A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKST4290 in Subjects with Parkinson's Disease on Stable Dopaminergic Treatment

Protocol Number:	AKST4290-211
Eudra CT Number:	2019-001657-42
IND Number:	142597
Clinical Phase:	2
Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
Study Agent:	AKST4290
Indications:	Parkinson's Disease
Authorized Representative:	[redacted]
Version Number:	V4.0
Version Date	22MAY2020
Replaces Version:	V3.1, 06JAN2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
b.i.d.	Twice per day
BLQ	Below the limit of quantification
BP	Blood pressure
CBC	Complete blood count
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CISI-PD	Clinical Impression of Severity Index – Parkinson's Disease
CK	Creatinine kinase
CK-MB	Creatinine kinase-MB
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma concentration
CMP	Clinical Monitoring Plan
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
[redacted]	[redacted]
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ENT	Ears, nose, throat
[redacted]	[redacted]
Eudra CT	European Union Drug Regulating Authorities Clinical Trials Database
FACS	Flow cytometry/fluorescence-activated cell sorting

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPLC-MS/MS	High performance liquid chromatography, tandem mass spectrometry
ICH	International Conference on Harmonization
ICH E6 R2	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigation New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
[redacted]	[redacted]
MDS-PD	Movement Disorder Society's Clinical Diagnostic Criteria for Parkinson's Disease
MDS-UPDRS	Movement Disorder Society's Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid results
NOS	No sample available
[redacted]	[redacted]
[redacted]	[redacted]
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDQ-39	Parkinson's Disease Quality of Life Questionnaire-39
[redacted]	[redacted]
PGX	Pharmacogenomic
pH	Potential of hydrogen
PK	Pharmacokinetic(s)
PP	Polypropylene

PT	Preferred Term
QRS	QRS interval on ECG
QT	QT interval on ECG
RBC	Red blood cell count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analytical plan
SE-ADL	Schwab and England Activities of Daily Living
SOC	System Organ Class
S-STS	Sheehan-Suicidality Tracking Scale
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
US	United States
wAMD	Wet age-related macular degeneration
WBC	White blood cell count
WOCBP	Women of childbearing potential

PROTOCOL APPROVAL PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKST4290 in Subjects with Parkinson's Disease on Stable Dopaminergic Treatment
Protocol Number:	AKST4290-211
Version/Date:	V4.0_22MAY2020
Sponsor Name and Address:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070

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

Approved by:

[redacted]		May 22, 2020
Sponsor Representative (print)	Signature	Date

STATEMENT OF COMPLIANCE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKST4290 in Subjects with Parkinson's Disease on Stable Dopaminergic Treatment
Protocol Number:	AKST4290-211
Version/Date:	V4.0_22MAY2020

By my signature, I:

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

_____ _____

Investigator's Signature Date

_____

Print Name

PROTOCOL SUMMARY

Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKST4290 in Subjects with Parkinson's Disease on Stable Dopaminergic Treatment
Précis:	This is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of AKST4290 in subjects with Parkinson's disease (PD). The study will enroll approximately 120 subjects who will be randomized in a 1:1 ratio to active treatment in Arm 1 (approximately 60 subjects) or placebo in Arm 2 (approximately 60 subjects). Subjects will take 400 mg of AKST4290 or placebo taken orally, twice per day (b.i.d.) for a total daily dose of 800 mg. The study duration for the subjects will be approximately 18 weeks including screening, 12 weeks of treatment, and 4 weeks of follow-up.
Objectives:	The primary objective of the study is to assess the effects of AKST4290 on motor function in the practically defined off-medication state, defined as ≥12 hours off levodopa, in subjects with PD. The secondary objectives include the assessment of the safety of AKST4290 in subjects with PD as well as the potential effects on clinical function and activities of daily living. The exploratory objectives include analysis of pharmacokinetic (PK) parameters following twice daily dosing with AKST4290. Additionally, flow cytometry, pharmacogenomic, and biomarker evaluations will be conducted on blood and plasma samples. Bradykinesia, tremor, general activity, and sleep may be assessed with a wearable device. In consenting subjects, fecal samples will be obtained at screening and following treatment to assess potential microbiome changes.
Endpoints:	Primary Endpoints: • Change from Baseline (Day 1) in motor function during the practically defined off-medication state, defined as ≥12 hours off levodopa, at Week 12 (Day 84) as measured by Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part 3. Secondary Endpoints: • Incidence of treatment-emergent adverse events (AEs) 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). • Incidence of abnormalities or clinically-significant changes from Baseline in laboratory test data, vital sign measurements, and electrocardiograms (ECGs). • Change from Baseline (Day 1) in clinical function, motor function, and activities of daily living at Week 12 (Day 84)

during the on-medication state as assessed by:

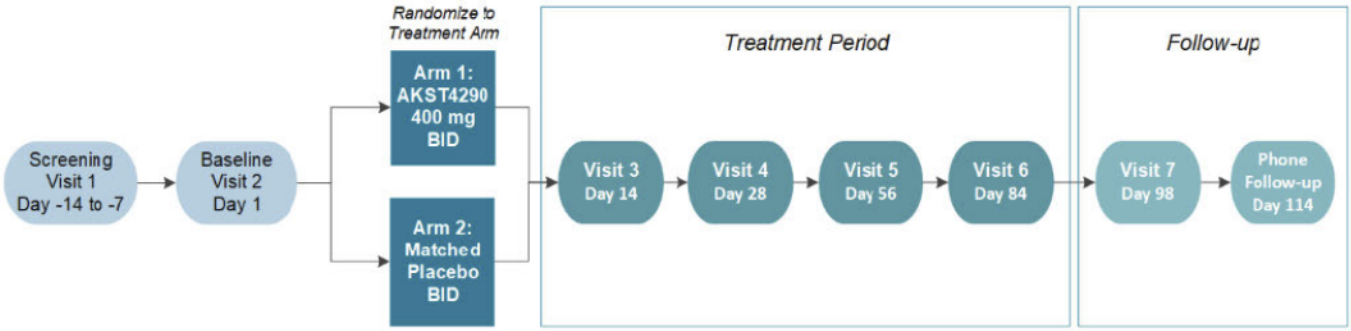
- MDS-UPDRS Parts 1-4
- Montreal Cognitive Assessment (MoCA)
- Schwab and England Activities of Daily Living (SE-ADL) Scale
- Clinical Impression of Severity Index – PD (CISI-PD)
- PD Quality of Life Questionnaire-39 (PDQ-39)
- Sheehan-Suicidality Tracking Scale (S-STS)
- 10-meter timed walk (will also be assessed in the off-medication state)
- Hauser 3-Day Patient Diary

Exploratory Endpoints:

- Changes in concentration of AKST4290 or its major metabolites in plasma at various time points.
- Flow cytometric analyses and evaluation of pharmacogenomic characteristics and biomarkers in blood and plasma samples.
- Changes in bradykinesia, tremor, general activity, and sleep as measured by an FDA-cleared wearable sensor device.
- In consenting subjects (optional): characterization of the composition and function of the fecal gut microbiome.

Population:	Approximately 120 subjects between 50 and 80 years of age with a diagnosis of PD on dopaminergic treatment. Assuming a drop-out rate of 10%, enrollment at this level will yield approximately 108 evaluable subjects.
Phase:	2
Number of Sites:	Approximately 30 sites are planned globally
Description of Study Agent:	AKST4290: [redacted]
Study Duration:	Approximately 15 months
Subject Participation:	Approximately 18 weeks

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

[redacted]

1.2 STUDY ORGANIZATION

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), Sponsor's medical expert and study monitor, Sponsor's representative(s), laboratories, steering committees, and oversight committees (including Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs), as applicable) will be maintained by the Sponsor, or their designee, and provided to the investigator.

2 INTRODUCTION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3 OBJECTIVES AND PURPOSE

The primary objective of the study is to assess the effects of AKST4290 on motor function in the practically defined off-medication state in subjects with PD. The secondary objectives include the assessment of the safety of AKST4290 in subjects with PD as well as the potential effects on clinical function, cognition, and activities of daily living. The exploratory objectives include analysis of PK parameters following twice daily dosing with AKST4290. Additionally, flow cytometry/fluorescence-activated cell sorting (FACS), pharmacogenomic, and biomarker evaluations will be conducted on blood and plasma samples. Bradykinesia, tremor, general activity, and sleep may be assessed with a wearable sensor device. In consenting subjects, fecal samples will be obtained at screening and following treatment to assess potential microbiome changes.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study conducted at approximately 30 sites globally. During the screening period (Day -14 through Day -7), subjects will undergo all screening assessments to assess eligibility. In consenting subjects, fecal samples will also be collected at screening for microbiome assessment. During the Baseline Visit (Day 1), subjects will be randomized in a 1:1 ratio to AKST4290 (Arm 1) or placebo (Arm 2). Subjects will then complete motor assessment in both on-medication and off-medication states, as well as testing for non-motor symptoms of PD, activities of daily living and quality of life.

Safety and tolerability assessments will occur at every visit. Motor function and secondary endpoints will be conducted at Baseline and at periodic interim visits following dosing. In the event of early termination, a subject who has received at least 1 dose (400 mg) of AKST4290 or placebo, will undergo the end of treatment procedures unless the subject has withdrawn consent. A comprehensive efficacy and safety assessment of all data *in toto* will be conducted at the end of the study.

The overall duration of the study/recruitment period is approximately 10 months from study initiation (i.e., following consent of first subject) to study completion (i.e., last subject, last visit). The subject participation period is approximately 18 weeks from Screening through End of Study, unless prematurely discontinued.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Primary Endpoint:

- Change from Baseline (Day 1) in motor function during the practically defined off-medication state, defined as ≥12 hours off levodopa, at Week 12 (Day 84) as measured by the MDS-UPDRS Part 3.

4.2.2 SECONDARY ENDPOINTS

Secondary Endpoints:

- Incidence of treatment-emergent AEs and SAEs identified by MedDRA PT and grouped by MedDRA SOC.
- Incidence of abnormalities or clinically-significant changes from Baseline in laboratory test data, vital sign measurements, and ECGs.
- Baseline (Day 1) and longitudinal change in clinical function, motor function, and activities of daily living at Week 12 (Day 84) during the on-medication state as assessed by the following:
  - MDS-UPDRS Parts 1-4 (Fahn 1987, Goetz 2008)(Section 17.1)
  - MoCA (Nasreddine 2005)(Section 17.2)
  - SE-ADL Scale (Schwab 1968)(Section 17.3)
  - CISI-PD (Martinez-Martin 2006)(Section 17.4)
  - PDQ-39 (Peto 1998)(Section 17.5)
  - S-STS (Sheehan 2014)(Section 17.6)
  - 10-meter timed walk (Lang 2016)(also assessed in the off-medication state)
  - Hauser 3-Day Patient Diary (Hauser 2000, Hauser 2004)(Section 17.8)

4.2.3 EXPLORATORY ENDPOINTS

Exploratory Endpoints:

- Changes in concentrations of AKST4290 or its major metabolites in plasma at various time points.
- Flow cytometric analyses (FACS) and evaluation of pharmacogenomic characteristics and biomarkers in blood and plasma samples.
- Changes in bradykinesia, tremor, and sleep activity as measured by a wearable sensor device.
- In consenting subjects (optional): characterization of the composition and function of the fecal gut microbiome (Schwiertz 2018, Singh 2019).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

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

1. Aged 50-80 years at time of enrollment, inclusive.
2. Diagnosis of clinically established or clinically probable PD according to MDS-PD criteria (Postuma 2015) (Section 17.7) with at least 1 year of PD symptoms.
3. Modified Hoehn and Yahr ≤2.5.
4. Have notable motor worsening during off-medication state.
5. Clear-cut improvement of motor response to levodopa medications, as assessed by the investigator.
6. Must be on stable dopaminergic therapy (e.g., levodopa, dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors, amantadine), for at least 8 weeks prior to enrollment and remain on stable dose during the 12-week treatment period.
7. If on medications for cognition (e.g., rivastigmine, galantamine, donepezil, memantine), must be on stable dosage for at least 8 weeks prior to baseline.
8. If on antidepressant or neuroleptic medications, must be on stable dosage for at least 8 weeks prior to enrollment.
9. Ability to travel to clinic in the practically defined off-medication state, defined by withdrawal of levodopa prior to the clinic visit for at least 12 hours, or ability to stay overnight in an inpatient medical setting one night prior to off-medication assessment.
10. Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening. WOCBP must agree to use highly effective

contraception which includes combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, or vasectomized partner (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. Male subjects must be willing to use a barrier method contraception.

11. The subject must be able to follow the study procedures, receive the treatment in the established timeframe, and continue during the follow-up interval.
12. The subject must be able to understand the procedures and agree to complete the required assessments.
13. Provide a signed and dated informed consent form in accordance with local regulations and/or IRB/IEC guidelines.

5.2 EXCLUSION CRITERIA

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

1. Secondary or atypical parkinsonian syndromes, for example, patients with parkinsonism from encephalitis, metabolic disorders, vascular parkinsonism, drug-induced parkinsonism, multiple system atrophy, corticobasal ganglia degeneration, progressive supranuclear palsy, Lewy body dementia.
2. Medical history or condition:
   - Uncontrolled diabetes mellitus, with hemoglobin A1c (HbA1c) > 8%.
   - Myocardial infarction or stroke within 12 months of screening.
   - Significant cardiac arrhythmia.
   - Active bleeding disorder.
   - Major surgery within 1 month of screening or planned within the study period.
   - Current, active liver disease: > 3-fold elevation of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] over upper limit of normal).
   - Uncontrolled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite adequate treatment during the 3 months prior to dosing.
   - Positive screening test result for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
3. [redacted]
4. [redacted]
5. [redacted]
6. Renal function as defined by estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation (Section 17.9).
7. [redacted]
8. [redacted]
9. History of any brain surgery for PD (e.g., pallidotomy, deep brain stimulation, or fetal tissue transplant).
10. [redacted]
11. Clinically relevant abnormal laboratory value at screening, including hematology, blood chemistry,

or urinalysis (laboratory testing may be repeated once during the screening phase).

12. Conditions affecting the peripheral or central nervous system, unless related to PD, that would affect the ability to adequately perform the MDS-UPDRS and motor assessments: i.e., severe sensory neuropathy affecting arm or leg function, or stroke affecting motor or gait function.
13. Significant alcohol or drug abuse within past 2 years.
14. Based on ECG reading, subjects with a risk of QT prolongation including:
    - A baseline prolongation of QTc (using Fridericia's formula: ≥ 450 ms in men and ≥ 470 ms in women) with confirmation on a repeat ECG.
    - A history of additional risk factors for Torsades de pointes arrhythmia (e.g., heart failure, hypokalemia, family history of Long QT Syndrome, etc.).
    - The use of concomitant medications known to prolong the QT/QTc interval.
15. Significant medical conditions (as determined by medical history, examination, and clinical investigations at screening) that may, in the opinion of the investigator, result in the any of the following:
    - Put the patient at risk because of participation in the study.
    - Influence the results of the study.
    - Cause concern regarding the patient's ability to participate in the study.
    - Inclusion of vulnerable persons by local regulation (e.g., imprisoned or institutionalized).
16. Malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years (treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed).
17. Concurrent participation in another interventional clinical trial; prior clinical trial subjects must have been off study agents for at least 30 days for small molecules, 4 months for disease modifying therapies, and 1 year for vaccine or immunotherapy trials prior to screening.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The Sponsor does not anticipate any specific challenges in meeting recruitment goals of enrolling and retaining a total of 120 subjects in this study. Subjects will be recruited continuously until the planned sample size is achieved. Subjects who withdraw or are withdrawn during Screening, as well as subjects who discontinue, may be replaced (see Section 5.4.2 Handling of Participant Withdrawals or Termination).

The expected length of participation in the study of approximately 18 weeks is not expected to be challenging to subjects. Financial support for meal and miscellaneous expenses will be available during the study, as appropriate and based on local regulations and guidelines. Use of visit transport services may also be incorporated into the trial to support the subject in maintaining study visit compliance. A description of the study will be included in local clinical trial databases, as required.

5.4 SUBJECT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

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

- Occurrence of an AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the investigator, Sponsor, or medical monitor. The investigator must follow the subject until the AE resolves or is stable unless the subject is lost to follow up.
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.

- Pregnancy.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

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

Approximately 120 subjects (AKST4290: 60; placebo: 60) will be enrolled in the study with the intent of obtaining ~108 evaluable subjects. Subjects who discontinue or are unblinded prior to Visit 6 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced. Subjects who are withdrawn due to adverse drug events or adverse reactions based on study procedures will not be replaced.

Subjects who have received at least 1 dose (400 mg) but are withdrawn or withdraw from the study will be encouraged to complete the end of treatment procedures. The primary reason for study discontinuation will be documented on the case report form (CRF).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

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

- (Immediate) risk to subject safety.
- Unsatisfactory subject enrollment.
- Unacceptable protocol deviations/violations as assessed by the medical monitor.
- Inaccurate or incomplete data entry and recording/fabricated data.
- Investigational site non-compliance with ICH/GCP.
- Unacceptable emergent safety profile.

6 STUDY AGENT

6.1 STUDY AGENT AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The study agent will be manufactured, labeled, packaged, and distributed by Alkahest, Inc.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

AKST4290 is a film-coated pink, oblong tablet manufactured by Alkahest, Inc., with a unit strength of 200 mg. The study agent (AKST4290/placebo) will be delivered to the site and labeled for investigational use only according to the relevant regulatory requirements for clinical studies.

For further details and information on AKST4290, including packaging and labeling, see the Investigator's Brochure.

6.1.3 PRODUCT STORAGE AND STABILITY

The study agent will be kept in its original packaging in a secure limited access storage area at 15° C - 30° C. A temperature log must be maintained to make certain the study agent is stored at the correct temperature. If the storage conditions are found to be outside the specified range, the site must immediately notify the sponsor or designee.

6.1.4 DOSING AND ADMINISTRATION

The study agent will be self-administered orally b.i.d. (2 x 200 mg per dose), approximately 12 hours apart, for a total daily dose of 800 mg. AKST4290 should be taken 1 hour before meals or 2 hours following a meal. Training on study agent administration will be conducted prior to initial dose. During the treatment period (Visits 2-6), subjects will be instructed to wait to administer their first daily dose until they are asked to do so by study personnel for documentation of precise administration times (following PK testing).

6.1.5 ROUTE OF ADMINISTRATION

The study agent will be administered orally.

6.2 STUDY AGENT ACCOUNTABILITY

The investigator and/or pharmacist will receive the study agent and placebo delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol and informed consent(s) by the IRB or IEC.
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site.
- Approval/notification of the appropriate regulatory authority(ies).
- Availability of the curriculum vitae of the principal investigator.
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol.

The investigator and/or pharmacist must maintain records of the study agent's and placebo's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused study agent.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study agent, placebo, and trial subjects. The investigator/pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study agent and placebo received from the sponsor. At the time of final study agent and placebo reconciliation, the investigator/pharmacist must verify that all unused or partially used portion of study agent and placebo have been returned by the clinical trial subject and that no remaining study agent and placebo is retained by the investigator.

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

The disposal of used, partially used, or wasted study agent and placebo must be conducted in accordance with the institution's drug disposal policy. At study initiation, the clinical study monitor will evaluate the site's standard operating procedure for study agent disposal/destruction to ensure it complies with study requirements. At the end of the study, following final study agent and placebo reconciliation by the monitor, the study site will be instructed by the sponsor to return or destroy all unused study agent and placebo. A copy of the institution's

drug disposal policy should be maintained or referenced in the Investigator Site File (ISF) if applicable.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

7.1.1.1 Screening Procedures

During screening, the following will be conducted:

- Assessment of PD, including modified Hoehn and Yahr.
- Medical history.
- Demographics.
- Review of medications.
- Vital signs.
- Physical examination.
- 12-Lead ECG.
- Blood and urine collection for laboratory evaluations.

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

7.1.1.1.1 Assessment of Parkinson's Disease and Cognitive Impairment

The diagnosis of PD will be verified using MDS-PD criteria (Postuma 2015) (Section 17.7). The prerequisite to apply the MDS-PD criteria is the presence of the cardinal symptoms of Parkinson's Disease, defined as bradykinesia, in combination with either resting tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors (Postuma 2015). The stage of the disease will be classified using the modified Hoehn and Yahr scale.

7.1.1.1.2 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject during screening. The medical history should focus on recent history, with an emphasis on the history of motor symptoms related to PD. Additionally, the medical history should include:

- Current/past illnesses and conditions.
- Current symptoms of any active medical condition.
- Surgeries and procedures.
- Allergies.
- Family history in biological parents, siblings, and offspring of PD, AD, or other dementias or neurological disorders.
- Social history (e.g., exercise, smoking, alcohol, illegal substances) and current living situation
- Cause of parental death (if not living).
- Prior imaging, CSF assessments, or other relevant diagnostic test results, including genetics.

7.1.1.1.3 Demographics

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

7.1.1.1.4 Review of Medications

The investigator or designee should obtain a complete list of the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject in the past

12 months and any dose changes of medications for PD in the last 3 months. Assessment of eligibility should include a review of permitted and prohibited medications. Any additions, discontinuation, or dosage changes in medication during the course of the study will be recorded.

7.1.1.1.5 Vital Signs

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

7.1.1.1.6 Full Physical Examination

A full physical examination will be performed and documented to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic and lymphatic systems. The complete neurological examination will include, but not be limited to mental status, 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, bulk, and abnormal movements; reflexes (biceps, triceps, knees, ankles, and plantar); coordination (finger-to-nose, heel-knee-shin); sensory function (light touch, pinprick, and vibration); and gait. Height will be measured at screening and weight will be monitored during the trial.

7.1.1.1.7 12-Lead ECG

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph. A 12-lead ECG will be performed after the subject has rested quietly for at least 5 minutes in a supine position. In some cases, it may be appropriate to repeat abnormal ECGs to rule out technical factors contributing to ECG artifacts or abnormality. It is important that leads are placed in the same positions each time for consistency. The overall conclusion with the interpretation of the ECGs will be recorded on the appropriate CRF. The interpretation of the ECGs will be recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant. Corrected QTc intervals will be calculated using Fridericia's correction formula and entered into the CRF.

7.1.1.1.8 Screening Biological Specimen Collection

For screening evaluation, blood will be drawn by a qualified medical provider, and urine specimens will also be collected (see Section 7.1.1.2.7).

7.1.1.1.9 Administration of Dopaminergic Medication

Subjects will be instructed by site personnel to take their prescribed dopaminergic medication following completion of the off-medication assessments on Visit 2 (Day 1), Visit 4 (Day 28), Visit 6 (Day 84), and Visit 7 (Day 98).

7.1.1.2 Procedures to Assess Safety

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

- Review of AEs.
- Review of medications.
- Vital signs.
- S-STS.
- 12-Lead ECGs.
- Targeted physical examinations and weight.
- End of Study (or Early Termination) physical examination.
- Blood draw and urine collection for laboratory evaluations.

7.1.1.2.1 Review of Adverse Events
AEs will be reviewed, documented, and reported as required at each visit, beginning at Screening. For definitions, guidance, and additional information regarding AEs, refer to Section 8.

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

7.1.1.2.3 Vital Signs
Refer to Section 7.1.1.1.5 for a description of vital signs. Vital signs will be collected at every visit (see the Schedule of Events).

7.1.1.2.4 Sheehan-Suicidality Tracking Scale
Refer to Section 7.1.1.3.6 for a description of the S-STS.

7.1.1.2.5 12-Lead ECG
Refer to Section 7.1.1.1.7 for information pertaining to 12-Lead ECGs.

7.1.1.2.6 Targeted Physical Examination
During the study period, a targeted physical examination, including auscultation of the heart and measurement of weight, will be performed per the Schedule of Events.

7.1.1.2.7 Blood and Urine Collection for Laboratory Evaluations
Blood samples and urine will be collected according to the Schedule of Events. Laboratory tests will include hematology, chemistry, coagulation, qualitative urinalysis, and pregnancy testing in WOCBP.

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelets
- Chemistry: glucose, sodium, potassium, calcium, inorganic phosphate, chloride, bicarbonate, magnesium, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, blood urea nitrogen, total protein, albumin, creatine phosphokinase (CPK), cholesterol (total), C-reactive protein (CRP)
- Serology (conducted at Screening only): HBV, HCV, and HIV
- Coagulation: activated partial thromboplastin time (aPTT), prothrombin time/international normalized ratio (INR)
- Urinalysis: pH, glucose, erythrocytes, leukocytes, protein, nitrite

Additional laboratory parameters may be reported as detailed in the laboratory manual. Glomerular filtration rate (GFR) will be estimated by the MDRD Formula utilizing serum creatinine (see Section 17.9). All safety laboratory measurements will be conducted by a CLIA-certified laboratory. Investigators will get guidance and instructions on laboratory sampling and processing through a separate Laboratory Manual provided by the central laboratory.

Serology will only be conducted at screening. Potential subjects with positive screening test result for HBV, HCV, or HIV will not be eligible for study participation.

The investigator is responsible for determining and documenting if out-of-range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the CRF and followed until resolution. Once resolved, the appropriate CRF page(s) will be updated.

Samples may be used for re-testing, further evaluation of an AE and/or assessment, and follow-up of other exploratory endpoints. Samples that remain after study testing is complete will be stored in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. Samples will be stored in a deidentified coded form. Subjects can opt out of storage of samples for future analysis.

7.1.1.3 Procedures to Assess Efficacy

Procedures to assess efficacy include motor and cognitive function testing, assessment of activities of daily living, and, in consenting subjects, microbiome assessment. Information regarding the timing and frequency of these procedures is provided in Section 7.3 and Section 15 Schedule of Events.

All testing will be conducted by qualified evaluators who have undergone standardized rater training and certification, as appropriate. The same evaluator should be used for the duration of each subject's participation unless a change in rater is unavoidable. The MDS-UPDRS Part 3 and 10-meter timed walk will be performed in the off-medication and on-medication states. All other assessments should be conducted in the on-medication state as listed in Section 7.3:

- MDS-UPDRS Parts 1-4
- MoCA
- SE-ADL
- CISI-PD
- PDQ-39
- S-STS
- 10-meter timed walk
- Wearable sensor device (as applicable)
- Fecal markers of intestinal inflammation and permeability (optional)
- Hauser 3-Day Patient Diary

Descriptions of each assessment are provided below.

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

The MDS-UPDRS (Fahn 1987, Goetz 2008) (Section 17.1) was developed to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The MDS-UPDRS has four components (Part 1, Mentation, Behavior, and Mood; Part 2, Activities of Daily Living; Part 3, Motor; Part 4, Complications). One of the core advantages of the UPDRS is that it was developed as a compound scale to capture multiple aspects of PD. The rating for each item is from 0 (normal) to 4 (severe). The total score for each Part is obtained from the sum of the corresponding item scores.

7.1.1.3.2 Montreal Cognitive Assessment

The MoCA (Nasreddine 2005) (Section 17.2) is a screening test easily administered by non-specialist staff. It assesses attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points with a score of 26 or more considered normal.

7.1.1.3.3 Schwab and England Activities of Daily Living Scale

The SE-ADL evaluates patients' perceptions of global functional capacity and dependence (Schwab 1968) (Section 17.3). Scoring is expressed in terms of percentage, in 10 steps from 100 to 0 (100%, normal status; 0%, bedridden with impaired vegetative functions), so that the lower the score, the worse the functional status. The rating is made by a trained clinician.

7.1.1.3.4 Clinical Impression of Severity Index – Parkinson's Disease

The CISI-PD is a severity index formed by four items (motor signs, disability, motor complications, and cognitive status), rated 0 (not at all) to 6 (very severe or completely disabled) (Martinez-Martin 2006) (Section 17.4). A total score is calculated by summing the item scores. The scale is completed by a clinician. It only takes a few minutes to complete once the state of the subject is known.

7.1.1.3.5 Parkinson's Disease Quality of Life Questionnaire-39

The PDQ-39 is a self-administered questionnaire of 39 questions relating to 8 key areas of health and daily activities, including both motor and non-motor symptoms (Peto 1998)(Section 17.5). The eight dimensions include: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. It is scored on a scale of 0-100 with lower scores indicating better health and high scores indicating more severe symptoms.

7.1.1.3.6 Sheehan-Suicidality Tracking Scale

The S-STS was developed to provide a brief but efficient instrument for use in assessing change in suicidal ideation and behavior while providing a comprehensive description of suicidal ideation and behavior. The primary goals in the design of the S-STS were for the scale to be: 1) short and inexpensive; 2) simple, clear, and easy to administer or self-rate; 3) highly sensitive (i.e., able to detect a high proportion of patients who are suicidal); 4) specific (i.e., able to screen out those who are not suicidal); 5) sensitive to change in suicidal ideation and behavior; 6) compatible with the regulatory categories of assessment for suicidal ideation and behavior; 7) useful in clinical as well as research settings; 8) useful in detecting an efficacy signal for anti-suicidal medications; and 9) capable of use in pediatric and geriatric settings (Sheehan 2014). The standard version of the S-STS (Section 17.6) is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0-4) ranging from "not at all" (0) to "extremely" (4). It also assesses the frequency of key phenomena and the overall time spent in suicidality.

7.1.1.3.7 10-Meter Timed Walk

The 10-meter walk test is a commonly used tool for assessing gait speed in individuals with gait limitations (Lang 2016). Gait speed is positively correlated with the amount of community ambulation and quality of life, and therefore it is an important measure of mobility in individuals with PD. This test has been validated in various populations and is a recommended outcome measure for use in patients with PD (Lang 2016).

7.1.1.3.8 Wearable Sensor Device

Wearable sensor devices have advanced in recent years to enable continuous measurement of health-related symptoms, which in Parkinson's include the motor and nonmotor features of bradykinesia, tremor, activity, and sleep. As applicable, subjects will be supplied the wearable sensor devices. Full information as to the operation and data capture from the devices will be included in the Investigator Site File (ISF).

7.1.1.3.9 Fecal Markers of Intestinal Inflammation and Permeability

Intestinal inflammation and increase intestinal permeability (both possibly fueled by dysbiosis) have been implicated in the multifactorial pathogenesis of PD (Schwiertz 2018). In consenting subjects, fecal samples will be collected at screening and at end of treatment and samples will be flash frozen for assessment. Full information as to procedure for collection and processing of samples will be included in the ISF.

7.1.1.3.10 Hauser 3-Day Patient Diary

The Hauser Patient Diary was developed to assess functional status over a period of time in patients with motor fluctuations and dyskinesia (Hauser 2000)(Section 17.8). It is a self-completed reference diary designed to separate dyskinesia that had a negative impact on patient-defined functional status from dyskinesia that did not. With this diary, the effect of an intervention can be expressed as the change in off-medication time and the change in on-medication time with troublesome dyskinesia (bad time).The sum can be used as an outcome variable and compared to baseline or across groups. In a follow-up study to the original evaluation of the

assessment, it was determined that compliance diminished after 3 days, but diaries completed on 3 consecutive days were simple, feasible, and improved compliance (Hauser 2004).

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g., whole blood, serum, urine) will be collected for laboratory evaluations including pregnancy testing in WOCBP in accordance with the Schedule of Events. Refer to the study's laboratory manual for complete information regarding all laboratory evaluations to be performed, sample collection procedures, and related requirements.

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

7.2.2 OTHER TESTS OR PROCEDURES

7.2.2.1 Study Agent Concentration and Pharmacokinetics

Plasma concentration measurements of AKST4290 and its major metabolites will be collected to assess systemic exposure to the study agent. For required and optional sampling time points and further details, please refer to Section 17.12.

7.2.2.1.1 Pharmacokinetic Endpoints

As far as feasible, the following PK parameter will be summarized descriptively:

- $C_{pre,ss,N}$ Pre-dose concentration of AKST4290 in plasma immediately before administration of the Nth dose

7.2.2.1.2 Methods of Sample Collections

For quantification of plasma concentrations of AKST4290 and its major metabolites, and for biomarker investigations (see Section 7.2.2.3), one blood sample of approximately 6 mL per sampling time point (see Section 17.12 Table of Pharmacokinetic, Biomarker, Pharmacogenomic, and FACS Sampling) will be taken from an antecubital or forearm vein into a potassium ethylenediaminetetraacetic acid (EDTA)-anticoagulant blood drawing tube.

The EDTA-anticoagulated blood samples will be centrifuged to collect plasma. For PK samples only, the obtained plasma will be split into 2 aliquots and stored in polypropylene tubes. At the selected time points with additional biomarker determinations, 5 instead of 2 aliquots of at least 0.5 mL plasma each will be prepared from the blood sample. The time from blood collection until the transfer of plasma aliquots into the freezer should not exceed 60 minutes, with interim sample storage on wet ice whenever possible. Samples will be positioned upright and will be frozen at approximately -20°C or below until shipment. These aliquots will be processed by the central laboratory. Details of plasma collection, sample handling, and shipment instructions will be provided in the Lab Manual.

7.2.2.1.3 Analytical Determinations

Concentrations of AKST4290 and metabolites (if feasible) in plasma samples will be determined by a validated high-performance liquid chromatography, tandem mass spectrometry (HPLC-MS/MS) assay. Leftover samples will be used for exploratory biomarker assessment (see Section 7.2.2.3).

7.2.2.2 Pharmacogenomic Evaluations

Pharmacogenetic analysis of prespecified genes is an exploratory endpoint. Samples for deoxyribonucleic acid (DNA) banking will be collected if participants signed a separate informed consent and is not required for study participation.

- Prespecified genes: DNA will be extracted from one blood sample and genotyped for common genetic variants of the following genes: [redacted]

Several gene mutations have been implicated in Parkinson's disease, notably the alpha-synuclein gene (SNCA), leucine-rich repeated kinase 2 (LRRK2) gene, and the PARKN gene. [redacted] Prespecified analyses will be performed at the end of the trial and the data will be part of the report. All remaining samples will be destroyed after the end of the trial.

- DNA banking (optional): One blood sample will be collected for retrospective, exploratory genotyping (e.g., to analyze disease or treatment-related gene variants). For information regarding future use of stored samples, see Section 12.5 Future Use of Stored Specimens.

7.2.2.3 Plasma Biomarkers

Measurement of biomarkers is exploratory. Investigations might include mechanism related markers [redacted] which could identify subsets of subjects who may benefit most from the treatment with AKST4290. Other disease-related markers may include inflammatory mediators or markers of oxidative stress. Biomarkers will be measured in plasma samples to investigate any change in response to treatment. After completion of the study, leftover samples may be used for further methodological and/or other, non-genetic biomarker investigations either by the sponsor, or designee. The study samples will be discarded after completion of the additional investigations, but not later than 3 years after the final study report has been archived. The exploratory biomarker measurements will be conducted either at the sponsor's laboratories or at external CROs using appropriate methodology (e.g., immunoassays, multiplex technology). A Laboratory Manual/ISF will describe the handling of the samples.

7.2.2.4 Blood Biomarkers by Flow Cytometry

Characterization of immune cells using FACS/complete blood count (CBC) is exploratory. For the investigations, one blood sample of approximately 6 mL per sampling time point will be collected. Specimens must be transported for testing within a specified time period. The exploratory biomarker measurements using FACS/CBC will be conducted either at the sponsor's laboratories or at external CROs using appropriate methodology (e.g., immunoassays, multiplex technology). A Laboratory Manual/ISF will describe the handling of the samples.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

7.3.1.1 Visit 1, Screening Visit (Day -14 to -7)

Assessments to be conducted in the following order:

- ☐ Signing of all applicable informed consents must be completed prior to any study-related assessments.
- ☐ Verify diagnosis of PD according to MDS PD criteria, including modified Hoehn and Yahr stage.

Remaining assessments (*may be conducted in any order*):

- ☐ Obtain medical history, including medical records and test results to support PD diagnosis if available.

- ☐ Collect demographic information.
- ☐ Review subject's current and prior medications.
- ☐ Review prohibited medications and substances with the subject.
- ☐ Collect vital signs.
- ☐ Collect (screening) laboratory samples.
- ☐ Perform pregnancy testing and review results in WOCBP.
- ☐ Perform full physical examination (including height).
- ☐ Perform 12-lead ECG.
- ☐ Verify the subject fulfills all the inclusion criteria and none of the exclusion criteria.
- ☐ For eligible subjects, review instructions for PDQ-39 and Hauser 3-Day Patient Diary and provide associated information and assessment materials; subjects should be instructed to bring completed materials to Visit 2.
- ☐ For eligible subjects, set up, review instructions for, and provide the home-based wearable sensor device to be collected at Visit 2.
- ☐ For consenting subjects, fecal sample collection (optional).

7.3.2 BASELINE

7.3.2.1 Visit 2, Baseline (Day 1)

Assessments to be conducted in the following order, *unless otherwise indicated*:

- ☐ Perform pregnancy testing and review results in WOCBP.
- ☐ Confirm subject meets all eligibility criteria.
- ☐ Randomize to AKST4290 or placebo.
- ☐ Confirm off-medication state (off-levodopa).
- ☐ Assessments to be conducted in the off-medication (off-levodopa) state (*may be conducted in any order*):
  - MDS-UPDRS Part 3.
  - 10-meter timed walk.
- ☐ Administration of dopaminergic medication (commence on-medication state) for remaining assessments that day.

The following assessments may be conducted in any order, *after randomization and prior to study agent administration*:

- ☐ Collect the wearable sensor device.
- ☐ Review AEs and concomitant medications.
- ☐ Perform targeted physical examination.
- ☐ Collect vital signs.
- ☐ Collect completed PDQ-39 and provide for the next visit.
- ☐ Collect completed Hauser 3-Day Patient Diary.
- ☐ Confirmation of on-medication state.
- ☐ Assessments to be conducted in the on-medication state (*may be conducted in any order*):
  - MDS-UPDRS Parts 1-4.
  - MoCA.
  - SE-ADL.
  - CISI-PD.
  - S-STS.
  - 10-meter timed walk.
- ☐ Collect laboratory samples.

Assessments to be conducted in the following order, *after all other assessments are completed*:

- ☐ Collect initial PK and biomarker samples 15 minutes prior to study agent administration (see Sections 7.2.2.1, 7.2.2.3, 17.12).
- ☐ Collect initial FACS/CBC samples 15 minutes prior to study agent administration (see Sections 7.2.2.4, 17.12).
- ☐ Collect pharmacogenomic sample (see Sections 7.2.2.2, 17.12).
- ☐ Dispense 5-week supply of AKST4290 or placebo.
- ☐ Study drug (AKST4290/placebo) administration (dose administered approximately 15 minutes after acquisition of initial PK sample).
- ☐ Study agent accountability.
- ☐ Collect PK and biomarker samples 1 hour following study agent administration (see Sections 7.2.2.1, 7.2.2.3, 17.12).
- ☐ Collect FACS/CBC samples 1 hour following study agent administration (see Sections 7.2.2.4, 17.12).
- ☐ Collect (*optional, with consent*) PK sample 2 hours following study agent administration (see Sections 7.2.2.1, 17.12).

7.3.3 TREATMENT

The examinations of each visit are specified in Section 15 Schedule of Events. In addition, please see Section 17.12 Table of Pharmacokinetic, Biomarker, Pharmacogenomic, and FACS Sampling for detailed information regarding these evaluations. Important note: to ensure accuracy of PK sampling, study agent (AKST4290/placebo) should be administered during the study visit to enable appropriate timing of PK sample acquisition.

7.3.3.1 Visit 3 (Day 14 ± 2) and Visit 5 (Day 56 ± 2)

Assessments to be conducted in the following order:

- ☐ Collect laboratory samples.
- ☐ Collect PK sample 15 minutes prior to study agent administration.
- ☐ Study agent (AKST4290/placebo) administration (dose administered approximately 15 minutes following acquisition of PK sample).

Remaining assessments (*may be conducted in any order*):

- ☐ Perform pregnancy testing and review results in WOCBP.
- ☐ Study agent accountability.
- ☐ Review AEs and concomitant medications.
- ☐ Perform targeted physical examination.
- ☐ Collect vital signs.
- ☐ Collect completed PDQ-39 and provide for next visit.
- ☐ Provide Hauser 3-Day Patient Diary for next visit (**Visit 5 only**).
- ☐ Assessments to be conducted in the on-medication state (*may be conducted in any order*):
  - MDS-UPDRS Parts 1-4.
  - SE-ADL.
  - CISI-PD.
  - 10-meter timed walk.
- ☐ Dispense 5-week supply of AKST4290 or placebo (**Visit 5 Only**).
- ☐ Collect wearable sensor device (**Visit 5 only**).
- ☐ Provide wearable sensor device to be collected at Visit 6 (**Visit 5 only**).

7.3.3.2 Visit 4 (Day 28 ± 2) and Visit 6 – End of Treatment (Day 84 ± 2) or Early Termination

Assessments to be conducted in the following order:

- ☐ Collect laboratory samples.
- ☐ Collect initial PK sample 15 minutes prior to study agent administration.
- ☐ Collect biomarker sample 15 minutes prior to study agent administration (**Visit 6 Only**).
- ☐ Collect FACS/CBC samples 15 minutes prior to study agent administration (**Visit 6 Only**).
- ☐ Study agent (AKST4290/placebo) administration (dose administered approximately 15 minutes after acquisition of initial PK sample).
- ☐ Confirmation of off-medication state (≥12 hours since last levodopa dose).
- ☐ Assessments to be conducted in the off-medication (off-levodopa) state and 45 minutes (± 15 minutes) after study agent administration (*may be conducted in any order*):
  - MDS-UPDRS Part 3.
  - 10-meter timed walk.
- ☐ Administration of dopaminergic medication (commence on-medication state) for remaining assessments that day.

Remaining assessments (*may be conducted in any order*):

- ☐ Collect vital signs.
- ☐ Perform pregnancy testing and review results in WOCBP.
- ☐ Review AEs and concomitant medications.
- ☐ Perform targeted physical examination.
- ☐ Collect completed PDQ-39 and provide for next visit.
- ☐ Collect completed Hauser 3-Day Patient Diary (**Visit 6 only**).
- ☐ Perform 12-lead ECG.
- ☐ Study agent accountability.
- ☐ Collect (*optional, with consent*) PK sample 1 hour following study agent administration (see Sections 7.2.2.1, 7.2.2.3, 17.12).
- ☐ Provide wearable sensor device (**Visit 4 only**).
- ☐ Collect wearable sensor device (**Visit 6 only**).
- ☐ Assessments to be conducted in the on-medication state: (*may be conducted in any order*)
  - MDS-UPDRS Parts 1-4.
  - MoCA (**Visit 6 Only**).
  - SE-ADL.
  - CISI-PD.
  - S-STS (**Visit 6 Only**).
  - 10-meter timed walk.
  - Fecal sample collection (*optional, with consent*) (**Visit 6 Only**).
- ☐ Dispense 5-week supply of AKST4290 or placebo (**Visit 4 Only**).
- ☐ Collect (*optional, with consent*) PK sample 2 hours following study agent administration (see Sections 7.2.2.1, 17.12).

7.3.4 FOLLOW-UP

7.3.4.1 Visit 7 (Day 98 ± 3 or 14 days after Early Termination)

Assessments to be conducted in the following order, *unless otherwise indicated*:

- ☐ Confirm off-medication state (≥ 12 hours off levodopa).
- ☐ Assessments to be conducted in the off-medication (off-levodopa) state (*may be conducted in any order*):

- MDS-UPDRS Part 3.
- 10-meter timed walk.

- ☐ Administration of dopaminergic medication (commence on-medication state) for remaining assessments that day.
- ☐ Review AEs and concomitant medications.
- ☐ Perform targeted physical examination.
- ☐ Collect vital signs.
- ☐ Collect laboratory, PK, and biomarker samples.
- ☐ Perform pregnancy testing and review results in WOCBP.
- ☐ Collect completed PDQ-39.
- ☐ Assessments to be conducted in the on-medication state (*may be conducted in any order*):
  - MDS-UPDRS Parts 1-4.
  - SE-ADL.
  - CISI-PD.
  - 10-meter timed walk.

7.3.4.2 Safety Follow-Up: Documented Phone Call (Day 114 ± 2 or 30 days after Early Termination)

- ☐ Review AEs and concomitant medications.

7.3.5 EARLY TERMINATION

In cases of early termination, if a subject has received at least 1 dose (400 mg) of AKST4290 or placebo, the site should try to perform all assessments scheduled at the Visit 6 - End of Treatment visit as well as the subsequent follow up visits unless the subject has withdrawn consent.

7.3.6 SCHEDULE OF EVENTS TABLE

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

7.3.7 END OF TRIAL/END OF STUDY

The end of trial/end of study will occur following the last subject's last visit. The approximate duration to conduct the trial to support full recruitment is approximately 10 months.

7.4 CONCOMITANT MEDICATIONS

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

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

[redacted]

[redacted]

8 ASSESSMENT OF SAFETY

Assessment of safety will be conducted by blinded study personnel except in extraordinary circumstances where knowledge of whether AKST4290 or placebo was received by a subject is essential. Any instances of unblinding will be managed as indicated in Section 10.6.3 Breaking the Study Blind/Subject Code.

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

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

An AE does include any:

- Exacerbation of a pre-existing illness.
- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study agent administration even though it may have been present prior to the start of the study (unless it can be demonstrated by medical record review that the onset of the event preceded the date/time of informed consent).
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

- Symptoms associated with disease not previously reported by the subject.
- Untoward medical occurrences considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments (e.g., change on physical examination, ECG findings), if they represent a clinically significant finding, that were not present at Baseline or worsened during the course of the study.
- Laboratory test abnormalities, if they represent a clinically significant finding, symptomatic or not, which were not present at Baseline or worsened during the course of the study.

An AE DOES NOT include a/an:

- Elective medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion).
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).
- Overdose of either study agent or concurrent medication without any signs or symptoms.
- Pregnancy.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Note: if either the investigator or the Sponsor believes that the event is serious, the event must be considered serious and evaluated for expedited reporting.

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

A serious adverse event (experience) or reaction is an untoward medical occurrence that, at any dose, fulfills one or more of the following criteria:

a. Results in death (i.e., the AE actually causes or leads to death).

b. Is life-threatening.
   - An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death; it does not include AEs which, had it occurred in a more severe form, might have caused death.

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

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

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

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

8.2.2 RELATIONSHIP TO STUDY AGENT

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

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

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

8.2.3 EXPECTEDNESS

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

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the

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

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

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

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

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

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

8.3.1 POST-STUDY AE AND SAE

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

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

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

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

***Note**: Causality assessment will be made only when the AE occurs after the subject has initiated at least

1 dose of the study agent. An AE occurring before the subject's exposure to study agent will always be labeled as "unrelated".

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

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

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

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

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

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

8.4.2.1 Timeframes for Reporting SAEs

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

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

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

- The SAE Report Form and relevant source documents, if applicable, must be completed and notified, faxed, or emailed to PPD PVG immediately (without culpable delay), but no later than 24 hours of observation or learning of the event.
  - [redacted]
  - [redacted]

- [redacted]
- Follow-up information must be sent to [redacted] immediately (without culpable delay), but no later than 24 hours of receipt of information by the investigational site.

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

8.4.2.2 SAE Information to Report

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

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

A blank SAE Report Form and instructions for SAE reporting will be provided to the site and will be maintained in the investigator's study file. The SAE Report Form must be completed and faxed or emailed to PPD PVG according to the timeframes specified in Section 8.4.2.1. The SAE Report Form should include copies of relevant source documents, if applicable. Reconciliation of any discrepancy noted during monitoring and amending the eCRF is required.

If new information about an SAE is received or corrections to data are needed, the investigator should complete a new SAE Report Form and check the "follow-up" box on the form. This follow-up SAE Report Form should be submitted within 24 hours of learning of the information, especially if the new information concerns seriousness, relatedness, or the event term of an AE.

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

[redacted]

8.4.4 REPORTING OF PREGNANCY

While pregnancy itself is not considered an AE, pregnancy occurring in a clinical study must be followed to collect information regarding the experiences of gestation and pregnancy with study agent exposure. The investigator must report any pregnancy that occurs in a female study subject or female partner of a male subject subsequent to first exposure to the study agent until End of Study, or 3 months following a subject's last dose in the event of early termination. All pregnancies will be reported to the IRB/IEC, Sponsor, and CRO. In the event of a pregnancy, treatment will be discontinued, and the subject will undergo continued safety follow-up through pregnancy outcome. The study blind can be broken for safety reasons if the information is required for the management of pregnancy. Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor's Study Team Lead and Quality Group (see Section 10.6.3).

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

8.5 STUDY HALTING RULES

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

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

Events that are more likely related to a specific study procedure, will not be considered "drug related" and will not contribute to the count of definitely-related SAEs that would trigger a Safety Evaluation Meeting.

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (i.e., 3 related events in the same SOC or a suspicious overall pattern, as defined above) a Safety Evaluation Meeting will be triggered, and dosing may be temporarily halted based on the observations. The Sponsor will inform investigators and the FDA and EMA in the event of any temporary halt in dosing at any time during the conduct of the study. The purpose of the meeting is for investigators, the Sponsor, and the CRO Medical Monitor(s) to discuss and evaluate the safety of the subjects using available aggregated safety data and without compromising study blinding, unless the Sponsor deems unblinding necessary for safety evaluation.

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

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

8.6 SAFETY OVERSIGHT

Safety oversight will be provided by the Sponsor's Program Physician or his or her designee and the CRO's Medical Monitor(s) in concert with the site investigators. There will be no formal Data Safety Monitoring Board (DSMB) established. As needed, Safety Evaluation Meetings will be convened as described in Section 8.5 to

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

9 CLINICAL MONITORING

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

- Monitoring for this study will be conducted by the study CRO in accordance with the Clinical Monitoring Plan (CMP).
- A mix of on-site and centralized risk-based monitoring will be conducted to ensure the safety of clinical subjects and the accuracy and completeness of study data.
- The Sponsor will be provided with copies of monitoring reports per the timelines specified within the CMP.
- Details of clinical site monitoring tasks and scope are documented in the study's CMP. The CMP describes in detail who will conduct monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be conducted, and the distribution of monitoring reports.
- Independent audits may be conducted by the Sponsor in accordance with a study-specific Quality Assurance Plan to ensure monitoring practices are conducted consistently across all participating sites, that monitors are following the CMP and sites conduct the study according to the protocol, GCP, and applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL DESIGN MODEL AND ANALYTICAL PLANS

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

10.2 STATISTICAL HYPOTHESES

The null and alternative hypotheses for this study are:

$H_0: \mu_C = \mu_T$ vs $H_A: \mu_C \neq \mu_T$.

Note: The symbol "μ" denotes the mean change from baseline in motor function during the practically defined off-medication state at Week 12 as measured by the MDS-UPDRS Part 3 for the control (C) and treated (T) groups.

10.3 ANALYSIS DATASETS

Study data will be analyzed in one of the following analysis sets:

- **Intent-to-Treat (ITT)** set will include all randomized subjects.
- **Modified Intent-to-Treat (mITT)/Evaluable** set will be a subset of the ITT subjects with baseline and Week 12 value for off-medication motor function as measured by the MDS-UPDRS Part 3.
- **Safety Evaluable** set will include all randomized subjects who receive at least 1 dose of the study agent.
- **Per-Protocol (PP)** set is a subset of ITT subjects who follow the protocol without any major deviation(s). A detailed description of the reasons for exclusion from the PP population will be included in the Statistical Analysis Plan (SAP)

Subjects will be analyzed in the treatment arm assigned at randomization for the ITT, mITT, and PP sets. For the Safety Evaluable set, subjects will be grouped according to actual treatment received.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Subject disposition and protocol deviations will be summarized descriptively by treatment arm. The comparability between the treatment arms in demographics and baseline characteristics will be assessed. Prior and concomitant medications will also be summarized by treatment arm.

All summary statistics will be descriptive unless noted otherwise. Descriptive summaries will include mean, standard deviation (STD), median, and range for continuous variables and counts, and percentages for categorical variables. Two-sided 95% confidence intervals (CIs) will be provided for the means and percentages as needed. For key outcome measures, the difference between the treatment arm and the 95% CI of the difference will be computed.

Detailed statistical methods will be outlined in the SAP for the study.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint is change from baseline to Week 12 in the off-medication motor function as measured by the MDS-UPDRS Part 3. The main analysis for the primary efficacy variable will be analyzed using mITT subjects.

A mixed-effect model for repeated measures (MMRM) will be employed to analyze the change from baseline scores at each visit over time up to Week 12. The model will include the fixed effects of treatment (stratified, by sex), baseline of the endpoint, visit, and treatment by visit interaction. An unstructured covariance structure will be used to model the within subject error. Least-square (LS) mean, standard error (SE), and 95% CI of the LS mean will be provided for each treatment arm at each visit. The difference in LS means between treatment arms and 95% CI of the difference will also be calculated. P-value for testing whether the difference is equal to zero will be provided. The p-value at Week 12 will be compared against the alpha significant level of 0.1.

The main analysis of the primary endpoint using the above MMRM will use all available data. To check the robustness of the results, the following sensitivity analyses will be performed:

- Analysis of covariance (ANCOVA) model on the observed change from baseline value at Week 12. The model includes treatment as the fixed effect and baseline of the endpoint as a covariate.
- The same MMRM model on data from the PP subjects.
- Depending on the status of missing data, multiple imputations may be employed to handle missing data and apply the MMRM on the imputed datasets.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary efficacy endpoints will be analyzed using the mITT set. Continuous endpoints will be analyzed using the same MMRM model used for the primary endpoint. Logistic regression models will be used for endpoints with categorical or ordinal responses.

Safety data will be analyzed using the Safety Evaluable set. Treatment-emergent adverse events will be summarized by MedDRA coding terms, and separate tabulations will be produced for treatment-related adverse events, serious adverse events, and discontinuations due to adverse events. Vital sign data and

findings from physical examinations will be tabulated for changes over time during the study period. Laboratory parameters will be summarized for changes across the study period using descriptive statistics.

10.4.4 PLANNED INTERIM ANALYSES

Safety will be monitored on an ongoing basis. If a Safety Evaluation Meeting is triggered (see Section 8.5), an ad hoc interim safety analysis will be performed. If such an ad hoc safety interim analysis is conducted, the treatment assignment will remain masked, unless unblinding is deemed necessary by the Sponsor for safety evaluation.

10.4.5 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments for multiplicity will be employed. All hypothesis tests will be performed at an alpha level of 0.1.

10.4.6 EXPLORATORY ANALYSES

Exploratory endpoints will be summarized descriptively. Treatment comparisons on exploratory endpoints, if performed, will be in the nature of hypothesis generation.

10.5 SAMPLE SIZE

A total of approximately 120 subjects will be randomized in a 1:1 ratio to active treatment (approximately 60 subjects) or placebo (approximately 60 subjects), with the intent of obtaining ~108 evaluable subjects.

The variability of change from baseline in the off-medication motor function as measured by MDS-UPDRS, Part 3 is approximately 6.4 and 7.6 points at Weeks 48 and 60, respectively, for the placebo group, and approximately 4.9 and 4.8 in a previous study of the compound Exenatide (Athauda 2017). Assuming the variability at Week 12 is similar to that at Week 48, and assuming the variability in the AKST4290 treated group is similar to that of Exenatide-treated subjects, the sample size for the study will based on STD = 6.4 and 4.9 for the control and treated respectively. With n=54 evaluable subjects in each arm, the study will have more than 85% power to detect a difference in means between arms when the true difference is 3 points based on a two-sided t-test at an alpha of 0.1. If the true difference is 4 points, the power increases to more than 95%.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

To minimize the potential bias at the time of randomization, the study will be double-blinded and randomized in a 1:1 ratio (active: placebo) based on a block randomization schema stratified by sex. The randomization will be web-based and centralized. The randomization codes will be generated by a statistician that has no involvement in the study other than generation and maintenance of the randomization codes.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Success of blinding will be assessed based on all occurrences (intentional or unintentional) of unblinding of blinded study subjects or study personnel (e.g., investigators, medical providers, cognitive/motor testing raters, the Sponsor or their representatives). All intentional and unintentional unblinding will be documented and reported.

10.6.3 BREAKING THE STUDY BLIND/SUBJECT CODE

The study blind can be broken for safety reasons if the information is required for the management of SAEs, severe AEs, or pregnancies. The Investigator can obtain the treatment allocation for their subject through the web-based randomization system (IRT). In the rare event the web-based system is unavailable or to contact the Medical Monitor, [redacted] 24-hour emergency Safety Hotline may be contacted at:

[redacted]

Before breaking the blind, every attempt should be made to discuss the need with the Sponsor Program Physician, or designee. When some degree of unblinding must occur, this should be limited to the fewest number of people on a need-to-know basis.

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

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

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

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

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

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

12.2 INSTITUTIONAL REVIEW BOARD

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB/IEC must be obtained before starting the study and should

be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

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

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

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT FORMS

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

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

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

The investigator or designee must utilize an IRB/IEC-approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent. A copy of the signed consent form will be provided to the subject. By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., date of screening).

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

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

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Subject confidentiality is held in strict trust by the participating investigators, their staff, the Sponsor, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other

information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

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

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

12.5 FUTURE USE OF STORED SPECIMENS

With the subject's approval and as approved by local IRB/IECs, de-identified biological samples may be stored at Alkahest, or designee, for future use. These samples could be used for research and to improve treatment. Alkahest will also be provided with a code-link that will allow linking the biological specimens with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects may choose whether the Sponsor can store and use samples for further research.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent for biospecimen storage will not be possible after the study is completed.

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

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

For each subject who receives the study agent or placebo, the CRF must be completed in a timely manner. The investigator will review and approve the CRF for each study subject after all data have been entered, the CRFs have been source document verified, and all queries have been resolved. This also applies to records for those

subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

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

13.1.1 INVESTIGATOR RESPONSIBILITIES

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

13.1.2 STUDY FILES

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (although not limited to) the following: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF, IRB/IEC approval with correspondence, informed consents, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and study-specific manuals (e.g., laboratory manual).

Subject clinical source documents would include (although are not limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiologic imaging, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

13.2 STUDY RECORDS RETENTION

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

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

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

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or with GCP. The noncompliance may

be either on the part of the subject, the investigator, or the study site staff. When deviations occur, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

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

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

> **Major Protocol Deviations** are departures from the approved protocol relating to the conduct of the study which may affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Major Protocol Deviations may result in data that are not deemed evaluable for the *per protocol* analysis and/or may require that subjects are discontinued from the study. Major Protocol Deviations are Significant Clinical Issues.
> *Note: Observations categorized as Major may include those situations where there is a pattern of deviation, numerous Minor observations, or other significant deviation.*

> **Minor Protocol Deviations** are departures from the approved protocol relating to the conduct of a study that does not affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Minor Protocol Deviations do not require review by the medical monitor. Minor Protocol Deviations would not generally preclude subject data from the *per protocol* analysis population.
> *NOTE: persistently missed or incomplete study procedures and/or study evaluations will be considered Major Protocol Deviations.*

> **Coronavirus Disease 2019 (COVID-19) Protocol Deviations** are departures from the approved protocol related to the COVID-19 pandemic. Window extensions and missed protocol assessments may be permitted to reduce the risk of COVID-19 exposure. Any deviation to the protocol to reduce the risk of COVID-19 will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. In addition, protocol deviations have been prospectively identified that can be implemented to reduce the risk of exposure while still maintaining appropriate safety monitoring and integrity of the study data. These prospective deviations (e.g. window assessments and missed assessments) are described in Section 15 Schedule of Events. These measures are temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows.

All deviations will be logged and tracked by the site and CRO. Periodic review of protocol deviations will serve an indicator of site performance.

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

13.4 PUBLICATION AND DATA SHARING POLICY

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

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

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

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

Data will be reviewed by all participating investigators prior to publication. The study Sponsor will have 90 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

14 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY

A separate financial disclosure agreement will be made between each Principal Investigator and Alkahest, Inc. or its authorized representative before the study agent is shipped. Each investigator will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed. Alkahest and the study CRO will evaluate any disclosed conflicts of interest and will establish a mechanism for their management.

15 SCHEDULE OF EVENTS

	Screening/Baseline		Treatment				Follow-Up	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6/EOT**	**7**	**Phone Call**
Day	**-14 to - 7**	**1**	**14**	**28**	**56**	**84**	**98**	**114**
Window (days)[a]			**±2**	**±2**	**±2**	**±2**	**±3**	**±2**
Week			**2**	**4**	**8**	**12**	**14**	**15**
Informed Consent[1]/Optional Consent: fecal sample	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion criteria	X	X						
Randomization to AKST4290 or placebo		X						
Modified Hoehn and Yahr	X							
Provide PDQ-39 to be completed prior to next visit	X	X	X	X	X	X		
Provide Hauser 3-Day Diary for next visit	X				X			
Confirmation of off-medication state		X		X		X	X	
Full physical examination	X							
Targeted physical examination		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
Laboratory tests	X	X	X	X	X	X	X	
Pregnancy testing[2]	X	X	X	X	X	X	X	
12-lead ECG	X			X		X		
MDS-UPDRS Part 3 – Off-medication		X		X		X	X	
10-meter timed walk – Off-medication		X		X		X	X	
Administration of dopaminergic medication		X		X		X	X	
MDS-UPDRS Part 1-4 – On-medication		X	X	X	X	X	X	
10-meter timed walk – On-medication		X	X	X	X	X	X	
MoCA		X				X		
SE-ADL and CISI-PD		X	X	X	X	X	X	
S-STS		X				X		
Collect PDQ-39		X	X	X	X	X	X	
Collect Hauser 3-Day Patient Diary		X				X		
Wearable sensor device[3]	X	X		X	X	X		
Fecal sample (optional)	X					X		
Dispense 5-week supply of AKST4290/placebo		X		X	X			
Study agent administration[4]		X	X	X	X	X		
Study agent accountability		X	X	X	X	X		
Pharmacokinetics blood sample[5,6]		X	X	X	X	X	X	
Biomarker plasma aliquots[5,6]		X				X	X	
FACS/CBC blood sample[5]		X				X		
Pharmacogenomics blood sample (and optional DNA banking sample)		X						
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications[7]	X	X	X	X	X	X	X	X
Trial completion								X

Notes:

a. Window extensions and missed protocol assessments may be permitted to reduce the risk of COVID-19 exposure. Any deviation to the protocol to reduce the risk of COVID-19 exposure will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. These measures are temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows (see Section 13.3).

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to any trial related procedures, which includes medication washouts and restrictions.

2. Pregnancy testing may be performed using serum or urine. Test should be performed at the site and results reviewed. Positive results should be confirmed by the central lab.
3. An at home wearable watch will be provided in clinic on Visits 1, 4 and 5. The watch will be collected at Visits 2, 5, and 6.
4. Study agent (AKST4290/placebo) will be self-administered in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-6). Training on study agent administration will be conducted at Visit 2. Study agent administration will be performed after all assessments during Visit 2 and at visit start at remaining visits (after collection of initial PK sample 15 minutes prior to study agent administration, if applicable). Please Section 7.3 for timing dependencies.
5. The PK sample is drawn ~15 minutes prior to study agent (AKST4290/placebo) administration at Visits 2-6. Biomarker and FACS/CBC samples are drawn ~15 minutes prior to study agent (AKST4290/placebo) administration at Visits 2 and 6. The PK, biomarker, and FACS/CBC samples are drawn ~1 hour after study agent administration at Visit 2. Additional (optional) PK samples are drawn at ~ 2 hours after study agent administration at Visit 2. Additional (optional) PK samples are drawn at ~ 1 hour and ~ 2 hours after study agent administration at Visits 4 and 6. For additional information regarding timing, see Section 17.12.
6. Biomarker plasma aliquots are drawn from the PK blood sample.
7. [redacted]

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17 APPENDICES

The neurocognitive and motor assessments, as well as assessments of activities in daily living in this section and associated information are provided as EXAMPLES ONLY. The actual assessments, related source documents, and instructions for administration and scoring are included in a rater reference manual or equivalent.

17.1 MOVEMENT DISORDER SOCIETY'S UNIFIED PARKINSON'S DISEASE RATING SCALE

The MDS-UPDRS (Fahn 1987, Goetz 2008) was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The MDS-UPDRS has four components (Part 1, Mentation, Behavior, and Mood; Part 2, Activities of Daily Living; Part 3, Motor; Part 4, Complications). For Parts 1-3, the rating for each item is from 0 (normal) to 4 (severe). The total score for each Part is obtained from the sum of the corresponding item scores. The estimated time for completion of Parts 1-3 is 20-30 minutes. In Part 4m, the rater uses historical and objective information to assess two motor complications, dyskinesias, and motor fluctuations that include off-medical state dystonia.

Unified Parkinson's Disease Rating Scale (UPDRS) Parts 1-4

Part 1. Activities of Daily Living

Intellectual Impairment
0 = Normal.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

Thought Disorder (Due to dementia or drug intoxication.)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

Depression
0 = None.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

Motivation/initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

Part 2. Activities of Daily Living

Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

Cutting Food and Handling Utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone but can still feed slowly.
4 = Needs to be fed.

Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required but can do some things alone.
4 = Helpless.

Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

Turning in Bed and Adjusting Bed Clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

Falling (Unrelated to Freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

Freezing When Walking
0 = None.
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

Sensory Complaints Related to Parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

Part 3. Motor Examination

Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face."
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more. (head, upper and lower extremities)

Tremor at Rest
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

Action or Postural Tremor of Hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Hand movements (Patient opens and closes hands in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Arising from Chair (Patient attempts to rise from a straight-backed chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time but can get up without help.
4 = Unable to arise without help.

Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Part 4. Motor Complications

Time Spent with Dyskinesias
0 = Normal: No dyskinesias.
1 = Slight: ≤ 25% of waking day.
2 = Mild: 26-50% of waking day.
3 = Moderate: 51-75% of waking day.
4 = Severe: > 75% of waking day.

Functional Impact of Dyskinesias
0 = Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions.
1 = Slight: Dyskinesias impact a few activities, but patient is able to perform all activities and participate in all

social interactions during dyskinetic periods.
2 = Mild: Dyskinesias impact many activities, but patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3 = Moderate: Dyskinesias impact many activities to the point that patient usually does not perform some activities or participate in some social activities during dyskinetic episodes.
4 = Severe: Dyskinesias impact function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

Time Spent in the Off State
0 = Normal: No Off time.
1 = Slight: ≤ 25% of waking day.
2 = Mild: 26-50% of waking day.
3 = Moderate: 51-75% of waking day.
4 = Severe: > 75% of waking day.

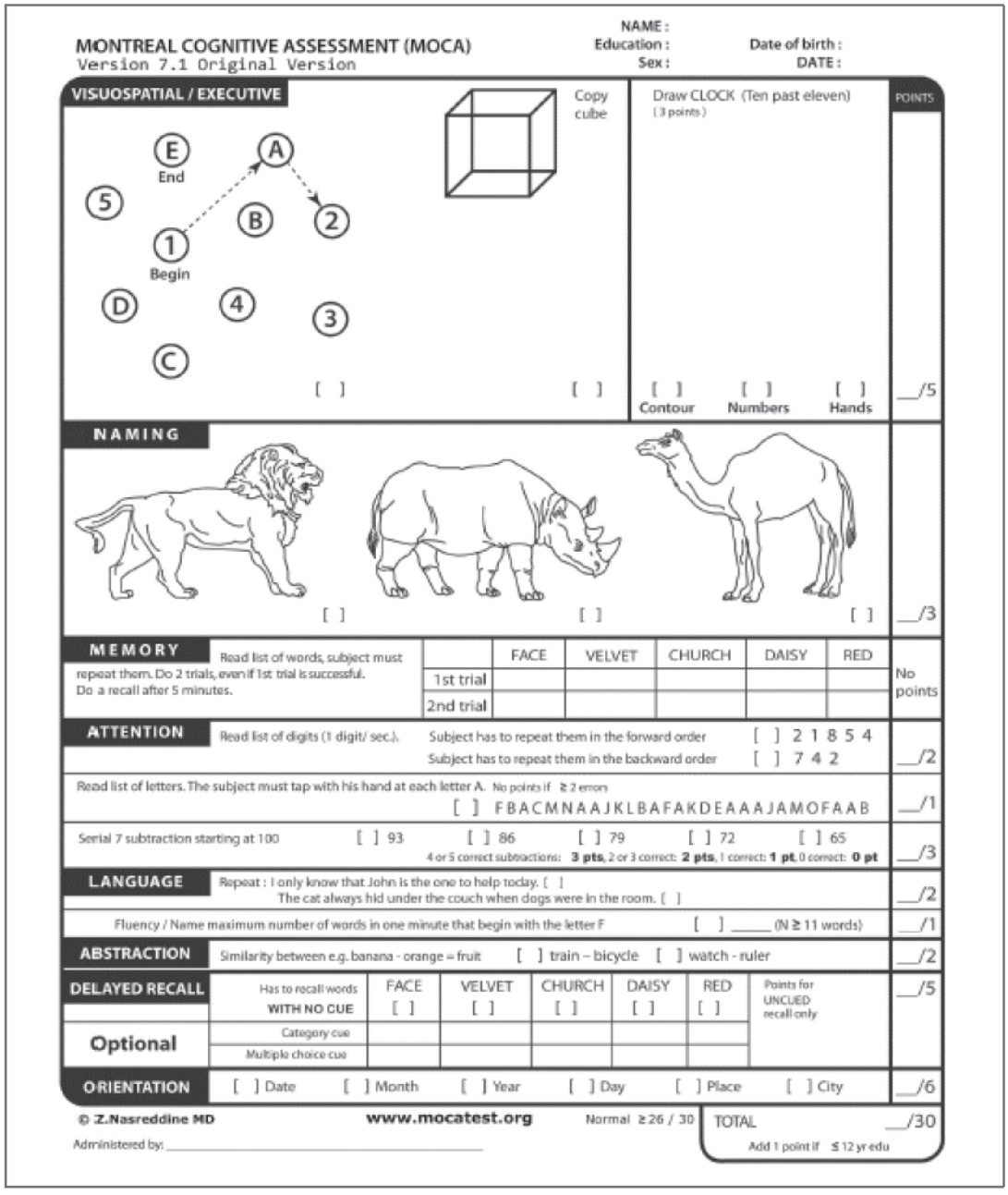
Functional Impact of Fluctuations
0 = Normal: No fluctuations or no impact by fluctuations on activities or social interactions.
1 = Slight: Fluctuations impact on a few activities, but during Off state, patient is able to perform all activities and participate in all social interactions that typically occur in the On state.
2 = Mild: Fluctuations impact many activities, but during Off state, patient usually performs all activities and participates in all social interactions that typically occur in the On state.
3 = Moderate: Fluctuations impact on the performance of activities during the Off state to the point that patient usually does not perform some activities or participate in some social interactions that are performed during On periods.
4 = Severe: Fluctuations impact on function to the point that, during Off, the patient usually does not perform most activities or participate in most social interactions that are performed during On periods.

Complexity of Motor Fluctuations
0 = Normal: No motor fluctuations.
1 = Slight: Off times are predictable all or almost all of the time (> 75%).
2 = Mild: Off times are predictable most of the time (51-75%).
3 = Moderate: Off times are predictable some of the time (26-50%).
4 = Severe: Off episodes are rarely predicable (< 25%).

Painful Off State Dystonia
0 = Normal: No dystonia or no Off time.
1 = Slight: ≤ 25% of time in Off state.
2 = Mild: 26-50% of time in Off state.
3 = Moderate: 51-75% of time in Off state.
4 = Severe: > 75% of time in Off state.

17.2 MONTREAL COGNITIVE ASSESSMENT

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



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING __/3

[ ] [ ] [ ]

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

17.3 SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING

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

Schwab And England Activities of Daily Living Scale

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. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness. 70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must 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 half, slower, etc. 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 be a 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.

17.4 CLINICAL IMPRESSION OF SEVERITY INDEX – PARKINSON'S DISEASE

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

Clinical Impression of Severity Index (CISI-PD)

Motor Signs

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

Disability

0 Normal
1 Minimal slowness and/ or clumsiness
2 Slowness and/ or clumsiness. No limitations
3 Limitation for demanding activities

Does not need help, or rarely, for basic activities of daily living (ADL)

4 Limitation to perform basic ADL Help is required for some basic ADL
5 Great limitation to perform basic ADL Help is required for most or all basic ADL
6 Severely disabled; helpless Complete assistance needed

Motor Complications (dyskinesia and fluctuations)

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

Cognitive Status

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

	Score
Motor signs	_____
Disability	_____
Motor Complications	_____
Cognitive Status	_____
CISI-PD Total score (Sum of the four items (0-24)):	_____

17.5 PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE-39

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

Parkinson's Disease Quality of Life Questionnaire-39

Due to having Parkinson's disease,
how often during the last month have you...

Please tick one box for each question

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2.	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3.	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4.	Had problems walking half a mile?	☐	☐	☐	☐	☐
5.	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6.	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8.	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please check that you have *ticked one box for each question* before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you...

Please tick one box for each question

		Never	Occasionally	Sometimes	Often	Always
9.	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10.	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13.	Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
14.	Had problems writing clearly?	☐	☐	☐	☐	☐
15.	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16.	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17.	Felt depressed?	☐	☐	☐	☐	☐
18.	Felt isolated and lonely?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you...

Please tick one box for each question

	Never	Occasionally	Sometimes	Often	Always
19. Felt weepy or tearful?	☐	☐	☐	☐	☐
20. Felt angry or bitter?	☐	☐	☐	☐	☐
21. Felt anxious?	☐	☐	☐	☐	☐
22. Felt worried about your future?	☐	☐	☐	☐	☐
23. Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24. Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25. Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26. Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27. Had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you...

Please tick one box for each question

		Never	Occasionally	Sometimes	Often	Always
28.	Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner, please tick here* ☐	☐	☐	☐	☐	☐
29.	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐
30.	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32.	Felt your memory was bad?	☐	☐	☐	☐	☐
33.	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	Had difficulty with your speech?	☐	☐	☐	☐	☐
35.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you...

Please tick one box for each question

	Never	Occasionally	Sometimes	Often	Always
36. Felt ignored by people?	☐	☐	☐	☐	☐
37. Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38. Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39. Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have *ticked one box for each question*.

Thank you for completing the questionnaire.

17.6 SHEEHAN SUICIDALITY TRACKING SCALE

SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS)

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

In the past (timeframe):

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

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

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

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

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

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15. IF ANSWER 14 IS POSITIVE ASK:

In the past (timeframe), how many times did you attempt suicide? ____

	When? dd/MMM/yyyy	How?	How serious was each attempt? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Attempt (halted by self, by another person or event, or not at all)
Level 1: You started the suicide attempt, but then **you decided to stop** and did not finish the attempt.
Level 2: You started the suicide attempt, but then **you were interrupted** and did not finish the attempt.
Level 3: You went through the suicide attempt **completely** as you meant to.

16. IF ANSWER 12 IS POSITIVE ASK:

In the past (timeframe), how many times did you take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? ____
(Include only the times when you stopped short of making an actual suicide attempt.)

	When? dd/MMM/yyyy	How?	How serious was each preparation? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Preparation
Level 1: You took active steps to prepare to kill yourself, but you did not start the suicide attempt.
Level 2: You were about to try to kill yourself, but then **you stopped yourself** just before harming yourself.
Level 3: You were about to try to kill yourself, but then **someone or something stopped you** just before harming yourself.

TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS OVER THE PAST (TIMEFRAME)**:**
Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent per day: ____ hours ____ minutes.
Most amount of time spent per day: ____ hours ____ minutes.

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17.7 MOVEMENT DISORDER SOCIETY'S PARKINSON'S DISEASE CRITERIA

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

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

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

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

Supportive criteria
(Check box if criteria met)

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

Absolute exclusion criteria: The presence of any of these features rules out PD:

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

Red flags

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

Criteria Application:

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

Provided for use in clinical trial documentation in Postuma 2015.

17.8 HAUSER 3-DAY PATIENT DIARY

The Hauser patient diary (Hauser 2000) was developed to assess functional status over a period of time in patients with motor fluctuations and dyskinesia. It is a self-completed reference diary designed to separate dyskinesia that had a negative impact on patient-defined functional status from dyskinesia that did not. With this diary, the effect of an intervention can be expressed as the change in off-medication time and the change in on-medication time with troublesome dyskinesia (bad time).The sum can be used as an outcome variable and compared to baseline or across groups.

PARKINSON'S DISEASE DIARY

NAME_____ DATE_____

Instructions: For each half-hour time period place one check mark to indicate your predominant status during most of that period.
ON = Time when medication is providing benefit with regard to mobility, slowness, and stiffness.
OFF = Time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness.
Dyskinesia = Involuntary twisting, turning movements. These movements are an effect of medication and occur during ON time.
Non-troublesome dyskinesia does not interfere with function or cause meaningful discomfort. **Troublesome dyskinesia** interferes with function or causes meaningful discomfort.
Tremor is shaking back and forth and is not considered dyskinesia.

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 AM					
:30					
7:00 AM					
:30					
8:00 AM					
:30					
9:00 AM					
:30					
10:00 AM					
:30					
11:00 AM					
:30					
12:00 PM					
:30					
1:00 PM					
:30					
2:00 PM					
:30					
3:00 PM					
:30					
4:00 PM					
:30					
5:00 PM					
:30					

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 PM					
:30					
7:00 PM					
:30					
8:00 PM					
:30					
9:00 PM					
:30					
10:00 PM					
:30					
11:00 PM					
:30					
12:00 AM					
:30					
1:00 AM					
:30					
2:00 AM					
:30					
3:00 AM					
:30					
4:00 AM					
:30					
5:00 AM					
:30					

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17.9 MODIFICATION OF DIET IN RENAL DISEASE FORMULA

Glomerular filtration rate (GFR) may be estimated based on the MDRD formula:

When serum creatinine is in mg/dL (conventional units), the GFR may be estimated based on the following MDRD formula:

GFR (mL/min/1.73 m^2) = 186 × (serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.210 if African American)

When serum creatinine is in µmol/L (SI units), the GFR may be estimated based on the following MDRD formula:

GFR (mL/min/1.73 m^2) = 186 × (serum creatinine/88.4)$^{-1.154}$ × (Age [years])$^{-0.203}$ × (0.742 if female) × (1.210 if African American)

17.10 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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17.11 CLINICAL EVALUATION OF LIVER INJURY

17.11.1 INTRODUCTION

Alterations of liver laboratory parameters [redacted] are to be further evaluated using the procedures described below.

17.11.2 PROCEDURES

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in cases in which the central laboratory is not immediately available (e.g., if the logistics are such that the subject´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by the local laboratory and results will be made available to the investigator and to Alkahest as soon as possible. If ALT and/or AST > 3-fold ULN combined with an elevation of total bilirubin >2-fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Alkahest as soon as possible.

In addition, the following should be reported in the CRF:

- Detailed history of current symptoms and concurrent diagnoses and medical history according to the DILI Checklist provided in the ISF.
- History of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the DILI Checklist provided in the ISF.
- History of exposure to environmental chemical agents (consider home and workplace exposure) according to the DILI Checklist provided in the ISF.

17.11.2.1 Clinical Chemistry

- Obtain an alkaline phosphatase, albumin, prothrombin time or INR, creatinine kinase (CK), creatinine kinase MB test (CK-MB,) ceruloplasmin, α-1 antitrypsin, transferrin amylase, lipase, glucose, cholesterol, triglycerides.

17.11.2.2 Serology

- Obtain a hepatitis A (anti-immunoglobulin M [IgM], anti-IGM), hepatitis B (hepatitis B antigen, anti-HBs, DNA), hepatitis C (anti-hepatitis C virus [HCV]), ribonucleic acid (RNA) if anti-HCV positive), hepatitis D (anti-IgM, anti-immunoglobulin G [IgG]), hepatitis E (anti-hepatitis E virus [HEV]), anti-HEV IgM, RNA if anti-HEV IgM positive), anti-smooth muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes (LKM) antibody, antimitochondrial antibody, Epstein Barr virus (vascularized composite allotransplantation [VCA] IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM).

17.11.2.3 Hormones

- Thyroid-stimulating hormone.

17.11.2.4 Hematology

- Thrombocytes, [redacted].

17.11.2.5 Ultrasound

- Provide an abdominal ultrasound to rule out biliary tract, pancreatic, or intrahepatic pathology (e.g., bile duct stones or neoplasm).

17.11.2.6 Observation/Repeat Testing

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g., by reflex testing will be followed up based on medical judgment and GCP.

17.12 PHARMACOKINETIC, BIOMARKER, PHARMACOGENOMIC, AND FACS SAMPLING

17.12.1 TABLE OF PHARMACOKINETIC, BIOMARKER, PHARMACOGENOMIC, and FACS SAMPLING

Visit	Time Point	Time for Database Setup	PK Blood	Extra Biomarker Aliquot from PK Blood Sample	PGX Blood	FACS & CBC
2	Prior to (i.e., within 15 min before study agent administration)	-0:15 h	X	X	X	X
	0:00	0:00 h	Study agent administration			
	1:00 ± 15 minutes	1:00 h	X	X		X
	2:00 ± 30 minutes (optional)	2:00 h	X			
3	-00:15 min (i.e., within 15 min before study agent administration)		X			
4	-00:15 min (i.e., within 15 min before study agent administration)		X			
	0:00	0:00 h	Study agent administration			
	1:00 ± 15 minutes (optional)	1:00 h	X			
	2:00 ± 30 minutes (optional)	2:00 h	X			
5	-00:15 min (i.e., within 15 min before study agent administration)		X			
6 (EOT)	-00:15 min (i.e., within 15 min before study agent administration)		X	X		X
	0:00	0:00 h	Study agent administration			
	1:00 ± 15 minutes (optional)	1:00 h	X			
	2:00 ± 30 minutes (optional)	2:00 h	X			
7	Any time during visit – preferably at the end of all visit procedures		X	X		

17.13 PHARMACOKINETIC MEASURES AND EVALUATION

17.13.1 TIMING OF PHARMACOKINETIC BLOOD SAMPLING

For the time schedules of pharmacokinetic blood samples, please refer to Section 17.12.1.

17.13.2 PHARMACOKINETIC SAMPLE HANDLING AND SHIPMENT

Methods of pharmacokinetic sample collection are described in Section 7.2.2.1.2. Further instructions for sampling procedures, and for handling, storage and shipment of the samples will be provided in the Laboratory Manual in the ISF.

17.13.3 PHARMACOKINETIC DATA EVALUATION

For pharmacokinetic analysis and displays, concentrations will be presented in the same format as reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters.

17.13.4 HANDLING OF MISSING BIOANALYTICAL DATA

In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first timepoint with a concentration above the quantification limit. All other BLQ and/or NOP values of the profile will be ignored. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should be excluded.

Descriptive statistics of concentrations will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the '2/3' rule is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA, NOP are included). Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available.

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 4.0 dated 22MAY2020
Replaces: Protocol Version 3.1 dated 06JAN2020

The following table describes changes from Version 3.1 (dated 06JAN2020) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V3.1_06JAN2020 ***Now reads:*** V4.0_22MAY2020	Version control.
Throughout	Minor grammar, content, and style updates.	Minor content updates for clarity/accuracy/style of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
Protocol Summary, Schematic of Study Design, 4.1, 5.3	Subject duration is 18 weeks which includes Screening (-14 to -7 days prior to Baseline), treatment (12 weeks), and 4 weeks of follow-up.	Content revised for accuracy.
Protocol Summary, 3, 4.2.3, 7.1.1.3, 7.1.1.3.8 (removed section – subsequent sections renumbered), 7.3, 15, 16.1	The Zeno walkway assessment was removed from the trial.	The Zeno walkway was not available at any participating study sites.
5.1	• Updated Inclusion Criterion #8: ○ ***Previously read:*** "If on antidepressant medications, must be on stable dosage for at least 8 weeks prior to enrollment." ○ ***Now reads:*** "If on antidepressant medications or neuroleptic medications, must be on stable dosage for at least 8 weeks prior to enrollment."	Removed [redacted] as a prohibited medication and included guidance for stable dosage of all neuroleptic medications 8 weeks prior to enrollment.

5.2	• Updated Exclusion Criterion #3: ○ ***Previously read:*** "[redacted] ○ ***Now reads:*** "[redacted]	Exclusion revised to provide narrower window of prohibited medication usage.
	• Updated Exclusion Criterion #4: ○ [redacted]	Updated exclusion based on findings from a clinical drug-drug interaction study.
	• Updated Exclusion Criterion #5: ○ [redacted]	Updated exclusion based on findings from a clinical drug-drug interaction study.
	• Exclusion Criterion #6 removed: ○ [redacted]	Removed exclusion based on findings from a clinical drug-drug interaction study.
	• Exclusion Criterion #7 removed: ○ [redacted]	Removed exclusion based on findings from a clinical drug-drug interaction study.

	[redacted] • Exclusion Criterion #8 removed: ○ [redacted] • Updated Exclusion Criterion #6 (previously #9): ○ [redacted] • Updated Exclusion Criterion #8 (previously #11): ○ [redacted] • Previous Exclusion Criteria #10 and #12-#20 renumbered to #7 and #9-#17, respectively, and appropriate cross-reference were added.	Removed exclusion based on findings from a clinical drug-drug interaction study. Updated exclusion based on findings from a clinical drug-drug interaction study. Removed [redacted] as a prohibited medication and included guidance for stable dosage of all neuroleptic medications 8 weeks prior to enrollment. Revised numbering for clarity.
7.2.2.1, 7.3, 15, 17.12	Additional optional PK evaluations were added at Visit 2 (optional PK at +2 hours) and Visits 4 and 6 (optional PK samples at +1 hour and + 2 hours).	New (optional) sample collections and analyses were added to improve PK evaluation.
7.3, 15	Text was modified for clarity related to order of assessments.	Clarification of the order (or lack of specified order) for particular assessments.
7.5, 15, 17.10	Content updates made to ensure all revisions in the Exclusion Criteria related to prohibited medications and substances, as well as precautions and monitoring, were correctly included/described.	Updated content based on findings from a clinical drug-drug interaction study.

13.3, 15, 17.10	Content added re: flexibility for window extensions and missed protocol assessments related to COVID-19. Any deviation to the protocol to reduce the risk of COVID-19 will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. These measures are temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows.	New content to account for potential protocol deviations related to COVID-19.

Protocol Version 3.1 dated 06JAN2020
Replaces: Protocol Version 3.0 dated 02DEC2019

The following table describes changes from Version 3.0 (dated 02DEC2019) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V3.0_02DEC2019 ***Now reads:*** V3.1_06JAN2020	Version control.
Throughout	Minor grammar, content, and style updates.	Minor content updates for clarity/accuracy/style of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
5.1	The contraceptive method "sexual abstinence" has been removed from Inclusion Criterion #10 as it is not considered a highly effective contraceptive method without supplementation.	Content revision for alignment with regulatory guidance regarding highly effective methods of contraception.
8.4.2.1	Protocol previously indicated that an SAE Report Form and SAE follow-up information could be sent to [redacted] within 24 hours of receipt of information by the investigational site. The language has been amended to indicate that these items must be sent immediately (without culpable delay), but no later than 24 hours of receipt of information by the investigational site.	Content revision to provide clarity of urgency of reporting of SAE Report Forms and follow-up information.

Protocol Version 3.0 dated 02DEC2019
Replaces: Protocol Version 2.0 dated 24JUL2019

The following table describes changes from Version 3.0 (dated 02DEC2019) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V2.0_24JUL2019 ***Now reads:*** V3.0_02DEC2019	Version control.
Table of	Minor content updates.	Minor updates required to reflect

Contents		revised content.
List of Abbreviations	Deleted TB; revised IRB definition, added CPK (creatine phosphokinase) and CRP (C-reactive protein).	Minor updates required for accuracy and to reflect revised content.
Protocol Summary, 4.2.3, 16.1	Updates to exploratory endpoint in last bullet: ***Previously read:*** Protocol Summary: "In consenting subjects (optional): changes in fecal markers of intestinal inflammation (calprotectin and lactoferrin) and permeability (alpha-1 antitrypsin and zonulin)." Section 4.2.3: "In consenting subjects (optional): changes in fecal markers of intestinal inflammation (calprotectin and lactoferrin) and permeability (alpha-1 antitrypsin and zonulin) (Schwiertz 2018)." ***Now reads:*** Protocol Summary: " In consenting subjects (optional): characterization of the composition and function of the fecal gut microbiome." Section 4.2.3: "In consenting subjects (optional): characterization of the composition and function of the fecal gut microbiome (Schwiertz 2018, Singh 2019)."	Content revised to provide additional flexibility in evaluation of microbiome; recent supporting reference added (Singh 2019).
4.1, 7.3.1.1, 15	Changed screening period window from "Day -10 through Day -7" to "Day -14 through Day -7"	Revised to allow more time for sites to schedule subjects.
5.1	• Inclusion Criterion #10: ***Previously read:*** • Female subjects must not be pregnant or breastfeeding. Women and men of childbearing potential (WOCBP) must have a negative pregnancy test at Screening. WOCBP and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. Male subjects must be willing to use a barrier method contraception while participating in the study. ***Now reads:*** • Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening. WOCBP must agree to use highly effective contraception which includes combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of	Provided additional details regarding highly effective contraception.

	ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. Male subjects must be willing to use a barrier method contraception.	
5.2	• Updated Exclusion Criterion #2 to remove tuberculosis testing (by QuantiFERON testing) at screening. • Updated Exclusion Criterion #4: ○ [redacted] • Updated Exclusion Criterion #5: ○ [redacted] • Updated Exclusion Criterion #6: ○ [redacted]	Deleted tuberculosis testing at screening since it is not required. Content revised to provide cross-reference to listing of prohibited medications and substances. Content revised to clarify potential drug interactions with cross-reference to listing of prohibited medications and substances. Content revised to clarify potential drug interactions with cross-reference to listing of prohibited medications and substances.

	[redacted] • Updated Exclusion Criterion #7: ○ [redacted] • Added Exclusion Criterion #8: ○ [redacted] • Previous Exclusion Criteria #8-#19 renumbered to #9-#20 and appropriate cross-reference were added.	Content revised to clarify potential drug interactions with cross-reference to list of prohibited medications and substances. Criteria renumbered due to addition of Exclusion Criterion #8 and cross-reference to list of prohibited medications and substances was added. Criteria renumbered due to addition of Exclusion Criterion #8 and cross-reference to list of prohibited medications and substances were added, as appropriate.
7.1.1.2.7	• Removed Serology testing for TB from Blood and Urine Collection for Laboratory Evaluations • Added the following examinations to Chemistry: creatine phosphokinase (CPK), cholesterol (total), and C-reactive protein.	Positive screening for TB is no longer an Exclusion Criterion. Addition of laboratory tests for required monitoring.
7.5	Content updates made to ensure all prohibited medications and substances, per the revised Exclusion Criteria, were described.	Content revised to clarify additional prohibited medications and substances.
8.4.2.1	SAE Reporting Information: ***Previously read:*** • "All SAEs occurring during the study should be reported immediately. • The SAE Report Form and relevant source documents, if applicable, must be completed and emailed to [redacted] within 24 hours of observation or learning of the event. • Follow-up information must be sent to the CRO within 24 hours of receipt of information by the	Timeframe for Reporting SAEs have been updated to clarify contact information.

	investigational site." ***Now reads:*** • "The SAE Report Form and relevant source documents, if applicable, must be completed and notified, faxed, or emailed to [redacted] within 24 hours of observation or learning of the event. ○ [redacted] • Follow-up information must be sent to [redacted] within 24 hours of receipt of information by the investigational site."	
8.4.2.2	SAE Reporting Information: ***Previously read:*** "The SAE Report Form must be completed and emailed to [redacted] according to the timeframes specified in Section 8.4.2.1." ***Now reads:*** "The SAE Report Form must be completed and faxed or emailed to [redacted] according to the timeframes specified in Section 8.4.2.1."	Revised since the SAE reporting information was updated.
17.10, 17.10.1	Content and table updated with expanded list of prohibited medications and substances due to revised Exclusion Criteria (see Section 5.2 revisions described above).	Content revised to clarify additional prohibited medications and substances.
17.10.2	Table added with expanded list of prohibited medications and substances due to revised Exclusion Criteria (see Section 5.2 revisions described above).	Content developed to clarify additional prohibited medications and substances.

Protocol Version 2.0 dated 24JUL2019
Replaces: Protocol Version 1.2 dated 17MAY2019

The following table describes changes from Version 1.2 (dated 17MAY2019) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V1.2_17MAY2019 ***Now reads:*** V2.0_24JUL2019	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for

		clarity/accuracy of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
List of Abbreviations	Added HBV, mITT, and TB	Updated abbreviations to include Hepatitis B virus (HBV), Modified intent-to-treat (mITT), and Tuberculosis (TB).
Protocol Summary, 5.1	Changed age range inclusion criterion from "40 to 80 years of age" to "50 to 80 years of age"	Effort to reduce number of WOCBP participating in the study to reduce probability of pregnancy during the trial.
Protocol Summary, 4.1	Number of Sites: ***Previously read***: "Approximately 10 in the United States (US) and up to 10 in Germany" ***Now reads***: "Approximately 30 sites are planned globally"	Expanding geographic range to support timely recruitment and additional geographic representation.
5.1	Updated Inclusion Criterion #10 follows: ***Previously read:*** • Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening. WOCBP and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. Birth control methods considered acceptable for this study include double-barrier methods; hormonal contraceptives that are injected, implanted, or taken orally; or an intrauterine device. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. ***Now reads:*** • Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening.	Alignment with Clinical Trial Facilitation Group recommendations on use of contraceptives in clinical trials.

		WOCBP and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. Male subjects must be willing to use a barrier method contraception while participating in the study.	
5.2	Updated Exclusion Criteria as follows: • Exclusion Criterion #2, bullet 5, removed: [redacted] • Exclusion Criterion #2, bullet 6 (previously bullet 7): ***Previously read:*** • Hepatic impairment. ***Now reads:*** • Current, active liver disease: > 3-fold elevation of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] over upper limit of normal). • Exclusion Criterion #2, bullet 7 (previously bullet 8): ***Previously read:*** • Uncontrolled systemic hypertension. ***Now reads:*** • Uncontrolled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite adequate treatment during the 3 months prior to dosing. • Exclusion Criterion #4: ***Previously read:*** • [redacted] ***Now reads:***	Exclusion was a carryover from earlier phase study. Warfarin and factor Xa anticoagulants added to Exclusion Criterion #4 as these are CYP3A4/5 and/or P-gp substrates that have a narrow therapeutic index; also clarifies that acetylsalicylic acid is not prohibited. Criterion clarified with additional descriptive content to aid investigators in determining eligibility. Criterion clarified with additional descriptive content to aid investigators in determining eligibility.

	• [redacted] • Exclusion Criterion #7: ***Previously read:*** • [redacted] ***Now reads:*** • [redacted]	Criterion clarified with additional descriptive content/examples to aid investigators in determining eligibility. Criterion clarified to include [redacted] to standardize with recommendations in the Investigator's Brochure.
5.4.2	Added language to clarify that subjects who have withdrawn due to adverse drug events or adverse reactions based on study procedures will not be replaced.	Provide clarification around handling of participant withdrawal and subject replacement.
7.1.1.1.9, 7.3.2.1, 7.3.3.2, 7.3.4.1	Added/defined Administration of dopaminergic medication as a study procedure and updated language in the Study Schedule sections from "Commence on-medication state" to "Administration of dopaminergic medication"	Align with Schedule of Events and provide clarification around the administration of dopaminergic medication.
7.1.1.2.7	Added Serology testing for HBV, HCV, HIV, and TB to Blood and Urine Collection for Laboratory Evaluations	Positive screening for HBV, HCV, HIV, and/or TB is an Exclusion Criterion, but was missing from the laboratory evaluations. Added detail to clarify these assessments will be performed at Screening.
7.3.7	Added definition for end of trial/end of study.	Clarify definition end of trial/end of study (last patient last visit) vs end of treatment (each subject's last visit).
7.5	Content updates made to ensure that all prohibited medications, per the Exclusion Criteria, were described.	Further clarification of all prohibited medications and alignment with Investigator's Brochure.
8.1.1	Modification of AE definition to remove language that indicated worsening of PD symptoms is not an AE.	Alignment to local law and EU rules (2011/C/172/01/EC, CT-3) regarding definition of AE as it pertains to worsening of a pre-existing illness.
10.6.3	Added additional detail on unblinding procedures including how to proceed if the web-based randomization system is not available.	Provide additional details on unblind procedures
17.9	Modified MDRD formula to include two formulas. One is used when serum creatinine results are provided in SI units (µmol/L) and the second when serum creatinine are provided in conventional units (mg/dL).	Provide clarification on which MDRD formula to use based on units of serum creatinine results.
17.10	Introductory content and Table 17.10.1 updated to include moderate as well as strong CYP3A4/5 and/or P-gp inhibitors and inducers.	Updated content for standardization with Investigator's Brochure

Protocol Version 1.2 dated 17MAY2019
Replaces: Protocol Version 1.1 dated 18APR2019

The following table describes changes from Version 1.1 (dated 18APR2019) with justifications provided.

Section	Description	Justification
Cover page	Addition of EudraCT No. Update Authorized Representative from Jonas Hannestad to Esther Rawner	Required for Germany. Internal personnel change of responsibilities.
Throughout	Protocol version update. ***Previously read:*** V1.1_18APR2019 ***Now reads:*** V1.2_17MAY2019	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
List of Abbreviations	EMA/European Medicines Agency and b.i.d./twice per day added to list of abbreviations.	Missing abbreviation/definitions added.
Statement of Compliance	Added EMA/European Medicines Agency to content in bullets 3 and 5.	Added per regulatory requirements for a global study with European sites.
Protocol Summary, 4.1	Number of Sites: ***Previously read:*** "Approximately 15 in the United States (US) and up to 10 in Germany" ***Now reads:*** "Approximately 10 in the United States (US) and up to 10 in Germany"	Proposed number of sites in the US reduced.
Protocol Summary, 4.2.2	Secondary Endpoint added: • Hauser 3-Day Patient Diary.	Addition of secondary endpoint to measure changes in on/off time.
Protocol Summary, 4.2.3	Exploratory Endpoint added: • In consenting subjects (optional): changes in fecal markers of intestinal inflammation (calprotectin and lactoferrin) and permeability (alpha-1 antitrypsin and zonulin).	Optional fecal sample added for assessment of microbiome.
2.2	Additional details on dose selection added.	Provide additional pharmacokinetic data and justification for dose selection.
2.2	Content added re: optional fecal sample for assessment of microbiome: "In addition, an optional assessment will be conducted in consenting subjects to evaluate potential microbiome changes as assessed by fecal markers of intestinal inflammation (calprotectin and lactoferrin) and permeability (alpha-1 antitrypsin and zonulin) at screening and following treatment (Schwiertz 2018)."	Added descriptive content re: optional fecal sample for assessment of microbiome.

3	Content added: re: optional fecal sample for assessment of microbiome: "In consenting subjects, fecal samples will be obtained at screening and following treatment to assess potential microbiome changes. "	Added descriptive content re: optional fecal sample for assessment of microbiome.
4.1	Content revised re: optional fecal sample for assessment of microbiome: ***Previously read:*** " During the screening period (Day -10 through Day -7), subjects will undergo all screening assessments to assess eligibility. " ***Now reads:*** "During the screening period (Day -10 through Day -7), subjects will undergo all screening assessments to assess eligibility. In consenting subjects, fecal samples will also be collected at screening for microbiome assessment."	Added descriptive content re: optional fecal sample for assessment of microbiome.
5.2	Updated exclusion criteria #2 to include the following: "Positive screening test result for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or tuberculosis (by QuantiFERON testing)."	Added for additional safety and per regulatory requirements for a global study with European sites.
6.2	Bullet content deleted: • Availability of a signed FDA Form(s) 1572 and Financial Disclosure Form(s) for the principal investigator and site sub-investigator(s) Bullet content revised: ***Previously read:*** • Approval of the study protocol and informed consent by the IRB or IEC. ***Now reads:*** • Approval of the study protocol and informed consent(s) by the IRB or IEC. ***Previously read:*** • Approval/notification of the appropriate regulatory authority. ***Now reads:*** • Approval/notification of the appropriate regulatory authority(ies).	Content is not applicable to all global sites; removed per regulatory request. Content revised to reflect potential (optional) consent for participation in microbiome assessment. Content revised to reflect addition of EMA as a regulatory authority throughout.
7.1.1.3	Content revised: ***Previously read:*** "Procedures to assess efficacy include motor and cognitive function testing and assessment of activities of daily living." ***Now reads:*** "Procedures to assess efficacy include motor and cognitive function testing, assessment of activities of daily	Content added re: fecal sample added assessment of microbiome.

	living, and, in consenting subjects, microbiome assessment." Assessments added: "10. Fecal markers of intestinal inflammation and permeability (optional)." "11. Hauser 3-Day Patient Diary."	
7.1.1.3.10	Content added re: assessment of microbiome: "7.1.1.3.10 Fecal Markers of Intestinal Inflammation and Permeability Intestinal inflammation and increase intestinal permeability (both possibly fueled by dysbiosis) have been implicated in the multifactorial pathogenesis of PD (Schwiertz 2018). In consenting subjects, fecal samples will be collected at screening and at end of treatment and samples will be flash frozen for assessment. Full information as to procedure for collection and processing of samples will be included in the ISF."	Added descriptive content re: optional fecal sample for assessment of microbiome.
7.1.1.3, 7.1.1.3.11, 7.3.1.1, 7.3.2.1, 7.3.3.1, 7.3.3.2	Description and assessment for Hauser 3-Day Diary added	The 3-Day Hauser Diary assessment was added to obtain information regarding potential functional improvement and/or decreases on off-time.
7.3.1.1, 7.3.3.2	Optional fecal sample added.	Optional fecal sample collection added for assessment of microbiome.
7.5	Additional details on prohibited medications, treatments, and medications added.	Provide clarification on prohibited oral supplements.
8.4.2.1, 8.5	EMA added to content.	Added per regulatory requirements for a global study with European sites.
10.3	Evaluable definition added and clarification to mITT/Evaluable set added	Addition of evaluable definition.
13.1.1	***Previously read:*** "Sub-investigators as listed on Form FDA 1572, or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required." ***Now reads:*** "Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required."	Content is not applicable to all global sites; removed per regulatory request.
15	Hauser 3-Day Patient Diary added to provide questionnaire at V1 and V5 and for collection of the questionnaire at V2 and V6 Optional consent for fecal sample and fecal sample collection (at screening [V2] and Visit 6/EOT).	Addition of secondary endpoint to measure changes in on/off time. Optional fecal sample consent and collection added for assessment of microbiome.
16.1, 16.2	Full references for ALK4290-101, Hauser 200, Hauser	New references added to list.

	2004, Schwiertz 2018, added to list. Full reference for Hauser et all (2000, 2004) added to list.	
17.8	Insertion of new Appendix for Hauser 3-Day Diary. Subsequent appendices, 17.8 through 17.12, sequentially renumbered throughout protocol.	Addition of Appendix for 3-Day Hauser Diary.

Protocol Version 1.1 dated 18APR2019
Replaces: Protocol Version 1.0 dated 10JAN2019

The following table describes changes from Version 1.0 (dated 10JAN2019) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V1.0_10JAN2019 ***Now reads:*** V1.1_18APR2019	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
List of Abbreviations	wAMD/ Wet age-related macular degeneration added to list of abbreviations.	Missing abbreviation / definition added.
Protocol Summary, 4.1	Number of Sites: ***Previously read:*** "Approximately 20 in the United States (US)" ***Now reads:*** "Approximately 15 in the United States (US) and up to 10 in Germany"	Number of sites in US reduced and up to 10 sites in Germany added.
2.3.1	Sentence regarding trials: ***Previously read:*** "In our ongoing European studies in treatment-naïve and refractory subjects with wAMD…" ***Now reads:*** "In our recently completed European studies in treatment-naïve and refractory subjects with wAMD…"	Content updated to indicate that studies in wAMD have been completed.
5.1, 5.2	Previous Inclusion Criteria #9 removed and included as Exclusion Criteria #8. Current Inclusion Criteria #10: ***Previously read:*** "… prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should	Renal function requirements were previously split between Inclusion/Exclusion Criteria, but are now combined to prevent confusion. Content updated to reflect global regulatory requirements.

	inform her treating physician immediately." ***Now reads:*** "…prior to study entry. Birth control methods considered acceptable for this study include double-barrier methods; hormonal contraceptives that are injected, implanted, or taken orally; or an intrauterine device. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately." Bullets 2 and 9 updated in Exclusion Criteria #2 ***Previously read:*** "[redacted] ***Now reads***: "[redacted] ***Previously read:*** "Positive screening for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)" ***Now reads:*** "Known infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)." Exclusion Criteria #8: ***Previously read***: "…[redacted] ***Now reads:*** "…[redacted] Bullet 3 added to current Exclusion Criteria #11: "Inclusion of vulnerable persons by local regulation (e.g., imprisoned or institutionalized)."	Clarification of exclusion criteria and punctuation added. Clarification of exclusion criteria. Content updated to reflect global regulatory requirements.
5.4.1, 12.3.2, 12.5	Content related to "subject's legally authorized representative" removed.	Subjects must be able to provide consent; a subject's legally authorized representatives will not be allowed to provide consent and/or make decisions on behalf of the subject.
7.1.1.1, 7.1.1.1.1, 7.3.1, 15	"Hoehn and Yahr" assessment changed to "modified Hoehn and Yahr" assessment.	Content updated to reflect accurate terminology for assessment.
7.1.1.1.6	Content regarding the neurological exam: ***Previously read:*** "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	Content added to provide clarification on components of the neurological exam.

	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." ***Now reads:*** "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, bulk, and abnormal movements; reflexes (biceps, triceps, knees, ankles, and plantar); coordination (finger-to-nose, heel-knee-shin); sensory function (light touch, pinprick, and vibration); and gait."	
7.3.3.2	Sub-bullet #2 under "Assessments to be conducted in the on-medication state": ***Previously read:*** "MoCA" ***Now reads:*** "MoCA (**Visit 6 Only**)"	Content updated to reflect that MoCA will be conducted at Visit 6 only, rather than at Visit 4 and Visit 6 as noted in the previous version.
15	MoCA at Visit 4 removed.	Assessment was not required at Visit 4.
16.1	Full reference for Athauda et al 2017 added to list.	Missing reference added to list.