1.1)

Programming Note: : *Parameters will be Total Score, Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognitions, Communication, and Bodily Discomfort. Visits will be Baseline (Visit 2), Week 4 (Visit 9), Week 8 (Visit 10), Week 20 (Visit 18), and Week 24 (Visit 19). Add PDQ-39 to abbreviations. Update footnote to read "Note: PDQ-39 is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms. [1] The baseline value is the PDQ-39 Score from Visit 2 or before." SOURCE: Listing 16.2.6.6. Update footnote to reflect Per Protocol Set.*

Table 14.2.6.4
Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

(Same Shell as Table 14.2.1.2)

Programming Note: *Add PDQ-39 to abbreviations.SOURCE: Listing 16.2.6.6. Update footnote to reflect Per Protocol Set.*

Table 14.2.6.5
Summary of Change from Baseline in PDQ-39 Scores by Treatment
Complete Set

(Same Shell as Table 14.2.1.1)

***Programming Note:** : Parameters will be Total Score, Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognitions, Communication, and Bodily Discomfort. Visits will be Baseline (Visit 2), Week 4 (Visit 9), Week 8 (Visit 10), Week 20 (Visit 18), and Week 24 (Visit 19). Add PDQ-39 to abbreviations. Update footnote to read "Note: PDQ-39 is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms. [1] The baseline value is the PDQ-39 Score from Visit 2 or before." SOURCE: Listing 16.2.6.6. Update footnote to reflect Complete Set.*

Table 14.2.6.6
Mean Change from Baseline in PDQ-39 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

(Same Shell as Table 14.2.1.2)

***Programming Note:** Add PDQ-39 to abbreviations.SOURCE: Listing 16.2.6.6. Update footnote to reflect Complete Set.*

Table 14.2.7.1
Summary of GDS-15 Categories by Study Visit and Treatment
Evaluable Set

Study Visit Category	Placebo (N=XX)	GRF6021 (N=XX)
Baseline [1]		
0-4 No depression	XX (XX.X%)	XX (XX.X%)
5-10 Mild depression	XX (XX.X%)	XX (XX.X%)
11 + Severe depression	XX (XX.X%)	XX (XX.X%)
Week 8 (Visit 10)		
0-4 No depression	XX (XX.X%)	XX (XX.X%)
5-10 Mild depression	XX (XX.X%)	XX (XX.X%)
11 + Severe depression	XX (XX.X%)	XX (XX.X%)
Week 20 (Visit 18)		
0-4 No depression	XX (XX.X%)	XX (XX.X%)
5-10 Mild depression	XX (XX.X%)	XX (XX.X%)
11 + Severe depression		

Abbreviation: GDS-15 = Geriatric Depression Scale-15.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
[1] The baseline value is the SDS-15 assessment from Visit 2 or before.
SOURCE: Listing 16.2.6.7

Table 14.2.7.2
Summary of Change from Baseline in GDS-15 Total Score by Treatment
Evaluable Set

(Same Shell as Table 14.2.1.1)

Programming Note: *Parameter will be Total Score Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 20 (Visit 18). Add GDS-15 to abbreviations. Update footnote to read "Note: Each item is recorded as yes or no which is assigned a numeric value of 1 or 0, respectively. 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 11 + Suggestive of severe depression. [1] The baseline value is the PDQ-39 Score from Visit 2 or before."SOURCE: Listing 16.2.6.7.*

Table 14.2.7.3
Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

(Same Shell as Table 14.2.1.2)

Programming Note: *Add GDS-15 to abbreviations. SOURCE: Listing 16.2.6.7.*

Table 14.2.7.4
Summary of GDS-15 Categories by Study Visit and Treatment
Per Protocol Set
Same Shell as Table 14.2.7.1

Programming Note: *Add GDS-15 to abbreviations. Update footnote to reflect Per Protocol Set. SOURCE: Listing 16.2.6.7.*

Table 14.2.7.5
Summary of Change from Baseline in GDS-15 Total Score by Treatment
Per Protocol Set

Same Shell as Table 14.2.1.1

Programming Note: *Parameter will be Total Score Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 20 (Visit 18). Add GDS-15 to abbreviations. Update footnote to read "Note: Each item is recorded as yes or no which is assigned a numeric value of 1 or 0, respectively. 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 11 + Suggestive of severe depression. [1] The baseline value is the PDQ-39 Score from Visit 2 or before." SOURCE: Listing 16.2.6.7.Update footnote to reflect Per Protocol Set.*

Table 14.2.7.6
Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Add GDS-15 to abbreviations. SOURCE: Listing 16.2.6.7.*

Table 14.2.7.7
Summary of GDS-15 Categories by Study Visit and Treatment
Complete Set

Same Shell as Table 14.2.7.1
Programming Note: *Add GDS-15 to abbreviations. Update footnote to reflect Per Protocol Set. SOURCE: Listing 16.2.6.7.*

Table 14.2.7.8
Summary of Change from Baseline in GDS-15 Total Score by Treatment
Complete Set

Same Shell as Table 14.2.1.1
Programming Note: *Parameter will be Total Score Visits will be Baseline (Visit 2), Week 8 (Visit 10), and Week 20 (Visit 18). Add GDS-15 to abbreviations. Update footnote to read "Note: Each item is recorded as yes or no which is assigned a numeric value of 1 or 0, respectively. 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 11 + Suggestive of severe depression. [1] The baseline value is the PDQ-39 Score from Visit 2 or before." SOURCE: Listing 16.2.6.7.Update footnote to reflect Per Protocol Set.*

Table 14.2.7.9
Mean Change from Baseline in GDS-15 Total Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Add GDS-15 to abbreviations. SOURCE: Listing 16.2.6.7.*

Table 14.2.8.1
Summary of Change from Baseline in dCDT Score by Treatment
Evaluable Set

(Same Shell as Table 14.2.1.1)
Programming Note: *Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add dCDT to abbreviations. Update footnote to read "[1] The baseline value is the dCDT Score from Visit 2 or before." SOURCE: Listing 16.2.6.8.*

Table 14.2.8.2
Mean Change from Baseline in dCDT Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Evaluable Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Add dCDT to abbreviations. SOURCE: Listing 16.2.6.8.*

Table 14.2.8.3
Summary of Change from Baseline in dCDT Score by Treatment
Per Protocol Set

(Same Shell as Table 14.2.1.1)
Programming Note: *Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add dCDT to abbreviations. Update footnote to read "[1] The baseline value is the dCDT Score from Visit 2 or before." SOURCE: Listing 16.2.6.8.*

Table 14.2.8.4
Mean Change from Baseline in dCDT Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Per Protocol Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Paramter will be dCDT total score. Add dCDT to abbreviations. SOURCE: Listing 16.2.6.8.*

Table 14.2.8.5
Summary of Change from Baseline in dCDT Score by Treatment
Complete Set

(Same Shell as Table 14.2.1.1)
Programming Note: *Visits will be Baseline (Visit 2), Week 1 (Visit 8), Week 8 (Visit 10), Week 13 (Visit 16), and Week 20 (Visit 18). Add dCDT to abbreviations. Update footnote to read "[1] The baseline value is the dCDT Score from Visit 2 or before." SOURCE: Listing 16.2.6.8.*

Table 14.2.8.6
Mean Change from Baseline in dCDT Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from ANCOVA
Complete Set

(Same Shell as Table 14.2.1.2)
Programming Note: *Paramter will be dCDT total score. Add dCDT to abbreviations. SOURCE: Listing 16.2.6.8.*

Table 14.2.8.7
dCDT Classification by Study Visit and Treatment
Evaluable Set

Study Visit Statistic	Placebo (N=XX)	GRF6021 (N=XX)
Baseline [1]		
Within normal limits	XX (XX.X%)	XX (XX.X%)
Indeterminate	XX (XX.X%)	XX (XX.X%)
Outside normal limits	XX (XX.X%)	XX (XX.X%)
Unanalyzable	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 8)		
Within normal limits	XX (XX.X%)	XX (XX.X%)
Indeterminate	XX (XX.X%)	XX (XX.X%)
Outside normal limits	XX (XX.X%)	XX (XX.X%)
Unanalyzable	XX (XX.X%)	XX (XX.X%)
Week 8 (Visit 10)		
Within normal limits	XX (XX.X%)	XX (XX.X%)
Indeterminate	XX (XX.X%)	XX (XX.X%)
Outside normal limits	XX (XX.X%)	XX (XX.X%)
Unanalyzable	XX (XX.X%)	XX (XX.X%)

Continue for other visits.

Abbreviation: dCDT = Digital clock drawing test.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
[1] The baseline value is the dCDT Score from Visit 2 or before.
SOURCE: Listing 16.2.6.8

Table 14.2.8.8
dCDT Classification by Study Visit and Treatment Treatment
Per Protocol Set

(Same shell as Table 14.2.8.7)
Programming Note: *Update footnote to reflect Per Protocol Set*

Table 14.2.8.9
dCDT Classification by Study Visit and Treatment Treatment
Complete Set

(Same shell as Table 14.2.8.7)
Programming Note: *Update footnote to reflect Complete Set*

Table 14.2.9.1
Screening Safety MRI Results by Study Visit and Treatment
Evaluable Set

Visit: Screening Test Category	Placebo (N=XX)	GRF6021 (N=XX)
Presence of MRI Abnormalities		
Yes	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)
Nonevaluable	XX (XX.X%)	XX (XX.X%)
Abnormalities Present		
Cerebral edema	XX (XX.X%)	XX (XX.X%)
Abnormality Primary Location		
Right frontal	XX (XX.X%)	XX (XX.X%)
Right temporal, non hippocampal	XX (XX.X%)	XX (XX.X%)
Right parietal	XX (XX.X%)	XX (XX.X%)
Right occipital	XX (XX.X%)	XX (XX.X%)
...		
Abnormality Status		
Present	XX (XX.X%)	XX (XX.X%)
Presence is questionable	XX (XX.X%)	XX (XX.X%)
Abnormality Sequence		
3DT1	XX (XX.X%)	XX (XX.X%)
FLAIR	XX (XX.X%)	XX (XX.X%)
T2*	XX (XX.X%)	XX (XX.X%)
T2	XX (XX.X%)	XX (XX.X%)
DWI	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)
Microhemorrhage	XX (XX.X%)	XX (XX.X%)
Abnormality Primary Location		
Right frontal	XX (XX.X%)	XX (XX.X%)
...		
Abnormality Status		
Present	XX (XX.X%)	XX (XX.X%)
Presence is questionable	XX (XX.X%)	XX (XX.X%)
Abnormality Sequence		
3DT1	XX (XX.X%)	XX (XX.X%)
...	XX (XX.X%)	XX (XX.X%)

Abbreviations: MRI = magnetic resonance imaging; PD = Parkinson's Disease.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
SOURCE: Listing 16.2.6.10

Table 14.2.9.1 (cont.)
Screening MRI Results by Study Visit and Treatment
Evaluable Set

Visit: Screening

Test Category	Placebo (N=XX)	GRF6021 (N=XX)
White matter disease present		
No lesions (including symmetrical, well-defined caps or bands)	XX (XX.X%)	XX (XX.X%)
Focal lesions	XX (XX.X%)	XX (XX.X%)
Beginning confluence of lesions	XX (XX.X%)	XX (XX.X%)
Diffuse involvement of entire region, with or without involvement of U-fibers	XX (XX.X%)	XX (XX.X%)
Non Evaluable	XX (XX.X%)	XX (XX.X%)
Potential alternative diagnosis to PD		
Yes	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)
Nonevaluable	XX (XX.X%)	XX (XX.X%)

Abbreviations: MRI = magnetic resonance imaging; PD = Parkinson's Disease.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
SOURCE: Listing 16.2.6.10

Programming Note: *Continue for Visit 16 for subjects who consented to additional MRI. Only categories with at least 1 subject should be presented for the following tests: Abnormalities Present, Abnormality Primary Location, and Abnormality Sequence.*

Potential abnormalities are: Cerebral edema, Microhemorrhage, Microhemorrhage (>1cm); Superficial siderosis; Subdural hemorrhage/hematoma; Epidural haemorrhage; Subarachnoid haemorrhage; Intraventricular haemorrhage; Stroke involving a major vascular territory; Lacunar infarct (10-15 mm); Cortical infarct; Other infarct; Cerebral contusion; Encephalomalacia; Aneurysm or Vascular malformation; Hydrocephalus; Infective lesion; Meningioma ≥ 1 cm in diameter; Meningioma < 1 cm in diameter; Arachnoid cyst ≥ 1 cm in diameter; Arachnoid cyst < 1 cm in diameter; Other space occupying lesion or Brain tumor; Other.

Potential Abnormality primary locations are: Right frontal; Right temporal, non hippocampal; Right parietal; Right occipital; Right chippocampus; Right cerebellum; Mid-brain; Medulla; Leptomeninges; Left frontal; Left temporal, non hippocampal; Left parietal; Left occipital; Left chippocampus; Left cerebellum; Hydrocephalus; Pons; Deep grey matter structures; Ventricular system; All brain;Other.

Potential abnormality sequences are: DT1; FLAIR; T2; T2; DWI; Other*

Table 14.2.9.2
Screening Safety MRI Results by Study Visit and Treatment
Per Protocol Set

(Same shell as Table 14.2.9.1)

Table 14.2.9.3
Volumetric MRI Results by Study Visit and Treatment
Evaluable Set

Test: Volume (mm³), Visit: Screening

Location Laterality Statistic	Placebo (N=XX)	GRF6021 (N=XX)
Whole Brain		
Bilateral		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Lateral Ventricles		
Bilateral		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Intracranial		
Bilateral		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Cortical		
Left		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Right		
n	XX	XX

Abbreviations: MRI = magnetic resonance imaging.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment.
SOURCE: Listing 16.2.6.11

Programming note: *For Visit: Screening, Additional locations for Test:* Volume (mm³) *will be Hippocampus (left, right, bilateral). Repeat table for Test: Cerebral Cortex Average Thickness (mm) and Cerebral Cortex Thickness Average Change (mm). Locations will be Cortical (left, right, bilateral), Mayo (bilateral), Prefrontal Lobe (left, right, bilateral), Whole Temporal Lobe (left, right, bilateral),Superior Temporal Lobe (left, right, bilateral), Medial Temporal Lobe (left, right, bilateral), Lateral Parietal Lobe (left, right, bilateral), Inferior Parietal Lobe (left, right, bilateral), Precuneus (left, right, bilateral), Isthmuscingulate (left, right, bilateral), Entorhinal Cortex (left, right, bilateral). Repeat table for Test: Atrophy (mm³). Locations will be the same as Test: Volume with the exception of Intracranial.*
Repeat table for Visit: Week 13 (Visit 16).

Table 14.2.9.4
ASL MRI Results by Study Visit and Treatment
Evaluable Set

Visit: Screening Location Laterality Statistic	Placebo (N=XX)	GRF6021 (N=XX)
Frontal Lobe		
Left		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Right		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Bilateral		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
Cingulate Cortex		
Left		
n	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX

Abbreviations: ASL = arterial-spin labeling; MRI = magnetic resonance imaging.
Note: Percentages are n/Number of subjects in the Evaluable Set*100. Subjects are summarized by randomized treatment. Cerebral blood flow measurements are presented in mL/100g/min.
SOURCE: Listing 16.2.6.12

Programming note: *For Visit: Screening, Additional locations will be Frontal lobe, Cingulate cortex, Parietal lobe, Temporal lobe, Occipital lobe, Striatum, Cerebellum, Thalamus, Pallidum, Substantia nigra, Hippocampus. Left, Right, and Bilateral sides will be present for all.*
Repeat table for Visit: Week 13 (Visit 16).

Table 14.3.1.1
Summary of Adverse Events by Treatment
Safety Set

Category	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least 1 TEAE			
n (Percentage, %)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
95% CI for percentage	XX.X%, XX.X%	XX.X%, XX.X%	XX.X%, XX.X%
Difference in percentage		XX.X%	
95% CI for difference in percentage		XX.X%, XX.X%	
P Value [1]		X.XXXX	
Subjects with an SAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
n (Percentage, %)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
95% CI for percentage	XX.X%, XX.X%	XX.X%, XX.X%	XX.X%, XX.X%
Difference in percentage		XX.X%	
95% CI for difference in percentage		XX.X%, XX.X%	
P Value [1]		X.XXXX	

Abbreviations: AESI = adverse event of special interest; CI = confidence interval; CRF = case report form; TEAE = treatment emergent adverse event; SAE = serious adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. AESIs are TEAEs that are of special interest as defined by the protocol and are only recorded if the PI considers them as Adverse Events.
[1] P value from Chi-square test.
[2] Related TEAEs are those marked as Possibly Related or Definitely Related on the CRF.
SOURCE: Listing 16.2.7.1

Table 14.3.1.1 (cont.)
Summary of Adverse Events by Treatment
Safety Set

Category	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Maximum Severity of TEAE			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with a Related TEAE [2]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with a TEAE Leading to Discontinuation of Study Drug (CRF)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with a TEAE Leading to Discontinuation of Study Drug (Derived)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with an AE leading to Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with an AESI	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: AESI = adverse event of special interest; CI = confidence interval; CRF = case report form; TEAE = treatment emergent adverse event; SAE = serious adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. AESIs are TEAEs that are of special interest as defined by the protocol and are only recorded if the PI considers them as Adverse Events. If the reason for discontinuation entered on the study completion CRF was "Adverse Event" and the AE occurred between the start of the first infusion in Period 1 through the final infusion in Period 2, the derived action taken was set to 'study drug withdrawn' regardless of what was indicated on the CRF since treatment is administered during two distinct periods and not on a continuous basis.
[1] P value from Chi-square test.
[2] Related TEAEs are those marked as Possibly Related or Definitely Related on the CRF.
SOURCE: Listing 16.2.7.1

***Programming note:** If Fisher's exact test is used, update footnote [1] accordingly.*

Table 14.3.1.2
Incidence of Treatment Emergent Adverse Events by SOC, PT, and Treatment
Safety Set

System Organ Class Preferred Term	Placebo (N=XX)	GRF6021 (N=XX)	Overall (N=XX)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. Subjects are counted once for each SOC and once for each PT. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Programming note: *SOC & PT text should be in proper case in table, as shown in the shell. Ensure correct MedDRA version is printed in footnote.*

Table 14.3.1.3
Incidence of Treatment Emergent Adverse Events by Maximum Severity, SOC, PT, and Treatment
Safety Set

System Organ Class Preferred Term Maximum Severity	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Any Event (Total)			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1			
Any Event (Total)			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1			
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. Subjects are counted once for each SOC and once for each PT. The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with a missing severity were counted as Severe. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Programming note: *SOC & PT text should be in proper case in table, as shown in the shell. Ensure correct MedDRA version is printed in footnote.*

Table 14.3.1.4
Incidence of Treatment Emergent Adverse Events by Relationship, SOC, PT, and Treatment
Safety Set

System Organ Class Preferred Term Maximum Severity	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Any Event (Total)			
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1			
Any Event (Total)			
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1			
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: CRF = case report form; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. AEs were coded using MedDRA version 21.0 A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. Subjects are counted once for each SOC and once for each PT. Subjects are classified according to the closest relationship if the subject reported one or more events. Related TEAEs are those marked as Possibly Related or Definitely Related on the CRF. AEs with a missing relationship will be considered related for this summary. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Programming note: *SOC & PT text should be in proper case in table, as shown in the shell. Ensure correct MedDRA version is printed in footnote.*

Table 14.3.2.1
Incidence of Adverse Events Leading to Withdrawal by SOC, PT, and Treatment
Safety Set

Same shell as Table 14.3.1.2

Programming note: AEs leading to withdrawal will be based on derived action taken in this table. The following should be added to Note: If the reason for discontinuation entered on the study completion CRF was "Adverse Event" and the AE occurred between the start of the first infusion in Period 1 through the final infusion in Period 2, the derived action taken was set to 'study drug withdrawn' regardless of what was indicated on the CRF since treatment is administered during two distinct periods and not on a continuous basis.

Table 14.3.2.2
Incidence of Serious Adverse Events by SOC, PT, and Treatment
Safety Set

Same shell as Table 14.3.1.2

Programming note: *Add SAE to abbreviations.*

Table 14.3.2.3
Incidence of Adverse Events of Special Interest by SOC, PT, and Treatment
Safety Set

Same shell as Table 14.3.1.2

Programming note: *Add AESI to abbreviations.*

Table 14.3.2.4
Incidence of Adverse Events with Terms Associated with Blood Pressure Changes by Infusion Period, SOC, PT, and Treatment
Safety Set

Infusion Period System Organ Class Preferred Term	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Any Occurrence			
System Organ Class 1			
Preferred Term 1 (Blood Pressure Decreased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2 (Blood Pressure Increased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2			
Preferred Term 1 (Blood Pressure Decreased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2 (Blood Pressure Increased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Starting During Infusion Period 1			
System Organ Class 1			
Preferred Term 1 (Blood Pressure Decreased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2 (Blood Pressure Increased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2			
Preferred Term 1 (Blood Pressure Decreased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2 (Blood Pressure Increased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Starting After Infusion Period 1			
System Organ Class 1			
Preferred Term 1 (Blood Pressure Decreased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2 (Blood Pressure Increased)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
...			

Abbreviations: CRF = case report form; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. AEs were coded using MedDRA version 21.0 A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. Subjects are counted once for each SOC and once for each PT. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Programming Note: *Continue for "Starting During Infusion Period 2" and "Starting After Infusion Period 2."*

Table 14.3.3.1
Listing of Adverse Events Leading to Study Drug Discontinuation
All Subjects

Subject ID	Treatment [1]	TEAE/ Intercurrent	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day) Start Time / End Date (Study Day) End Time	Severity/ Relationship	Outcome/ Study Drug Action Taken (CRF)/ Other Action Taken	Derived Action Taken	Serious?/ Criteria Met	AESI? [2]
XXXXXX	XXXXXX	XXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (XX) HH:MM/ DDMMMYYYY (XX) HH:MM	XXXXXXXXX/ XXXXXXXX	XXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	XXXXX XXXXX XXXXX	XX/ XXXXXXXXX	XXX
	XXXXXX	XXXX	XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	DDMMMYYYY (XX) HH:MM / Ongoing	XXXXXXXXX/ XXXXXXXX	XXXXXXXXXXXXX	XXXXX	XX	XXX
	XXXXXX	XXXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXX	DDMMMYYYY (XX) HH:MM / DDMMMYYYY(XX) HH:MM	XXXXXXX/ XXXXXXX	XXXXXXXXXXXXXX	XXXXX	XX	XXX

Abbreviation: TEAE = treatment emergent adverse event.
Note: Study day is calculated relative to the date of first dose. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. An intercurrent AE is an AE that is reported after consent has been signed and prior to initial dosing. If the reason for discontinuation entered on the study completion CRF was "Adverse Event" and the AE occurred between the start of the first infusion in Period 1 through the final infusion in Period 2, the derived action taken will be set to 'study drug withdrawn' regardless of what was indicated on the CRF since treatment is administered during two distinct periods and not on a continuous basis.
[1] Treatment is based on treatment received.
[2] AESIs are TEAEs that are of special interest as defined by the protocol and are only recorded if the PI considers them as Adverse Events.

Programming note: *"Other Action Taken" will be either None, Medication Required, Relevant Procedure, or Other; if specify text is needed, concatenate "Relevant Procedure:" or "Other:" with the text. If Serious? is Yes, concatenate all serious criteria marked as Yes with a semicolon. If no events meet the criteria for display, present "No events are reported." SOC & PT text should be in proper case in table, as shown in the shell. Ensure correct MedDRA version is printed in footnote. AESI will be Yes or No*

Table 14.3.3.2
Listing of Serious Adverse Events
Safety Set

(Same shell as Table 14.3.3.1)

Table 14.3.3.3
Listing of Deaths
Safety Set

(Same shell as Table 14.3.3.1)

Table 14.3.3.4
Listing of Adverse Events of Special Interest
Safety Set

(Same shell as Table 14.3.3.1)
Programming note: *Include column which contains Higher Level Term, Higher Level Group Term, and Lower Level Term next to the SOC/PT/Verbatim Term column.*

Table 14.3.5.1.1
Summary of Hematology Laboratory Results by Study Visit and Treatment
Safety Set

Parameter: XXXXXXXXX

Study Visit	Placebo (N=XX)		GRF6021 (N=XX)		Overall (N=XX)	
Statistic	Observed	CFB	Observed	CFB	Observed	CFB
Baseline [1]						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 1 (Visit 6)						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Continue for other parameters and visits. Sort alphabetically by parameter.

Abbreviation: CFB = change from baseline.
Note: Subjects are summarized by treatment received.
[1] The baseline value for each variable is the value recorded prior to the first dose.
SOURCE: Listing 16.2.8.1.1

Programming Note: *Comprehensive labs will be performed at screening/Visit 1, Visit 6, Visit 8, Visit 9, Visit 14, Visit 16, Visit 17, and upon exit/Visit 19.*

Table 14.3.5.1.2
Shift from Baseline in Hematology Laboratory Results by Study Visit and Treatment
Safety Set

Parameter: XXXXXXX

Study Visit Category	Baseline [1] Placebo (N=XX) Low n (%)	Normal n (%)	High n (%)	Missing n (%)
Week 1 (Visit 6)				
Low	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
High	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 8)				
Low	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
High	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Continue for other parameters and treatment groups (GRF6021 and overall). Sort alphabetically by parameter.

Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
[1] The baseline value for each variable is the value recorded prior to the first dose.
SOURCE: Listing 16.2.8.1.1

Programming Note: *Comprehensive labs will be performed at screening/Visit 1, Visit 6, Visit 8, Visit 9, Visit 14, Visit 16, Visit 17, and upon exit/Visit 19. If table width allows, all three treatment groups (Placebo, GRF6021, Overall) may be displayed in one table with the four shift categories (low, normal, high, missing) underneath (i.e 12 columns) rather than repeating the table for each treatment group (4 columns).*

Table 14.3.5.2.1
Summary of Serum Chemistry Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.1; SOURCE: Listing 16.2.8.1.2)

Table 14.3.5.2.2
Shift from Baseline in Serum Chemistry Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.2; SOURCE: Listing 16.2.8.1.2)

Table 14.3.5.3.1
Summary of Quantitative Urinalysis Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.1; SOURCE: Listing 16.2.8.1.3)

Table 14.3.5.3.2
Shift from Baseline in Quantitative Urinalysis Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.2; SOURCE: Listing 16.2.8.1.3)

Table 14.3.5.3.3
Summary of Qualitative Urinalysis Laboratory Results by Study Visit and Treatment
Safety Set

Parameter: XXXXXXXX

Study Visit Category	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Baseline [1]			
Category 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 6)			
Category 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Continue for other parameters. Sort alphabetically by parameter.

Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
[1] The baseline value for each variable is the value recorded prior to the first dose.
SOURCE: Listing 16.2.8.1.3

Table 14.3.5.4.1
Summary of Coagulation Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.1; SOURCE: Listing 16.2.8.1.5)

Table 14.3.5.4.2
Shift from Baseline in Coagulation Laboratory Results by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.2; SOURCE: Listing 16.2.8.1.5)

Table 14.3.6.1.1
Summary of Vital Signs by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.1; visits include Visit 1- Visit 19; parameters include Temperature (C), Respiration Rate (breaths per min), Sitting Systolic Blood Pressure (mmHg), Standing Systolic Blood Pressure (mmHg), and Supine Systolic Blood Pressure (mmHg), Heart Rate (bpm), Sitting Diastolic Blood Pressure (mmHg), Standing Diastolic Blood Pressure (mmHg), and Supine Diastolic Blood Pressure (mmHg), Weight (kg); SOURCE: Listing 16.2.8.2.)

Table 14.3.6.1.2
Summary of Blood Pressures of Special Interest by Study Visit and Treatment
Safety Set

Parameter: XXXXXXXX

Study Visit Category	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Baseline [1]			
SBP > 180mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP > 200 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP < 90 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 3) 15 MIN DURING INFUSION			
SBP > 180mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP > 200 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP < 90 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
CFB ≥ 30%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 3) 30 MIN DURING INFUSION			
SBP > 180mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP > 200 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SBP < 90 mmHg	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
CFB ≥ 30%	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Continue for other parameters. Sort alphabetically by parameter.

Abbreviations: CFB = change from baseline; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. Blood pressures of special interest are as follows: seated systolic blood pressure > 180 mmHg, seated systolic blood pressure > 200 mmHg, seated systolic blood pressure < 90 mmHg, seated diastolic blood pressure >110 mmHg, seated diastolic blood pressure > 120 mmHg, seated diastolic blood pressure < 50 mmHg, or a change of ≥ 30% from baseline in seated systolic and/or seated diastolic blood pressure.
[1] The baseline value for each variable is the value recorded prior to the first dose.
SOURCE: Listing 16.2.8.1.3

Programming Note: *Parameters include: Sitting Systolic Blood Pressure (mmHg) and Sitting Diastolic Blood Pressure (mmHg). For Sitting Diastolic Blood Pressure, the categories will be: DBP < 50, DBP >110, DBP > 120, and at post baseline visits, CFB ≥ 30%*

Table 14.3.6.2.1
Summary of 12-Lead Electrocardiogram by Study Visit and Treatment
Safety Set

(Same shell as Table 14.3.5.1.1; visits include Visit 1, Visit 7, Visit 11, and Visit 15; parameters include HR, QT, QTcF; SOURCE: Listing 16.2.8.3)

Table 14.3.6.2.2
Summary of 12-Lead Electrocardiogram Interpretation by Study Visit and Treatment
Safety Set

Study Visit Category	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Baseline [1]			
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Not Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 1 (Visit 7)			
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Not Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 13 (Visit 11)			
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Not Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Week 13 (Visit 15)			
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Not Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal, Clinically Significant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received.
[1] The baseline value for each variable is the value recorded prior to the first dose
SOURCE: Listing 16.2.8.3

Table 14.3.6.3
Summary of Sheehan-Suicidality Tracking Scale (S-STS) by Study Visit and Treatment
Safety Set

Study Visit / Statistic	Placebo (N=XX)		GRF6021 (N=XX)		Overall (N=XX)	
	Observed	CFB	Observed	CFB	Observed	CFB
Visit 1						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 1 (Visit 3)						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 1 (Visit 7)						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviation: CFB = change from baseline.
Note: Subjects are summarized by treatment received.
SOURCE: Listing 16.2.8.5

Table 14.3.6.4
Summary of Concomitant Medications by ATC Class Level 4, PT, and Treatment
Safety Set

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Placebo (N=XX) n (%)	GRF6021 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least 1 Concomitant Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; PT = Preferred Term.
Note: Percentages are n/Number of subjects in the Safety Set*100. Subjects are summarized by treatment received. Medications were coded using WHODrug version March 2018. Concomitant medications are all medications that were continuing or starting after first dose of study drug. A medication with a missing start date and a stop date that is either missing or on or after the treatment start date will be considered as concomitant. Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by PT within ATC, and then alphabetically. Subjects were counted only once for each ATC and PT.
SOURCE: Listing 16.2.8.6

Programming note: *ATC & PT text should be in proper case in table, as shown in the shell. Ensure correct WHODrug version is printed in footnote.*

14.3. Planned Listing Shells

Listing 16.2.1
Subject Disposition
All Subjects

Subject ID	Treatment [1]	Subject Status	Date of Completion/Discontinuation (Study Day)	Reason for Discontinuation	Date of Last Dose of Study Drug (Study Day)	Was the Blind Broken for This Subject?
XXXXXX	XXXXXX	Completed	DDMMMYYYY (XX)		DDMMMYYYY (XX)	
XXXXXX	XXXXXX	Early Terminated	DDMMMYYYY (XX)		DDMMMYYYY (XX)	
XXXXXX	XXXXXX	Did not complete per protocol Due to COVID-19	DDMMMYYYY (XX)		DDMMMYYYY (XX)	
XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (X)	XXXXXXXX: XXXXXX	DDMMMYYYY (X)	XXX
XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (XX)	XXXXXXXXXXXXXXXX	DDMMMYYYY (XX)	XXX; XXXXXX; XXXXX

Abbreviation: COVID-19 = novel coronavirus disease 2019; CRF = case report form; NA = not applicable.
Note: Study day is calculated relative to the date of first dose. A subject is considered to not have completed the study per protocol due to COVID-19 if they had any missing visits that affected treatment administration or collection of end of study efficacy assessments due to COVID-19. If a subject did not complete the study per protocol due to COVID-19, this category supersedes their study status on the study completion CRF.
[1] Treatment is based on treatment received.

Programming Note: *If reason for early termination is Other, concatenate the specify text as follows: "Other: XXXXXXXXX". If reason for early termination is lost to follow-up, concatenate with date of last contact and comments as follows: "Lost to follow-up; date of last contact: DDMMMYYYY; XXXXX". If reason for early termination is death, concatenate with cause of death and date of death as follows: "Lost to follow-up; XXXXX; date of death: DDMMMYYYY". If blind was broken, concatenate with date the blind was broken and reason for breaking the blind as follows: "Yes; DDMMMYYY; XXXXX"*

Listing 16.2.2.1
Inclusion and Exclusion Criteria Not Met
All Subjects

Subject ID	Treatment [1]	Date of Informed Consent (Study Day)	Visit	Visit Date (Study Day)	All Inclusion Criteria Met? [2]	Any Exclusion Criteria Met? [3]
XXXXXX	XXXXXX	DDMMMYYYY (-X)	Screening	DDMMMYYYY (-X)		
		DDMMMYYYY (-X)	Baseline		No: 02	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	Screening	DDMMMYYYY (-X)	No: 02	No
		DDMMMYYYY (-X)	Baseline		Yes	Yes: 03
XXXXXX	XXXXXX	DDMMMYYYY (-X)	Screening	DDMMMYYYY (-X)	Yes	No
		DDMMMYYYY (-X)	Baseline		Yes	No

Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.
IE Description:
Inclusion Criteria:
02 = Diagnosis of clinically established or clinically probable PD according to MDS-PD criteria with at least 1 year of PD symptoms.
Exclusion Criteria:
03 = Prior hypersensitivity reaction to any human blood product or any IV infusion; any clinically significant known drug allergy.

Programming note: *If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma as shown above. Decode any relevant criteria in the footnotes as shown in the example. If no criteria are present for a column, remove the [2] and/or [3] from the column header.*

Listing 16.2.2.2
Protocol Deviations
All Subjects

Subject ID	Treatment [1]	Event Type	Violation Level	Description	Excluded from Per Protocol Set?
XXXXXX	XXXXXXX	XXXXXXXXXXX	MAJOR	XXXXXXX	XX
		XXXXXXXXXXXXX	MINOR	XXXXXXXXXXXXXX	XXX
XXXXXX	XXXXXXX	XXXXXXXXXXX	MINOR	XXXXXXXXXXXXXXXXXX	XX
		XXXXXXXXXXXXXXX	MINOR	XXXXXXXXXX	XX
XXXXXX	XXXXXXXXX	XXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXX	XXX

[1] Treatment is based on treatment received.

Programming note: The structure of this listing may change depending on the information in the protocol deviations file.

Listing 16.2.3
Analysis Sets
All Subjects

Subject ID	Treatment [1]	ITT [2]	Safety [3]	Evaluable [4]	Per Protocol [5]	Reason(s) for Exclusion
XXXXXX	XXXXXX	Yes	Yes	Yes	No	Per Protocol; Had a major protocol deviation
XXXXXX	XXXXXXX	Yes	Yes	Yes	Yes	
XXXXXX	XXXXXX	No	No	No	No	Evaluable; Did not receive at least 4 of the 10 planned doses

[1] Treatment is based on treatment received.
[2] The ITT Set includes all randomized participants.
[3] The Safety Set includes all subjects who received at least one dose of study product.
[4] The Evaluable Set includes all subjects who receive at least 5 of the 10 planned doses and complete through Visit 8.
[5] The Per Protocol Set is a subset of the Evaluable Set comprised of subjects who receive all 10 planned doses, who complete Visit 18 and Visit 19 in window, and who have no protocol deviations that could affect the assessment of efficacy.
[6] The Complete Set is a subset of the PP Set comprised of subjects who did not have any changes to any of the following concomitant medications preferred terms reported at any time on study: Dopaminergic agents (e.g. Rotigotine [Neupro Patch], Duopa Pump, Sinemet [Carbidopa, Levodopa], Carbidopa, Rytary), Pregabalin (Lyrica), Amantadine, Antipsychotics (e.g. Pimavanserin Tartate [Nuplazid], Clozapine, Quetiapine Fumarate [Seroquel]), or benzodiazepines (e.g. Alprazolam). This includes those that were stable per protocol prior to first dose and either changed dose or stopped on study as well as those that began on study.

Programming note: Concatenate all reasons for exclusion with a semi-colon.

Listing 16.2.4.1
Demographics and Baseline Characteristics
All Subjects

Subject ID	Treatment [1]	Sex	Child-Bearing Potential?	Date of Birth	Age (years)	Ethnicity	Race	Weight (kg)	Height (cm)	ApoE Genotype	Disease Duration (years)
XXXXXX	XXXXXX	XXXX		DDMMMYYY	XX	XXXXXXX	XXXXXXX	XX.X	XX.X	XXX	XX.X
XXXXXX	XXXXXX	XXXXXX	No	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XXX	XX.X
XXXXXX	XXXXXX	XXXXXX	Yes	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XXX	XX.X
XXXXXX	XXXXXX	XXXX		DDMMMYYY	XX	XXXXXXX	XXXXX	XX.X	XX.X	XXX	XX.X
XXXXXX	XXXXXX	XXXXXX	No	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XXX	XX.X
XXXXXX	XXXXXX	XXXX		DDMMMYYY	XX	XXXXXX	XXXXXX	XX.X	XX.X	XXX	XX.X

Abbreviations: ApoE = Apolipoprotein E; PD = Parkinson's disease.
Note: Height and weight are the values at Screening. Disease duration = [Enrollment date – PD onset date (as recorded on the Medical History CRF) + 1] / 365.25.[1] Treatment is based on treatment received.

Programming Note: *If race is other, concatenate "Other:" with specify text. If subject has multiple races, concatenate them.*

Listing 16.2.4.2.1
Medical History
All Subjects

Subject ID	Treatment [1]	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ End Date (Study Day)/
XXXXXX	XXXXXXXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)
		XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	MMMYYYY (X)/ Ongoing
		XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	MMMYYYY (X)/ Ongoing
XXXXXX	XXXXXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)

Note: Study day is calculated relative to the date of first dose. Medical history was coded using MedDRA version 21.0. Only subjects with medical history recorded are listed.
[1] Treatment is based on treatment received.

Programming note: SOC & PT text should be in proper case in table, as shown in the shell.

Listing 16.2.4.2.2
Family Medical History
All Subjects

Subject ID	Treatment [1]	Was Family Medical History Collected?	Family Member	Living/Deceased	Age at Time of Death	Cause of Death	History of Neurological Disease?	Neurological Disease(s)
XXXXXX	XXXXXX	Yes/No	XXXXXXX	XXXXXX	XX	XXXXXXX	Yes/No	XXXXXXX

[1] Treatment is based on treatment received.

Programming Note: *If not collected, concatenate reason. If neugological disease is 'other' concatenate specify field.*

Listing 16.2.4.2.3
Social History/Exercise-Activity Level
All Subjects

			Social History	Exercise/Activity Level					
Subject ID	Treatment [1]	Was Social History/Exercise-Activity Level Assessed?	Describe Where You Currently Live	Bike for 10 Minutes Consistently?	How Many Days Do You Bike for 10 Minutes?	Time spent Walking or Bicycling for Travel on a Typical Day (minutes)	Do Any Sports, Fitness, or Recreational Activitites?	How Many Days Per Week Do You Do Sports, Fitenss, or Recreational Activities?	Time Spent doing Sports, Fitenss, or Recreational Activities on a Typical Day (Minutes
XXXXXX	XXXXXX	Yes/No	XXXXXXX	Yes/No	XX	XXX	Yes/No	XX	XXX

[1] Treatment is based on treatment received.

Programming Note: *If not done, concatenate explanation. If neugological disease is 'other' concatenate specify field. If 'Other' concatenate specify field.*

Listing 16.2.4.3
Alcohol, Tobacco, and Substance Use
All Subjects

		Tobacco Smoking History			Alcohol					
Subject ID	Treatment [1]	Smoking History/# Years Smoked	# per day: Cigarettes/ Cigars/ Pipes	If Ex-Smoker, Date Stopped (Study Day)	Have you consumed alcohol in the past 6 months?	# drinks containing alcohol do you have on a typical day when you are drinking?	How often do you have 6+ drinks on 1 occasion?	Did anybody ever tell you when you were younger that you had a problem with alcohol?	Have you ever had problems related to consuming alcohol?	Subject used illicit substances (including marijuana) in the past? / Describe
XXXXXX	XXXXXXXXX	XXXXXXXXXXX / XX	XX XXX X	DDMMMYYYY (X)	XXX	XX	XXXXXXxx	XXX	XXX	XX
XXXXXX	XXXXXXXXXX	XXXXXXXXXXX / X		DDMMMYYYY (X)	XXX	XX	XXXXXXxx	XXX	XXX	XX

Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Listing 16.2.4.4
Modified Hachinski Ischaemia Scale (MHIS)
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Parameter	Result
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	Abrupt onset of dementia	Present/Absent
				Stepwise deterioration of dementia	Present/Absent
				Somatic complaints	Present/Absent
				Emotional incontinence	Present/Absent
				History or presence of hypertension	Present/Absent
				History of strokes	Present/Absent
				Focal neurological symptoms	Present/Absent
				Focal neurological signs (on examination)	Present/Absent
				Total Score	XX

Abbreviation: MHIS = Modified Hachinski Ischaemia Scale.
Note: Study day is calculated relative to the date of first dose. MHIS is collected at Screening Visit 1 only.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.*

Listing 16.2.4.5
Hoehn and Yahr Scale
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Hoehn and Yahr Stage
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	X: XXXXXX

Note: Study day is calculated relative to the date of first dose. Hoehn and Yahr is collected at Screening Visit 1 only.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason. For stage, include the number and text.*

Listing 16.2.5
Drug Infusion
All Subjects

Subject ID	Treatment [1]	Was the Infusion Performed?	Time Point	Date/Time of Infusion (Study Day)	Rate (mL/hour)	Actual Volume Administered (mL)	Pump Manufacturer and model
XXXXXX	XXXXXX	XXX	Time X	DDMMMYYYY/ HH:MM (XX)	XX	XX	XXXXXXX

Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Listing 16.2.6.1
MoCA
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	MoCA Version	Date/Time of Assessment (Study Day)	Parameter	Result
XXXXXX	XXXXXX	XXX	X.X	DDMMMYYYY/ HH:MM (XX)	Visuospatial/Executive	XX
					Naming	XX
					Memory	XX
					Attention	XX
					Language	XX
					Abstraction	XX
					Delayed Recall	XX
					Orientation	XX
					Add 1 point if <=12 years of education	XX
					Total Score	XX

Abbreviation: MoCA = Montreal Cognitive Assessment.
Note: Study day is calculated relative to the date of first dose.
MoCA Total score = sum of individual item scores, with a range from 0 to 30.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.*

Listing 16.2.6.2
D-KEFS Verbal Fluency Test
All Subjects

					Letter Fluency				Category Fluency			Category Switching		
Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Interval	F	A	S	Total Correct	Animals	Boys' Names	Total Correct	Fruits/Furniture	Total Correct Score	Total Correct Score
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	1-15 seconds	XX	XX	XX	XX	XXX	XXX	XX	XXX	XX	XX
				16-30 seconds	XX	XX	XX		XXX	XXX		XXX		
				31-45 seconds	XX	XX	XX		XXX	XXX		XXX		
				46-60 seconds	XX	XX	XX		XXX	XXX		XXX		

Abbreviation: D-KEFS = Delis-Kaplan Executive Function System.
Note: Study day is calculated relative to the date of first dose.
D-KEFS Letter Fluency Total Correct Score = sum of F+A+S correct responses from 1-15, 16-30, 31-46, and 46-60 seconds.
D-KEFS Category Fluency Total Correct Score = sum of Animals and Boys' Names correct responses from 1-15, 16-30, 31-46, and 46-60 seconds
D-KEFS Category Switching Total Correct Score = sum of Fruits/Furniture correct responses from 1-15, 16-30, 31-46, and 46-60 seconds.
D-KEFS Total Correct Score = sum of D-KEFS Letter Fluency Total Correct Score, Category Fluency Total Correct Score, and D-KEFS Category Switching Total Correct Score.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason. Total scores over the minute will be displayed on the first row only.*

Listing 16.2.6.3
MDS-UPDRS
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Primary Source of Information	Date/Time of Assessment (Study Day)	Parameter	Result
XXXXXX	XXXXXX	XXX	XXXXXXXXX	DDMMMYYYY/ HH:MM (XX)	Cognitive impairment	X = XXXX
					Hallucinations and psychosis	X = XXXX
					Depressed mood	X = XXXX
					Anxious mood	X = XXXX
					Apathy	X = XXXX
					Features of dopamine dysregulation syndrome	X = XXXX
					Sleep problems	X = XXXX
					Daytime sleepiness	X = XXXX
					Pain and other sensations	X = XXXX
					Urinary problems	X = XXXX
					Constipation problems	X = XXXX
					Lightheadedness on standing	X = XXXX
					Fatigue	X = XXXX
					Part 1 Score	XX = XXXX

Abbreviation: MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale.
Note: Study day is calculated relative to the date of first dose.
MDS-UPDRS Part 1 score = sum of all Part 1 individual item scores. Part 1 consists of 13 items on a scale of 0 (normal) to 4 (severe), so the Part 1 score ranges from 0 to 52.
MDS-UPDRS Part 2 score = sum of all Part 2 individual item scores. Part 2 consists of 13 items on a scale of 0 (normal) to 4 (severe), so the Part 2 score ranges from 0 to 52.
MDS-UPDRS Part 3 score = sum of all Part 3 individual item scores. Part 3 consists of 22 33 items on a scale of 0 (normal) to- 4 (severe), so the Part 3 score ranges from 0 to 132.
MDS-UPDRS Parts 1-3 total score = sum of Part 1, Part 2, and Part 3 scores. If any of the individual part scores are missing, the total score will be set to missing.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.Continue for Parts 2 and 3. Insert a blank row and add a row for Total Score after Part 3.*

Listing 16.2.6.4
SE-ADL Scale
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Level of Independence
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XXX% = XXXXXXXXXXX

Abbreviation: SE-ADL = Schwab & England Activities of Daily Living.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.*

Listing 16.2.6.5
CISI-PD
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Asessment	Result
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	Motor Signs	X = XXXXXXX
				Disability	X = XXXXXXX
				Motor Complications (dyskinesia and fluctuations)	X = XXXXXXX
				Cognitive Status	X = XXXXXXX
				CISI-PD Total Score	XXX

Abbreviation: CISI-PD = Clinical Impression of Severity Index-Parkinson's Disease.
Note: Study day is calculated relative to the date of first dose.
CISI-PD total score = sum of the four individual item scores (motor signs, disability, motor complications, and cognitive status) rated 0 (not at all) to 6 (very severe or disabled), with a range of 0 to 24.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.*

Listing 16.2.6.6
PDQ-39
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Domain	Question	Result
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	Mobility	Had difficulty doing the leisure activities you would like to do?	XXXX
					Had difficulty looking after your home, for example, housework, cooking or yardwork?	XXXX
					Had difficulty carrying grocery bags?	XXXX
					Had problems walking half a mile?	XXXX
					...	...
					Mobility subscale score	XXX
					....	
					Total score	XXX

Abbreviation: PDQ-39 = Parkinson's Disease Quality of Life Questionnaire-39.
Note: Study day is calculated relative to the date of first dose.
PDQ-39 Mobility subscore = sum of 10 items in the Mobility domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Activities of Daily Living subscore = sum of 6 items in the Activities of Daily Living domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Emotional Well-Being subscore = sum of 6 items in the Emotional Well-Being domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Stigma subscore = sum of 4 items in the Stigma domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Social Support subscore = sum of 3 items in the Social Support domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Cognitions subscore = sum of 4 items in the Cognitions domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Communication subscore = sum of 3 items in the Communication domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Bodily Discomfort subscore = sum of 3 items in the Bodily Discomfort domain (converted from a range of 0 [never] to 4 [always/cannot do at all] to a range of 0 to 100), divided by the maximum possible score on the scale and multiplied by 100.
PDQ-39 Total score = mean of all of the PDQ-39 subscores.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason. After each question and answer is listed, list the Total score and the scores for the following subscales: Mobility, Activities of Daily Living, Emotional Well-Being, Stigma, Social Support, Cognitions, Communication, Bodily Discomfort.*

Listing 16.2.6.7
GDS-15
All Subjects

Subject ID	Treatment [1]	Was Assessment Completed?	Date/Time of Assessment (Study Day)	Question	Result
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	Are you basically satisfied with your life?	X
				Have you dropped many of your activities and interests?	X
				Do you feel that your life is empty?	X
				Do you often get bored?	X
				...	...
				Total Score	X

Abbreviation: GDS-15 = Geriatric Depression Scale-15.
Note: Study day is calculated relative to the date of first dose.
GDS-15 Total score = sum of the 15 item questionnaire, with a range of 0 to 15. Each question is answered "yes" or "no". Question numbers 1, 5, 7, 11, 13 indicate presence of depression when answered positively (yes) while the remaining questions indicate presence of depression when answered negatively (no). One point is counted for each depressive answer. A score of 0-4 indicates no depression, a score of 5-10 is suggestive of a mild depression, and a score of 11 or more is suggestive of severe depression.
[1] Treatment is based on treatment received.

Programming Note: *If assessment was not completed, concatenate reason.*

Listing 16.2.6.8
dCDT
All Subjects

Subject ID	Treatment [1]	Handedness of Subject at Test Time	Date/Time of Test (Study Day)	dDCT Score	dCDT Classification	Cognitive Feature	Result
XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY/ HH:MM (XX)	XXX	XXXXXX	Stroke Count Conformity on command clock	XX
						Total Time on command clock	XX
						Ink Length on command clock	XX
						Drawing Size on command clock	XX
						Drawing Process Efficiency on command clock	XX
						Noise on command clock	XX
						Drawing Efficiency Composite Scale	XX

Abbreviation: dCDT = Digital clock drawing test.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming Note: *Continue listing for simple motor, information processing, and spatial reasoning composite scales and cognitive features.*

Listing 16.2.6.9
Patient Questionnaire Status
All Subjects

Subject ID	Treatment [1]	Visit (Study Day)	Was the subject in the "On" status for Cognitive and Motor Testing?
XXXXXX	XXXXXX	XXXXXXXXX (XX)	Yes/No

[1] Treatment is based on treatment received.

Listing 16.2.6.10
Safety MRI Results
All Subjects

Subject ID	Treatment [1]	Visit	Presence of MRI Abnormalities?	Abnormality	Abnormality Sequence	Abnormality Slice Number	Abnormality Primary Location	Abnormality Status	Is White Matter Disease Present?	Potential alternative diagnosis to PD?	Comments
XXXXXX	XXXXXX	XXXXXX	Yes/No/Nonevaluable	XXXXXXX	3DT1/ FLAIR/ T2*/ T2/ DWI/ Other	XXX	XXXXXXXX	Present/ Presence is questionable	No lesions (including symmetrical, well-defined caps or bands)/ Focal lesions/ Beginning confluence of lesions/ Diffuse involvement of entire region, with or without involvement of U-fibers / Non evaluable	Yes/ No/ Non-evaluable/	XXXXX

Abbreviations: MRI = Magnetic Resonance Imaging; PD = Parkinson's Disease.
[1] Treatment is based on treatment received.

Programming Note: *If abnormality or abnormality primary location is 'Other' concatenate specify field with a semicolon in the cell.*

Listing 16.2.6.11
Volumetric MRI Results
All Subjects

Subject ID	Treatment [1]	Visit	Test	Location	Laterality	Result (unit)
XXXXXX	XXXXXX	XXXXXX	Volume	Whole Brain	Bilateral	XXX
				Lateral Ventricles	Bilateral	XXX
				Intracranial	Bilateral	XXX
				Cortical	Left	XXX
				Cortical	Right	XXX
				Cortical	Bilateral	XXX
				...		

Abbreviations: MRI = Magnetic Resonance Imaging.
[1] Treatment is based on treatment received.

Programming Note: *Include all location/lateriality/test results for all visits. Sort by visit, test, location.*

Listing 16.2.6.12
ASL MRI Results
All Subjects

Subject ID	Treatment [1]	Visit	Test	Location	Laterality	Result (unit)
XXXXXX	XXXXXX	XXXXXX	CBF	Frontal Lobe	Left	XXX
			CBF		Right	XXX
			CBF		Bilateral	XXX
			CBF	Cingulate Cortex	Left	XXX
			CBF		Right	XXX
			CBF		Bilateral	XXX
				...		

Abbreviations: ASL = arterial-spin labeling; CBF = cerebral blood flow; MRI = Magnetic Resonance Imaging.
[1] Treatment is based on treatment received.

Programming Note: *Include all location/lateriality/test results for all visits. Sort by visit, test, location.*

Listing 16.2.7.1
Adverse Events
All Subjects

Subject ID	Treatment [1]	TEAE/ Intercurrent	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day) Start Time / End Date (Study Day) End Time	Severity/ Relationship	Outcome/ Study Drug Action Taken (CRF)/ Other Action Taken	Derived Action Taken	Serious?/ Criteria Met	AESI? [2]
XXXXXX	XXXXXX	XXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (XX) HH:MM/ DDMMMYYYY (XX) HH:MM	XXXXXXXXX/ XXXXXXXX	XXXXXXXXXXXX/ XXXXXXXXXXXXX/ XXXXXXXXXXXXXXXX	XXXXX XXXXX XXXXX	XX/ XXXXXXXXX	XXX
	XXXXXX	XXXX	XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	DDMMMYYYY (XX) HH:MM / Ongoing	XXXXXXXXX/ XXXXXXXX	XXXXXXXXXXXXX	XXXXX	XX	XXX
	XXXXXX	XXXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXX	DDMMMYYYY (XX) HH:MM / DDMMMYYYY(XX) HH:MM	XXXXXXX/ XXXXXXX	XXXXXXXXXXXXXX	XXXXX	XX	XXX

Abbreviation: CRF = case report form; TEAE = Treatment emergent adverse event.
Note: Study day is calculated relative to the date of first dose. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the time of treatment with the study agent. This will include any AE with onset prior to time of treatment with study agent and increased severity after the treatment administration. An intercurrent AE is an AE that is reported after consent has been signed and prior to initial dosing. If the reason for discontinuation entered on the study completion CRF was "Adverse Event" and the AE occurred between the start of the first infusion in Period 1 through the final infusion in Period 2, the derived action taken will be set to 'study drug withdrawn' regardless of what was indicated on the CRF since treatment is administered during two distinct periods and not on a continuous basis.
[1] Treatment is based on treatment received.
[2] AESIs are TEAEs that are of special interest as defined by the protocol and are only recorded if the PI considers them as Adverse Events.

Programming note: "Other Action Taken" will be either None, Medication Required, Relevant Procedure, or Other; if specify text is needed, concatenate "Relevant Procedure:" or "Other:" with the text. If Serious? is Yes, concatenate all serious criteria marked as Yes with a semicolon. If no events meet the criteria for display, present "No events are reported." SOC & PT text should be in proper case in table, as shown in the shell. Ensure correct MedDRA version is printed in footnote. AESI will be Yes or No

Listing 16.2.8.1.1
Clinical Laboratory Data: Hematology
All Subjects

Subject ID	Treatment [1]	Parameter (unit)	Date of Assessment (Study Day)	Standard Results	Change from Baseline [2]	Reference Range [3]	Reference Range Flag	Accession Number	Comments/Reason Not Done
XXXXXX	XXXXXXXX	Red Blood Cell Count	DDMMMYYYY (X)	XX		XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY	XXX	XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	
			DDMMMYYYY (X)	XX ND	XX	XX – YY		XXXXXXX	XXXXXXX
			DDMMMYYYY (X)	XX	XX	XX – YY		XXXXXXX	

Abbreviations: A = abnormal; CS = clinically significant; H = high; L = low; ND = not done.
Note: Study day is calculated relative to the date of first dose of study drug.
[1] Treatment is based on treatment received.
[2] Baseline is the Screening Visit 1.
[3] Reference range is used to identify potentially clinically significant laboratory values.

Programming note: update abbreviations to reflect actual data. If test was not done, set results to ND; make sure last column is populated accordingly

Listing 16.2.8.1.2
Clinical Laboratory Data: Serum Chemistry
All Subjects

(Same shell as Listing 16.2.8.1.1)

Listing 16.2.8.1.3
Clinical Laboratory Data: Urinalysis
All Subjects

(Same shell as Listing 16.2.8.1.1; remove "(unit)" from 2nd column header)

Listing 16.2.8.1.4
Clinical Laboratory Data: Urine Drug Screen and Pregnancy Tests
All Subjects

(Same shell as Listing 16.2.8.1.1; remove "(unit)" from 2nd column header; do not display Reference Range or Accession number columns)

Listing 16.2.8.1.5
Clinical Laboratory Data: Coagulation
All Subjects

(Same shell as Listing 16.2.8.1.1)

Listing 16.2.8.1.6
Clinical Laboratory Data: Immunology
All Subjects

(Same shell as Listing 16.2.8.1.1)

Listing 16.2.8.1.7
Clinical Laboratory Data: Serology
All Subjects

(Same shell as Listing 16.2.8.1.1; remove "(unit)" from 2nd column header)

Listing 16.2.8.2.1
Vital Signs
All Subjects

Subject ID	Treatment [1]	Study Visit	Date of Assessment (Study Day)	Body Temperature (C)	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Height (cm)	Weight (kg)	Abnormal?
XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (X)	XX.X	XX	XX	XX.X	XXX	XXX
		XXXXXX	DDMMMYYYY (X)	XX.X	XX	XX		XXX	
		XXXXXX	DDMMMYYYY (X)	XX.X	XX	XX		XXX	
		XXXXXX	DDMMMYYYY (X)	ND	ND	ND		ND	
		XXXXXX	DDMMMYYYY (X)	XX.X	XX	XX		XXX	

Abbreviation: ND = not done.
Note: Study day is calculated relative to the date of first dose. Abnormal vital signs are as follows: Heart rate > 100 beats per minute, Temperature > 37.5°C or < 36.5°C, Respiration rate > 20 breaths per minute or < 12 breaths per minute.
[1] Treatment is based on treatment received.

***Programming Note**: If a measurement is abnormal, place an asterisk (*) next to the value in the cell.*

Listing 16.2.8.2.2
Blood Pressure
All Subjects

Subject ID	Treatment [1]	Study Visit	Date of Assessment (Study Day)	Standing Blood Pressure (mmHg)		Supine Blood Pressure (mmHg)		Sitting Blood Pressure (mmHg)		Abnormal?	BPSI?
				Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic		
XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (X)	XXX	XX	XXX	XX	XXX	XX	XXX	XXX
		XXXXXX	DDMMMYYYY (X)	XXX	XX	XXX	XX	XXX	XX		
		XXXXXX	DDMMMYYYY (X)	XXX	XX	XXX	XX	XXX	XX		
		XXXXXX	DDMMMYYYY (X)	ND	ND	ND	ND	ND	ND		
		XXXXXX	DDMMMYYYY (X)	XXX	XX	XXX	XX	XXX	XX		

Abbreviation: BPSI = blood pressure of special interest; ND = not done.
Note: Study day is calculated relative to the date of first dose. Abnormal blood pressure vital signs are as follows: seated systolic blood pressure < 90 mmHg or > 180 mmHg, seated diastolic blood pressure < 50 mmHg or > 110 mmHg, or incidence of orthostatic hypotension (a decrease in systolic blood pressure of > 20 mm Hg and/or a decrease in diastolic blood pressure of > 10 mm Hg between supine and standing). BPSIs are as follows: seated systolic blood pressure > 180 mmHg, seated systolic blood pressure > 200 mmHg, seated systolic blood pressure < 90 mmHg, seated diastolic blood pressure >110 mmHg, seated diastolic blood pressure > 120 mmHg, seated diastolic blood pressure < 50 mmHg, or a change of ≥ 30% from baseline in seated systolic and/or seated diastolic blood pressure.
[1] Treatment is based on treatment received.

***Programming Note**: If a measurement is abnormal, place an asterisk (*) next to the value in the cell.*

Listing 16.2.8.3
12-Lead Electrocardiogram (ECG) Results
All Subjects

Subject ID	Treatment [1]	Was ECG Performed?	Date/Time of ECG (Study Day)	Overall Interpretation	Heart Rate (bpm)	QT Interval (msec)	QTcF Interval (msec)
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXX	XXX	XXX	XXX
		XX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	XXX	XXX	XXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXX	XXX	XXX	XXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXX; XXXXX	XXX	XXX	XXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	XXX	XXX	XXX
		XX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXX	XXX	XXX	XXX
		XXX	ND				
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXX;XXXXX	XXX	XXX	XXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	XXXX	XXXX	XXXX

Abbreviation: ND = not done.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming note: *If ECG was not performed, concatenate with reason.*

Listing 16.2.8.4
Echocardiogram Results
All Subjects

Subject ID	Treatment [1]	Was Echocardiogram Performed?	Date/Time of Echocardiogram (Study Day)	Cardiologist's Interpretation	If Abnormal, Describe
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXX	XXXXXXXXXXX
		XX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXX	XXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXX	XXXXXXXXXXX
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	XXXXXXXXXXX
		XX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXX	
		XXX	ND		
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXXX	
		XXX	DDMMMYYYY/ HH:MM (XX)	XXXXXXXXXXX	XXXXXXXXXXX

Abbreviation: ND = not done.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming note: *If Echocardiogram was not performed, concatenate with reason.*

Listing 16.2.8.5.1
Physical Examination
All Subjects

Subject ID	Treatment [1]	Was Physical Exam performed?	Date/Time Performed (Study Day)	Body System	Result	Reason Not Done	If Abnormal, Describe
XXXXXX	XXXXXXX	XXX	DDMMMYYYY/ HH:MM (-X)	General Appearance	Normal		
				Skin	Abnormal, CS		XXXXXXXX
				Head and Neck	Normal		
				Lymph Nodes	Normal		
				Thyroid	Normal		
				Musculoskeletal	Normal		
				Extremeties	Normal		
				Cardiovascular	Normal		
				Lungs	Normal		
				Abdomen	Normal		
				Neurological	Normal		

Abbreviations: CS = clinically significant; NCS = not clinically significant.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming Note: *If Exam was not performed, concatenate reason.*

Listing 16.2.8.5.2
Targeted Physical Examination
All Subjects

Same shell as Listing 16.2.8.4.1. Body Systems will be: Heart, Lungs, and Peripheral Edema.

Listing 16.2.8.6
S-STS
All Subjects

Subject ID	Treatment [1]	Was Questionnaire Collected?	Date/Time Collected (Study Day)	Total Scale Score
XXXXXX	XXXXXX	XXX	DDMMMYYYY/ HH:MM (XX)	XX

Abbreviation: S-STS = Sheehan Suicidality Tracking Scale.
Note: Study day is calculated relative to the date of first dose.
[1] Treatment is based on treatment received.

Programming Note: *If questionnaire was not collected, concatenate reason.*

Listing 16.2.8.7
Prior and Concomitant Medications
All Subjects

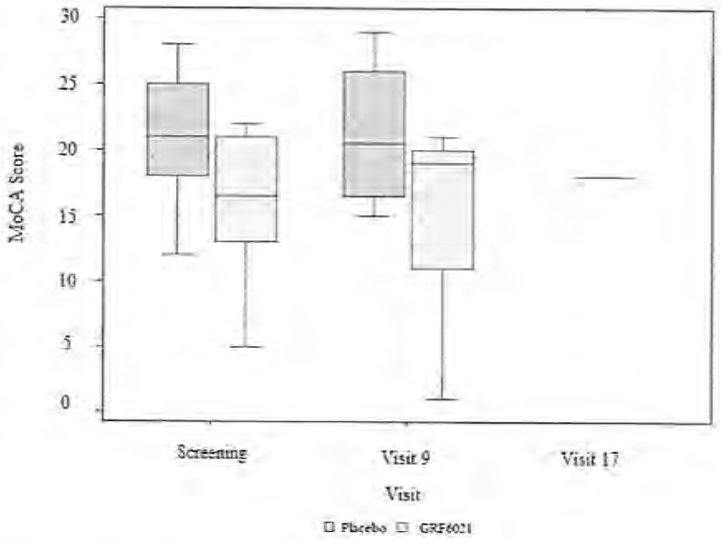
Subject ID	Treatment [1]	Taken Prior to First Dose of Study Drug?	Indication	ATC Class (Level 4)/ Preferred Term (ATC Level 5)/ Verbatim Term	Start Date (Study Day)/ End Date (Study Day)	Dose (unit)	Route/ Frequency
XXXXXX	XXXXXX	XXX	XXXXXXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXX (XXX)	XXXXXXXX/ XXXXXXX
		XX	XXXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	DDMMMYYYY (X)/ Ongoing	XXX (XXX)	
		XXX	XXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXX (XXX)	

Abbreviation: ATC = anatomic therapeutic chemical; NA = Not applicable.
Note: Study day is calculated relative to the date of first dose. Medications were coded using WHO-DDE version March 2018.
[1] Treatment is based on treatment received.

Programming note: If Dose unit, Route or Frequency is Other, display other specify text only (ie, do not display "Other: XXXXXX" but just "XXXXXX "). Sort by subject, start date, end date, ATC level 4 & PT. ATC & PT text should be in proper case in table, as shown in the shell. If ongoing, put "Ongoing" for end date.

14.4. Planned Figure Shells

Figure 14.2.1.1
Boxplots of MoCA Total Scores by Visit and Treatment
Evaluable Set



Programming notes: Each treatment group will be graphed using a different color. Boxplots will be displayed at each visit.
Reference Table: 14.2.1.1
SOURCE: Listing 16.2.6.1

Figure 14.2.1.2
Boxplots of MoCA Total Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Reference Table: 14.2.1.3. SOURCE: Listing 16.2.6.1.

Figure 14.2.2.1
Boxplots of D-KEFS Total Scores by Visit and Treatment
Evaluable Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.2.1. SOURCE: Listing 16.2.6.2.

Figure 14.2.2.2
Boxplots of D-KEFS Total Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.2.3. SOURCE: Listing 16.2.6.2.

Figure 14.2.3.1
Boxplots of MDS-UPDRS Parts 1-3 Scores by Visit and Treatment
Evaluable Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.1. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.2
Boxplots of MDS-UPDRS Parts 1-3 Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.3. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.3
Boxplots of MDS-UPDRS Part 1 Scores by Visit and Treatment
Evaluable Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.1. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.4
Boxplots of MDS-UPDRS Part 1 Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.3. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.5
Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment
Evaluable Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.1. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.6
Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.3. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.7
Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment
Evaluable Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.1. SOURCE: Listing 16.2.6.3.

Figure 14.2.3.8
Boxplots of MDS-UPDRS Part 2 Scores by Visit and Treatment
Per Protocol Set

Same Shell as Figure 14.2.1.1. Update Y-axis to reflect appropriate score and update X-axis for the appropriate visits. Reference Table: 14.2.3.3. SOURCE: Listing 16.2.6.3.

Figure 14.3.1.1
Boxplots of Hematology Data by Parameter, Visit, and Treatment
Safety Set

Y-axis: Parameter: XXXXXX (unit)
X-axis: Week X (Visit X)
Programming notes: A separate graph will be produced for each parameter. Each treatment group will be graphed using a different color. Boxplots will be displayed at each visit. The appropriate visits will be displayed for each parameter.
Reference Table: 14.3.5.1.1
SOURCE: Listing 16.2.8.1.2

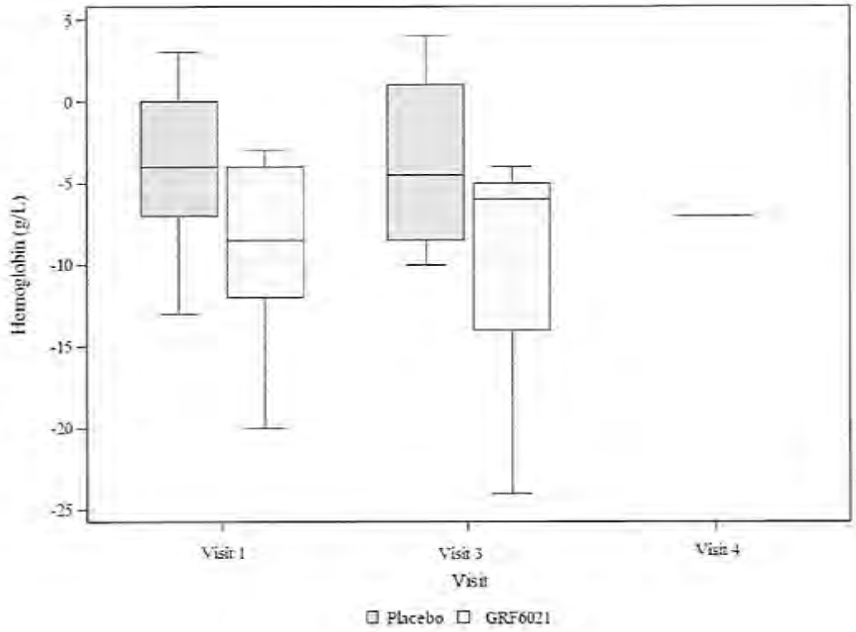


Figure 14.3.1.2
Boxplots of Serum Chemistry Laboratory Data by Parameter, Visit, and Treatment
Safety Set

(Same shell as Figure 14.3.1.1; Reference Table: 14.3.5.2.1; SOURCE: Listing 16.2.8.1.2)

Figure 14.3.1.3
Boxplots of Quantitative Urinalysis Laboratory Data by Parameter, Visit, and Treatment
Safety Set

(Same shell as Figure 14.3.1.1; Reference Table: 14.3.5.3.1; SOURCE: Listing 16.2.8.1.3)

Figure 14.3.2.1
Hematology: Mean (SD) by Parameter, Visit, and Treatment
Safety Set

Y-axis: Parameter: XXXXXX (unit)
X-axis: Week X (Visit X)
Programming notes: A separate graph will be produced for each parameter. Each treatment group will be graphed using a different color and symbol. Use light blue for placebo and green for GRF6021, as in the boxplots above. Mean and 1 standard deviation will be plotted. The appropriate visits will be displayed for each parameter.
Reference Table: 14.3.5.1.1
SOURCE: Listing 16.2.8.1.1

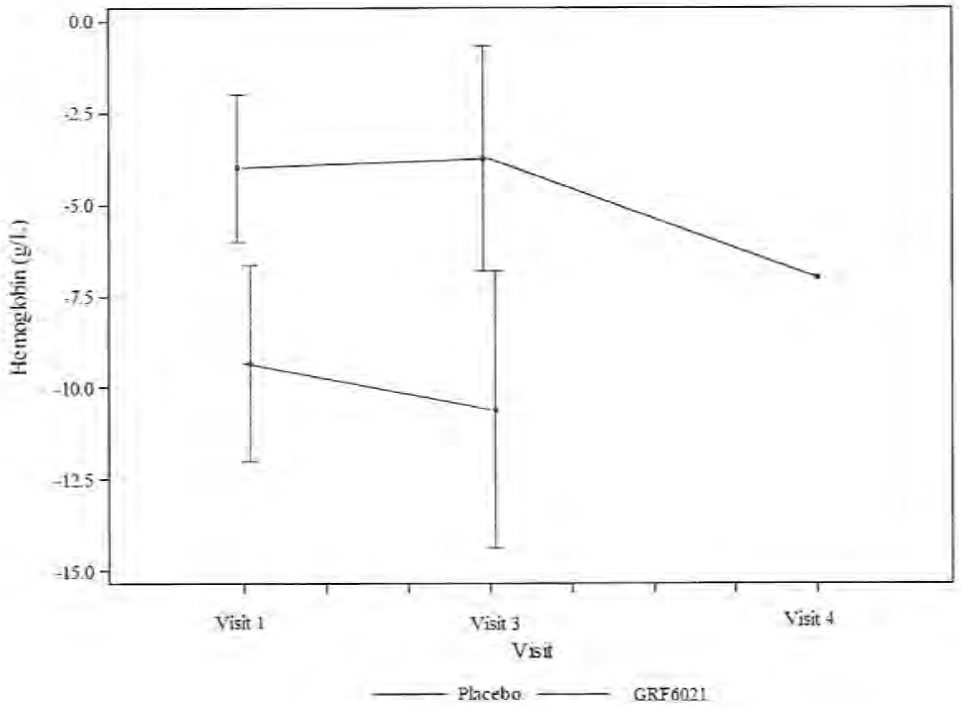


Figure 14.3.2.2
Serum Chemistry: Mean (SD) by Parameter, Visit, and Treatment
Safety Set
(Same shell as Figure 14.3.2.1; Reference Table: 14.3.5.2.1; SOURCE: Listing 16.2.8.1.2)

Figure 14.3.2.3
Quantitative Urinalysis: Mean (SD) by Parameter, Visit, and Treatment
Safety Set

(Same shell as Figure 14.3.2.1; Reference Table: 14.3.5.3.1; SOURCE: Listing 16.2.8.1.3)

Figure 14.3.3.1
Vital Signs Data by Parameter, Visit, and Treatment
Safety Set

(Same shell as Figure 14.3.1.1; Reference Table: 14.3.6.1; SOURCE: Listing 16.2.8.2.1 and 16.2.8.2.2)

Figure 14.3.3.2
Vital Signs: Mean (SD) by Parameter, Visit, and Treatment
Safety Set
(Same shell as Figure 14.3.2.1; Reference Table: 14.3.6.1; SOURCE: Listing 16.2.8.2.1 and 16.2.8.2.2)

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
CDR-CCB	Continuity and Power of Attention, Working Memory, and Episodic Memory on the Cognitive Drug Research Computerized Cognition Battery
CFR	code of federal regulations
CI	confidence intervals
CISI-PD	Clinical Impression of Severity Index-Parkinson's Disease
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
DB	database
DBL	database lock
DBP	diastolic blood pressure
dCDT	Digital clock drawing test

Abbreviation	Definition
DEA	drug enforcement administration
DIA	drug information association
D-KEFS	Delis-Kaplan Executive Function System
DOB	date of birth
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European medicines agency
FDA	food and drug administration
GCP	good clinical practice
GDS-15	Geriatric Depression Scale-15
HR	heart rate
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
ITT	intent-to-treat
IV	intravenous
MDS-UPDRS	the Movement Disorder Society's Unified Parkinson's Disease Rating Scale
MedDRA	medical dictionary for regulatory activities
MoCA	Montreal Cognitive Assessment

Abbreviation	Definition
MRI	Magnetic resonance imaging
N	number
NA	not applicable
NCS	non-clinically significant
PD	Parkinson's Disease
PD	protocol deviation
PDD	Parkinson's Disease with dementia
PD-MCI	PD with mild cognitive impairment
PE	physical examination
PP	per-protocol
PT	Preferred term
RR	respiratory rate or relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
S-STS	Sheehan Suicidality Tracking Scale
TEAE	treatment-emergent adverse event
tf-MRI	task-free functional MRI

Abbreviation	Definition
UPCR	Urine protein-to-creatinine ratio
WHO	world health organization
WHO-DD	world health organization drug dictionary

Appendix 2: Bracket Statistical Analysis Plan for CDR