Statistical Analysis Plan: ATH-1017-PD-0201

Study Title:	A Randomized, Placebo-Controlled, Double-Blind Study of ATH-1017 Treatment in Subjects with Parkinson's Disease Dementia or Dementia with Lewy Bodies
Study Number:	ATH-1017-PD-0201
Study Phase:	Phase 2
Sponsor:	Athira Pharma, Inc. 18706 North Creek Parkway Suite 104 Bothell, WA 98011 USA
NCT #:	NCT04831281
Version:	Final v1.0
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Confidentiality Statement

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Study Title: A Randomized, Placebo-Controlled, Double-Blind Study of ATH-1017 Treatment in Subjects with Parkinson's Disease Dementia or Dementia with Lewy Bodies

Study Number: ATH-1017-PD-0201

Prepared by: [redacted] *Electronically signed by: [redacted] Reason: I am the author of this document Date: Aug 10, 2023 09:30 GMT+5.5* Date: _____

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Aβ	Amyloid-β
AD	Alzheimer's disease
ADAS-Cog$_{13}$	Alzheimer's Disease Assessment Scale-Cognitive Subscale, 13-item version
[redacted]	[redacted]
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BILI	Bilirubin
CBC	Complete blood count
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
CPK	Creatine phosphokinase
CRO	Contract research organization
CPK	Creatine phosphokinase
C-SSRS	Columbia-suicide severity rating scale
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
ERP	Event-related potentials
ET	Early termination
FSH	Follicle-stimulating hormone

fT3	Free tri-iodothyronine
fT4	Free thyroxine
GBA	Glucocerebrosidase
GCP	Good Clinical Practice
GDS	Geriatric depression scale
GFAP	Glial fibrillary acidic protein
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GST	Global Statistical Test
Hb1Ac	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
IFN-γ	Interferon gamma
IMP	Investigational medicinal product
INR	International normalized ratio
IL	Interleukin
ITT	Intent-to-treat
LAR	Legally authorized representative
LBD	Lewy body dementia
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
[redacted]	[redacted]
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NfL	Neurofilament light chain
[redacted]	[redacted]
OD	Once-daily

PD	Parkinson's disease
PDD	Parkinson's disease dementia
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PK-PD	Pharmacokinetic-pharmacodynamic
PKC	Protein kinase C
PLCγ	Phospholipase C-gamma
PP	Per-protocol
PRN	As needed
PT	Prothrombin time
p-tau	Phosphorylated tau
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOP	Standard operating procedure
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells

4 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol v3.0 dated 05 Nov 2021.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

- To evaluate the clinical effects of ATH-1017 in subjects with Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB)
- To determine the safety and tolerability of ATH-1017 in subjects with PDD or DLB

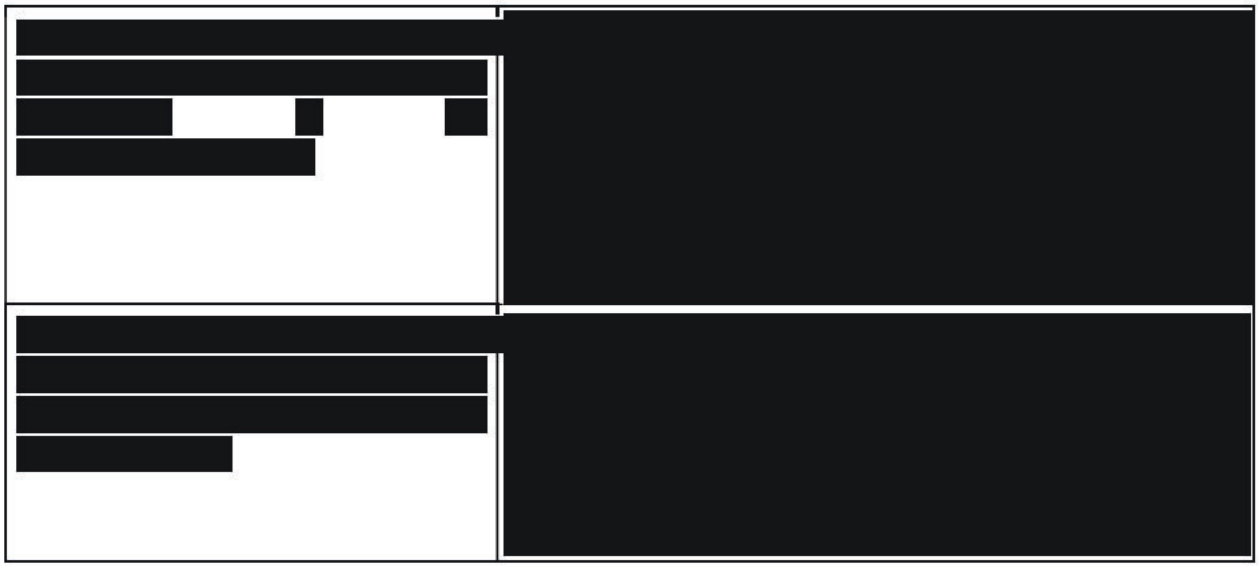
5.2 Secondary Objectives

- To evaluate the clinical efficacy of ATH-1017 separately on:
    1) Cognition and
    2) ERP P300 latency

Table 1. Study Objectives and Associated Endpoints

Primary Objectives	**Primary Endpoints**
To evaluate the clinical effects of ATH-1017 in subjects with PDD or DLB	The Global Statistical Test (GST) score (O'Brien, 1984) that combines the standardized change from baseline scores at Week 26 for cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale 13-item version [ADAS-Cog_{13}]) and ERP P300 latency, comparing ATH-1017 to placebo
To determine the safety and tolerability of ATH-1017 in subjects with PDD or DLB	Analysis of adverse events (AEs), including injection site AEs; changes from baseline for the following variables: vital signs, 12-lead electrocardiogram (ECG), and laboratory tests (chemistry, hematology, urinalysis); concomitant medication assessments, physical and neurological exams, Columbia-Suicide Severity Rating Scale (C-SSRS), and Geriatric Depression Scale (GDS)
Secondary Objectives	**Secondary Endpoints**
To evaluate the clinical effects of ATH-1017 separately on: (1) cognition and (2) ERP P300 latency	• ADAS-Cog13 score: change from baseline at Weeks 2, 12, 20, and 26 compared to placebo • ERP P300 latency: change from baseline at Weeks 2, 12, and 26 compared to placebo
[redacted]	[redacted]
[redacted]	[redacted]

Exploratory Objectives	Exploratory Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



6 STUDY DESIGN CONSIDERATIONS

This study (ATH-1017-PD-0201) is designed to demonstrate as a safety and proof of concept study of ATH-1017 in PDD and DLB subjects. Eligible participants will receive once daily (OD) subcutaneous (SC) injections of ATH-1017 (40 mg or 70 mg) or placebo, over a 26-week double-blind period, followed by a 4-week safety follow-up.

NOTE: This study was stopped early; safety listings and summaries will be performed as previously envisioned; however efficacy and biomarker analyses will be exploratory in nature.

6.1 Study Design

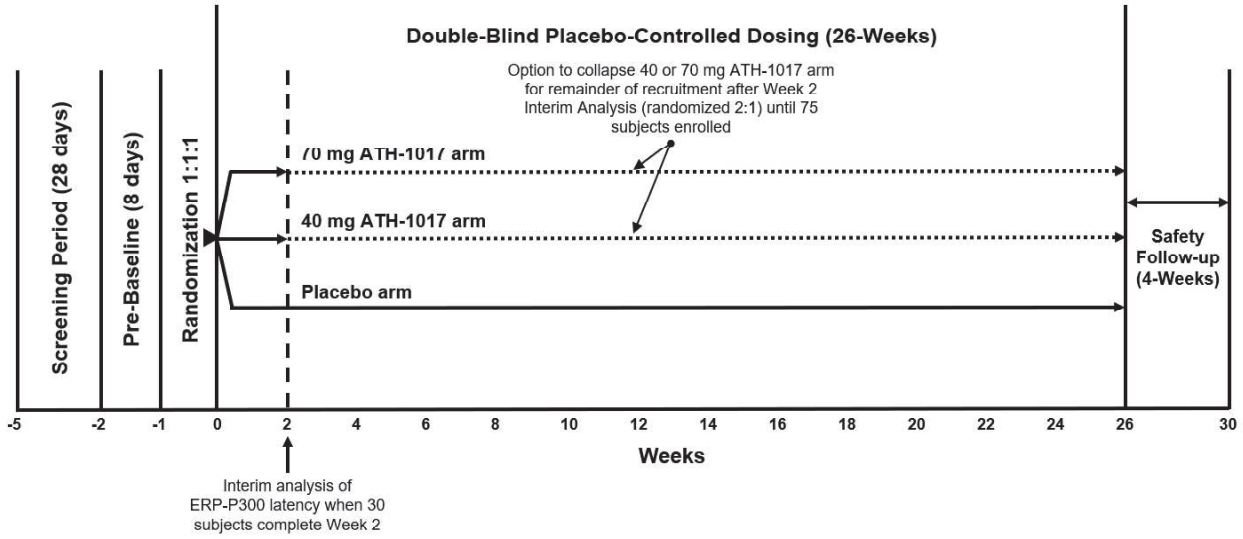
This is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose ranging study comparing ATH-1017 40 mg/day and ATH-1017 70 mg/day with placebo in subjects with a clinical diagnosis of PDD or DLB (Postuma et al, 2015; Emre, 2007; McKeith, 2017), and with a Montreal Cognitive Assessment (MOCA) score of 11 to 23 at Screening (see Figure 1 for a diagram of the study schema). The study will be conducted at a total of approximately 15 centers in the USA. Subjects and their caregivers will be required to sign an informed consent form (ICF) and will be evaluated against the inclusion/exclusion criteria during a screening period; all eligible subjects will have the option to be tested for glucocerebrosidase (GBA) genotype. Subjects who meet all inclusion/exclusion criteria will undergo baseline ERP P300 assessments at 2 separate baseline visits. At the first baseline assessment (Visit 2a, Pre-baseline, Day-10 to Day-3), ERP P300 data shall be uploaded for quality check immediately after completion of the visit. At the second baseline visit (Visit 2b, Baseline, Day 1), no more than 10 days after the Pre-baseline visit, eligible subjects will be randomized in a ratio of 1:1:1 to receive ATH-1017 40 mg/day, ATH-1017 70 mg/day, or placebo. At this Baseline visit (Visit 2b), subjects will undergo pre-dose baseline and post-dose ERP P300.

Study drug will be administered by SC injection OD preferably during daytime; subjects must not take another dose within 8 hours of the preceding dose. The first SC injection of study drug will be performed on site under supervision. The subject should withhold study drug administration on the day of subsequent clinic visits; study drug administration will be done on site under supervision of site staff at these visits. Each subject is required to have a primary caregiver willing to accept responsibility for supervising or, if required, administering study drug, and assessing the condition of the subject throughout the study in accordance with all protocol requirements. During the double-blind treatment period, clinic visits will take place on Day 1 and thereafter at Weeks 2, 6, 12, 16, 20, and 26, with a safety follow-up visit scheduled 4 weeks after completion of the double-blind period at Week 30 (see Appendix 2 for Schedule of Assessments). On Day 1, after completion of the first dose, subjects will remain on-site for 2 hours for post-treatment clinical observation. [redacted] ADAS-Cog13[redacted] assessments shall occur at clinic visits in the morning at approximately the same time they were performed during the initial baseline assessment (Visit 2b). Subjects will undergo post-baseline ERP P300 assessments at clinic visits (pre- and/or post-dose timepoints) as specified in Appendix 2.

Subjects may live at home, in a senior residential setting, or an institutional setting without the need for continuous nursing care and should not be likely to experience a change in living

conditions (e.g. institutionalization, moving to a different city, etc.), or change in primary caregiver, during participation in the trial period. The end of the study is defined as the date of the safety follow-up visit, Visit 9/Week 30. Subjects who terminate prior to Visit 8 are to complete the same assessments as Visit 8/early termination (ET).

Figure 1. Study Schema



6.1.1 Safety Review Committee/Data Monitoring Committee

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

6.1.2 Justification of Sample Size

A total sample size of 75 evaluable subjects (25 per treatment arm) was chosen empirically for this proof-of-concept study based on ERP P300 latency results obtained in the Phase 1a/b study, NDX-1017-0101; no formal sample size calculation was applied.

6.2 Efficacy Measures

A qualified, trained, and certified rater will administer questionnaires to the study subject and/or dedicated support person/caregiver.

6.2.1 Cognitive Variables & Pharmacodynamic Variable

6.2.1.1 Global Statistical Test (GST) score

A composite approach will be used to facilitate the assessment of an overall change in disease status/trajectory in the trial. The GST score will be defined as a single outcome variable based on standardizing and then combining individual patient-level change from baseline cognition (ADAS-Cog_{13}) and change from baseline in ERP P300 latency. The GST score will be determined for each patient at each time point and the resulting scores will define the efficacy outcome variable to be used in the primary efficacy analysis. A formal definition of the GST score is given in Appendix 1. The assessment will be performed as per Appendix 2 Schedule of Assessment.

6.2.1.2 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog_{13})

The ADAS-Cog13 is designed to measure cognitive symptom change in subjects with MCI as well as AD (Mohs et al, 1997). In addition to the standard 11 items present in the ADAS-Cog11 (word recall, commands, constructional praxis, naming objects and fingers, ideational praxis, orientation, word recognition, spoken language ability, comprehension of spoken language, word-finding difficulty, and remembering test instructions), the ADAS-Cog13 includes a test of delayed word recall and a number cancellation task. The test comprises 9 performance items and 4 clinician-rated items, with a total score ranging from 0 (no impairment) to 85 (severe impairment). Therefore, higher scores indicate more severe cognitive impairment. The assessment will be performed as per Appendix 2 Schedule of Assessment.

6.2.1.3 Pharmacodynamic Variables

Pharmacodynamic variables will consist of ERP P300 assessments through electroencephalogram (EEG) assessments. ERP P300 should be performed when the subject is not experiencing interfering motor disturbances that might affect the quality of ERP P300 data; if necessary, the time window for ERP P300 assessments can be extended.

ERP P300 is a method of recording brain activity elicited by external stimuli, e.g., an oddball auditory stimulus, and is a well-established functional biomarker, particularly of working memory access (Ally et al, 2006). ERP P300 is characterized by a stereotyped series of voltage deflections occurring after the respective odd tone to be counted, with early features (< 100 msec) corresponding to unconscious sensory transmission (auditory cortex, N100), and later features produced by cognitive processing in the ventral attentional network, i.e., P300, referring to the large positive deflection at roughly 300 msec in healthy adults (young or elderly). The P300 latency is sensitive to detecting reduced synaptic transmission related to cognitive decline in AD patients and other dementias (Olichney et al, 2011).

The EEG assessment will be performed as per Appendix 2 Schedule of Assessment.

[redacted]

[redacted]

6.2.2 Disease Condition

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] on a 5-point Likert-type scale (ranging from 0 to 4), with higher [redacted]

[redacted]

6.4 Safety Measures

6.4.1 Adverse Events

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AE (see Section 6.4.1.3).

6.4.1.1 Definitions

An AE is any untoward medical occurrence in a study subject which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease (new or exacerbated), temporally associated with the use of the IMP, whether or not considered related to the IMP.

Events meeting the definition of AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events not meeting the definition of AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen (note: preexisting conditions will be recorded as part of the subject's medical history).

6.4.1.2 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to the categories discussed in the sections below.

Intensity

The investigator will assess all AEs for severity in accordance with the following standard ratings:

- Mild: Ordinarily transient symptoms, does not influence performance of subject's daily activities. Treatment is not ordinarily indicated or may be minimal.

- Moderate: Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary to alleviate symptoms.

- Severe: Symptoms cause considerable discomfort. Substantial influence on subject's daily activities, or significantly affects clinical status. May be unable to continue in the study and intensive treatment may be necessary.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity recorded for the event should be noted.

Note: an event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (see later), NOT when it is rated as severe.

Causality

The investigator will assess the causality/relationship between the AE and IMP/study procedure. One of the categories described in Table 2 should be selected based on medical judgment, considering the definitions below and all contributing factors. In this study AEs will be considered related to IMP/study procedure if causality is ascribed as either related, probably related, or possibly related.

Table 2. Assessment of Relationship of Adverse Events to IMP/Study Procedure

Related	A clinical event, including laboratory test abnormality, which occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge† procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

*Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

†Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirement.

Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation in existing hospitalization; in general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant incapacity or substantial disruption of the 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, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect, or
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, headache may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.4.1.3 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality or seriousness, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

All AEs/SAEs that are still present after the last study drug administration (including AEs that have led to premature discontinuation), will be followed-up at the Safety follow-up visit. In case the AE/SAE is still ongoing after that timepoint, this will be followed up until its resolution or until otherwise agreed between the Sponsor and the investigator.

Additional safety data collected after the Safety follow-up visit to follow-up the ongoing AE will not be included into the clinical database, if this was already locked; therefore, the clinical database lock will not be delayed due to this situation. Any SAE will be followed up, if needed, after clinical database lock, and the information will be only stored in the safety database.

6.4.2 Pregnancy

Female subjects who become pregnant during the study will be withdrawn.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

6.4.3 Clinical Laboratory Assessments

The assessment will be performed as per Appendix 2 Schedule of Assessment. The following laboratory variables will be determined as outlined in Table 3 below:

Table 3. Clinical Laboratory Assessments

Test	Parameters	
Hematology	CBC Hb1Ac Hemoglobin Hematocrit Erythrocytes (RBC)	Leukocytes (WBC) Differential WBC Platelets

Biochemistry	Sodium Potassium Magnesium FSH (post-menopausal females only) [a] Calcium Chloride Glucose Creatinine ALP AST ALT	GGT CPK Total bilirubin Total protein Albumin Total Cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides TSH, fT3 and fT4 [a]
Coagulation	INR PT	aPTT
Serology	HBsAg[a] HCV [a]	HIV type 1 or type 2 [a]
Urinalysis	pH glucose ketones specific gravity HCG (females of child- bearing potential only)	nitrite protein bilirubin blood

AST = aminotransferase; ALP = alkaline phosphatase; ALT = alanine transaminase; CBC = complete blood count; CPK = creatine phosphokinase; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; Hb1Ac = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; aPTT = activated partial thromboplastin time; RBC = red blood cells; fT3 =free tri-iodothyronine; fT4 =free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells.
[a] Measured only at Screening for eligibility; not included in subsequent safety labs.

Any value outside the normal range will be flagged for clinical interpretation by the investigator or designee at the site. In this study, ALT or AST > 2 times the upper limit of normal, or Child-Pugh Class B and C (i.e., including total bilirubin, albumin, and INR values), will be exclusionary. For transaminase liver enzymes, a repeat laboratory assessment may be performed if outside of the normal range. If the transaminases remain elevated the investigator should consider stopping study medication and withdrawing the subject.

A medical alert for potential Hy's laws cases (possible drug-induced liver injury) will be issued based on lab values and supported by Medical Monitor interpretation.

Criteria for potential Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

For the Elevated Liver Tests summary, the list of lab test with criteria will be considered.

i) Alanine Aminotransferase (Normal <=ULN, >1 - 3 x ULN, >3 - 5 x ULN, >5 - 10 x ULN, >10 - 20 x ULN, >20 x ULN)
ii) Aspartate Aminotransferase (Normal <=ULN, >1 - 3 x ULN, >3 - 5 x ULN, >5 - 10 x ULN, >10 - 20 x ULN, >20 x ULN)
iii) Alkaline Phosphatase (Normal <=ULN, >1 - 2 x ULN, >2 x ULN)
iv) Bilirubin (Normal <= 2 x ULN, >2 x ULN)
v) Hy's Law: ALT/AST>=3xULN and BILI>=2xULN (Criteria Not Met, With ALP <2 x ULN, With ALP >=2 x ULN)
vi) Alkaline Phosphatase >=2 x ULN (Criteria Not Met, With ALT/AST <2X ULN, With ALT/AST >=2X ULN)

6.4.4 Vital Signs

The following vital signs will be measured:

- Blood pressure (supine) (systolic and diastolic [mmHg])
- Orthostatic blood pressure (systolic and diastolic [mmHg])
- Heart rate (bpm)
- Body temperature (°C) (oral, tympanic, temporal, or forehead infrared)
- Respiratory rate (breaths per minute)

Supine BP and HR recordings will be made after the subject has been supine for at least 5 minutes. The assessment will be performed as per Appendix 2 Schedule of Assessment. The first blood pressure will be the average of 3 measurements recorded after the subject is supine for 5 minutes; the second blood pressure will be recorded after the subject has stood for up to 3 minutes. A drop in blood pressure of ≥ 20 mmHg, or in diastolic blood pressure of ≥ 10 mmHg will be considered abnormal.

6.4.5 Weight

Additionally, weight (kg) and BMI (kg/m^2) will be measured under the same Vital sign assessment.

6.4.6 12-Lead Electrocardiogram

The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. The assessment will be performed as per Appendix 2 Schedule of Assessment. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, mean heart rate, QTcB and QTcF interval.

All ECGs must be evaluated by the investigator or qualified designee for the presence of abnormalities. Collection and analysis of ECG data will be performed by a central ECG vendor.

6.4.7 Physical and Neurological Examination

The physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

Neurological components include, but are not limited to, the following assessments: mental status, cranial nerves, muscle strength, tone, and bulk, reflexes, coordination, sensory function, and gait.

The assessment will be performed as per Appendix 2 Schedule of Assessment.

6.4.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS supports suicide risk assessment through a series of simple, plain-language questions. The responses assist in identifying whether a subject is at risk for suicide, assesses the severity and immediacy of that risk, and gauge the level of support that the subject may require. The assessment will be performed as per Appendix 2 Schedule of Assessment.

6.4.9 Geriatric Depression Scale (GDS)

The GDS is a self-report measure of depression in older adults with a "Yes/No" response format; The GDS was originally developed as a 30-item instrument. It has since been validated in a shortened form comprising 15 items (Sheikh and Yesavage, 1986). The total score range is 0 to 15, with a higher score indicating more severity. The assessment will be performed as per Appendix 2 Schedule of Assessment.

[redacted]

6.6 Genotyping

Blood sample(s) will be collected at Screening for analysis of GBA genotype in subjects who consented to genotyping.

[redacted]

[redacted]

[redacted]

7 STUDY POPULATIONS

7.1 Analysis Populations

7.1.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received test article. A subject is considered randomized when the IxRS provides the test article assignment (ie, completes a randomization transaction). Subjects will be analyzed according to the dose they were randomized to.

7.1.2 Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population will include all randomized subjects who took at least one dose of the study medication and who completed both an ADAS-Cog_{13} and ERP P300 assessment at Baseline and during at least one post-baseline visit. Subjects will be analyzed according to the dose they were randomized to.

7.1.3 Per Protocol (PP) Population

The per protocol population will include all mITT subjects who were medication compliant during the 26 weeks of double-blind treatment, completed both an ADAS-Cog_{13} and ERP P300 assessment during at least one post-baseline visit, and did not have any major protocol deviations. Subjects will be analysed based on actual treatment received.

All criteria for subject removal from PP are identified and confirmed prior to data base lock.

7.1.4 Safety Population

The Safety population will include all randomized subjects who received at least one dose of the study medication. Subjects will be analyzed based on actual treatment received.

[redacted]

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The following changes have been made in the analytical strategies:

Since the study is stopped early, minimal analyses will be performed.

- No interim analysis will be performed.
- Alternate statistical comparison tests can be implemented as appropriate.
- No statistical conclusion can be made based on the statistical test, if generated.
- Other than summary statistics, all exploratory and subgroup analysis are optional.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Efficacy and safety data will be summarized and presented by disease type (PDD or DLB), acetylcholinesterase inhibitor (AChEI) usage within disease type, treatment group, and time point in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage. Percentages are based on the number of subjects in each treatment group in the given population for AE summary tables, and additionally overall for medical history, prior and concomitant medications. For all other tables, percentages are based on the number of subjects with non-missing data in each treatment group and overall for the given population.

Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place. P-values will be quoted to 4 decimal places consistent with SAS PVALUEw.d format set to PVALUE6.4. P-values < 0.0001 will be presented as p<0.0001.

Listings will include all subjects with defined analysis population for each listing. Listings will generally be sorted by disease type, treatment, subject ID, parameter and visit date/study day. Unscheduled visits will also be included in the listings.

Days will be converted to weeks by dividing by seven. Days will be converted to months by dividing by 30.44. Days will be converted to years by dividing by 365.25. All data collected during the study will be analyzed and reported except as stated otherwise.

All data will be analyzed using the SAS® Version 9.4 or later.

9.2 Baseline Definition

For safety summaries, the last pre-randomization measurement is defined as the baseline value. For clinical effect measures baseline is defined as the last pre-randomization measurement.

GST score, ADCS-CGI-C, and CaGI-C are change scores, so no further calculation is required. Appendix 1 describes calculation of the baseline GST score for baseline covariate purposes. For all other efficacy measures, baseline is the average of all measurements prior to first dosing, or if only one measurement exists that value will be used.

9.3 Handling of Partial Dates

If partial dates are recorded for adverse event and concomitant medications, then partially dates will be filled as per Appendix 3. No imputation will be done for other partial dates.

9.4 Interim Analysis

This is an early closure study; no interim analysis will be performed.

9.5 Pooling Strategy for Study Sites

No pooling strategy will be performed due to the smaller number of subjects enrolled in the study.

9.6 Visit Windows / Unscheduled Visits

Visit windowing will be applied for the analyses which use visit categories. For categorical visit summaries, all visits including early termination assessments and unscheduled visits will be included with the closest scheduled post-baseline visit that includes the efficacy or safety assessment, based on number of days since Day 1. For the primary variable of ERP P300 latency effect, if multiple assessments fall within the same analysis window, pre- and post-dose measurement will be averaged within the analysis window for this variable. For all other efficacy assessments, if multiple efficacy assessments fall within the same analysis window (other than baseline), any non-missing efficacy assessments will be averaged. For all non-efficacy assessments, a last-within-window approach will be used.

The analysis windows for ERP P300, ADAS-Cog_{13} and COWAT are:

Analysis Visit	Protocol-Specified Day	Analysis-Specified Interval
Week 2	Day 14	Day 2-63
Week 12	Day 84	Day 64-112
Week 20	Day 140	Day 113-161
Week 26	Day 182	Day 162-196
Week 30	Day 210	Day 197-218

The analysis windows for C-SSRS, Physical and Neurological Exams, EG, Vital Signs, Labs are:

Analysis Visit	Protocol-Specified Day	Analysis-Specified Interval
Week 2	Day 14	Day 2-28
Week 6	Day 42	Day 29-63
Week 12	Day 84	Day 64-98
Week 16	Day 112	Day 99-126
Week 20	Day 140	Day 127-161
Week 26	Day 182	Day 162-196
Week 30	Day 210	Day 197-218

The analysis windows for GDS are:

Analysis Visit	Protocol-Specified Day	Analysis-Specified Interval
Week 12	Day 84	Day 2-133
Week 26	Day 182	Day 134-196
Week 30	Day 210	Day 197-218

The analysis visit windows for MMSE is:

Analysis Visit	Protocol-Specified Day	Analysis-Specified Interval
Week 12	Day 84	Day 2-112
Week 20	Day 140	Day 113-161
Week 26	Day 182	Day 162-218

The analysis windows for MDS-UPDRS, NMSS, ADCS-ADL23, ADCS-CGIC, ADCS-CaGIC, ADCS-CGIS, and PK are:

Analysis Visit	Protocol-Specified Day	Analysis-Specified Interval
Week 12	Day 84	Day 2-133
Week 26	Day 182	Day 134-218

10 STATISTICAL ANALYSIS METHODS

10.1 Subject Disposition

A summary table will be provided for all patients to display the number of subjects randomized, Safety Population, mITT Population, Per Protocol population, and patients who completed or discontinued the study with reason of study discontinuation, by treatment and overall. This summary will be produced for each disease type and AChEI usage within disease type.

Listings will present all information on the End of Study eCRF page and the Protocol Deviations. Another supportive listing will display patients excluded from any analysis population along with the reason(s) for exclusion.

Screen failure data will be listed by reason subjects were found to not be eligible for the study.

Randomization data will also be listed by subject, country, site, randomization number and randomization date.

10.2 Demographics and Baseline Characteristics

A summary table will be provided for demographic and baseline characteristics for safety population, presented by treatment and overall. This summary will be produced for each disease type and AChEI usage within disease type.

Variables to be summarized in this table are:

- Gender (male/female)
- Race (white, black or African American, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Asian, Other)
- Years of Education (years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Age (years)
- Age group (<=55, 56-60, 61-65, 66-70, 71-75, 76-80, 81-85)
- Disease Type (Dementia with Lewy bodies, Parkinson's Disease Dementia)
- Baseline MMSE total score
- Baseline MMSE group (Mild (MMSE>=20), Moderate (MMSE<20)),
- Baseline GBA Genotype
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI, kg/m^2)
- AChEI usage (Yes, No)

Listings will present all data on the demographics, baseline characteristics, clinical diagnosis, medical history CRF pages for safety population.

10.3 Prior and Concomitant Medications and Procedures

Medications received prior to the date of first dose of double-blind study medication are considered as prior medications. Medications will be considered as concomitant if the start date of the medication is on or after the date of first intake of investigational product or if the start date is prior to the first date of investigational product but the medication is ongoing during the treatment period in the study.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary and will be summarized by generic name and Anatomical Therapeutic Chemical (ATC) classification system level 3 for safety population, by treatment group and overall. This summary will be produced for each disease type and AChEI usage within disease type.

A listing will be generated for prior and concomitant medications. A separate listing will be generated for surgical procedures.

10.4 Treatment Compliance and Exposure

Duration of exposure, number of days dosed, compliance and drug holiday duration will be tabulated descriptively as per CRF response for safety population, by treatment and overall. This summary will be produced for each disease type and AChEI usage within disease type.

Duration of exposure for the treatment will be calculated as follows:

Duration of exposure in days = (Last dose date – First dose date) + 1

Duration of exposure also will be categorized as:

i) 0 to 2 weeks
ii) >2 to 6 weeks
iii) >6 to 12 weeks
iv) >12 to 16 weeks
v) >16 to 20 weeks
vi) >20 to 26 weeks
vii) >26 weeks

Drug compliance will be categorized as:

i) < 80%
ii) >=80%

10.5 Efficacy

Summary statistics will include change from baseline comparison of ATH-1017 with placebo using a two-sample t-test without baseline adjustment. All statistical tests will be carried out using a one-sided 2.5% significance level and all comparisons will be reported with 95% confidence intervals for mITT population unless otherwise stated. The comparison between ATH-1017 (40 mg and 70 mg pooled) and placebo will serve as the primary efficacy comparison. This summary will be produced for each disease type and AChEI usage within disease type also.

[redacted]

No adjustments will be made for multiple comparisons.

10.5.1 Primary Analysis

NOTE: The following description for the primary analysis was prepared to implement the intention of the protocol, however in view of the early stopping of the trial this analysis will not be performed, unless the simple summary statistics suggest a finding of interest, in which case this would be performed as an exploratory analysis.

The primary analysis will use a mixed model with repeated measures (MMRM) to compare the GST score between ATH-1017 and placebo at 26 weeks. In this MMRM model, GST score (a composite of the standardized change from baseline variables) will be considered as the outcome variable and the following fixed terms: baseline value, treatment arm, visit, treatment by visit interaction, baseline by visit by treatment interaction, GBA genotype, and baseline age. The correlations among repeated observations within a patient will be accounted for by specifying an unstructured covariance matrix. The least squares mean, and treatment differences will be estimated from the MMRM model.

The MMRM model summary will contains LSMEAN, Standard Error (SE), 95% CI at each visit by treatment (ATH-1017, Placebo) will be displayed. Also, LSMEAN for ATH-1017 difference from placebo, SE, 95% CI, and p-value at Week 26.

If convergence not met for the MMRM model, GST score between ATH-1017 and placebo at Week 26 will be compared using one sided t-test 2.5% significance level.

Additionally, the GST score will be listed and summarized for all visits. This summary will be produced for each disease type and AChEI usage within disease type also. A line plot with mean GST score and 95% CI over visit by treatment arm (40 mg ATH-1017, 70 mg ATH-1017 and placebo) will be displayed.

10.5.1.1 Subgroup Analyses

NOTE: These analyses are not planned due to the early termination of the trial but may be performed as exploratory if deemed worthwhile by the sponsor.

The analyses may be performed for subgroups of interest such as subgroups based on key demographic or clinical characteristics, e.g., gender, age group (< 65 years and >= 65 years of age), AChEI usage, and GBA genotype. The subgroup analyses will be applied to the mITT population.

No subgroup analyses are planned due to limited subjects enrolled in this study.

10.5.2 Secondary Analysis

NOTE: The following description for the secondary analyses was prepared to implement the intention of the protocol, however in view of the early stopping of the trial this analysis will not be performed, unless the simple summary statistics suggest a finding of interest, in which case these would be performed as exploratory analysis.

The separate key secondary variables ADAS-Cog13 and ERP P300 latency will be analyzed using the MMRM model. Change form baseline ADAS-Cog13 score and change form baseline ERP P300 latency will be used as the outcome variable and the following fixed terms: baseline value, treatment arm, visit, treatment by visit interaction, baseline by visit by treatment interaction, GBA genotype, and baseline age. in the MMRM model. Similar summary statistics will be presented that was used for analysis of the primary endpoint. If MMRM model do not converge, active treatment and placebo groups will be compared using one sided t-test 2.5% significance level at Week 26 for change for baseline secondary variables.

[redacted]

10.5.5 Interim Analysis

An interim analysis was planned to be performed when at least 30 subjects had completed the Week 2 visit. The analysis would have focused on the ERP P300 results and would be used to determine whether one or other of the 2 active doses of ATH-1017 (40 mg or 70 mg) is superior to the other (difference of 2 standard deviations). Based on the analysis, subjects would be enrolled with the superior dose.

In view of the early stopping of the trial, no interim analysis will be performed.

10.5.6 Final Analysis

This is an early closure study; other than summary statistics, all analyses are optional.

10.6 Safety and Tolerability

All safety analyses will be performed on the safety population.

10.6.1 Adverse Events

All adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as any adverse event that begins or worsens in severity on or after the first study drug dose date until follow-up period. Treatment Related AE includes probably related, possibly related or related AEs. Injection Site Reactions will be identified from high level term (HLT) as 'Injection Site Reactions'.

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories will be summarized for each treatment group, and overall. No comparisons of treatment groups will be performed.

- Any AE
- Any TEAE
- Any Treatment Related TEAE (possibly related; probably related; related)
- Any severe TEAE

- Any serious TEAE
- Any TEAE that led to discontinuation of study drug
- Any fatal TEAE
- All deaths

Treatment emergent adverse event (TEAE) incidence will be summarized and presented using primary MedDRA system organ classes (SOCs), and preferred terms (PTs).

- All TEAE
- Any Treatment Related-TEAE
- Study Drug Related Treatment-Emergent Adverse Events by Worst Severity
- Any serious TEAE by Worst Severity
- Any TEAE that led to discontinuation of study drug
- Treatment-Emergent Adverse Events Leading to Death
- Injection Site Reactions Treatment-Emergent Adverse Events

The following listings of adverse events will be prepared.

- All adverse events
- Drug Related Treatment-Emergent Adverse Events
- Injection Site Reactions Treatment-Emergent Adverse Events
- Serious Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events Leading to Study Discontinuation
- Death listing

10.6.2 Clinical Laboratory

Continuous blood clinical laboratory analytes observed values and change from baseline values will be summarized by analyte and visit using descriptive statistics (n, mean, median, SD, minimum, maximum) by treatment group. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments in each treatment group at a particular visit for the safety population. The latest non-missing clinical laboratory tests collected prior to dosing will be used as the baseline values.

Clinical laboratory results will be provided in data listings by treatment group, subject, lab category, visit and parameter.

10.6.3 Electrocardiograms

ECG values will be summarized by visit and treatment group using descriptive statistics (n, mean, median, SD, minimum, maximum) for PR interval, QT interval, QTcB interval, QTcF interval, RR interval, mean heart rate, and QRS duration.

The latest non-missing ECG value collected prior to dosing will be used as the baseline value. The baseline values will usually be the vital signs recorded at the Day 1 30 min pre-dose visit. In the case of repeated ECG parameters, the last collected values within that visit will be used for the summary tables.

ECG will be provided in a data listing by subject, treatment group, subject, visit, timepoint and parameter.

10.6.4 Vital Signs

Each vital sign will be summarized by treatment and by visit, using descriptive statistics (n, mean, median, SD, minimum, maximum) for the safety population for diastolic blood pressure, systolic blood pressure for both standing and supine position, heart rate and respiratory rate.

The latest non-missing vital sign value collected prior to dosing will be used as the baseline values. The baseline values will usually be the vital signs recorded at the baseline visit. In the case of repeated vital signs, the last collected values within that visit will be used for the summary tables.

Vital signs will be provided in a data listing by treatment group, subject, visit and parameter.

10.6.5 Physical and Neurological Examination

The physical and neurological examination normal/abnormal results will be listed by treatment group, subject, visit and parameter.

10.6.6 Columbia-Suicide Severity Rating Scale

Count and percentage of C-SSRS responses will be generated over the visit. This summary will also be produced for each disease type and AChEI usage within disease type.

10.6.7 Geriatric Depression Scale

Descriptive statistics for the results of GDS will be presented over the visit. This summary will also be produced for each disease type and AChEI usage within disease type.

[redacted]

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12 APPENDICES

Appendix 1. Derivation of GST scores.

A composite approach will be utilized to derive the GST score for each patient at each visit in order to support an overall assessment of disease based on the combination of the clinical and functional scores (change from baseline ADAS-Cog13 and change from baseline ERP P300 latency).

The following notation will be used to compute the GST score. Let x_{ijk} and y_{ijk} will denote the changes from baseline to the kth visit for the jth patient in the ith trial arm ($i = 1$ corresponds to placebo and $i = 2$ corresponds to ATH-1017) for ADAS-Cog13 and ERP P300 latency, respectively. To simplify notation, it will be assumed that the number of patients in a trial arm does not depend on the visit, i.e., n_1 patients in the placebo arm and n_2 patients in the ATH-1017 arm.

The GST score will be computed by applying the following algorithm to the ADAS-Cog13 and ERP P300 latency change scores. Beginning with ADAS-Cog13, the overall mean will be computed at the kth visit, i.e.,

$m_k = \frac{n_1\bar{x}_{1\cdot k}+n_2\bar{x}_{2\cdot k}}{n_1+n_2}$ where $\bar{x}_{1\cdot k}$ and $\bar{x}_{2\cdot k}$ are the arm-specific sample means. Next, the pooled standard deviation will be computed at the kth visit, i.e.,

$$s_k = \sqrt{\frac{(n_1-1)s_{1k}^2 + (n_2-1)s_{2k}^2}{n_1 + n_2 - 2}}$$

where s_{1k}^2 and s_{2k}^2 are the arm-specific sample variances. Finally, the standardized change scores will be defined as follows:

$$x_{ijk}^* = \frac{x_{ijk} - m_k}{s_k}$$

The standardized change scores for ERP P300 latency will be computed in a similar way and will be denoted by y_{ijk}^*.

The GST score for the change from baseline to the kth visit for the jth patient in the ith trial arm is defined as

$$\left(\frac{x_{ijk}^* + y_{ijk}^*}{2}\right)$$

Note that a negative sign is applied to y_{ijk}^* since an increase in the ERP P300 latency score indicates an unfavorable response. This algorithm will be applied to each post-baseline visit. Note that the GST score calculation for each post-baseline visit is a composite of standardized change from baseline components. In order to provide a baseline value for GST for covariate purposes, the baseline GST score will also be calculated. The calculation at baseline is slightly different, using the observed baseline ADAS-Cog13 and ERP P300 latency values, instead of change from

baseline. Those baseline measurements are standardized using the overall baseline mean and baseline pooled standard deviation for each variable.

Appendix 2. Schedule of Assessments and Procedures

				Double-blind placebo-controlled treatment period (26-week)							Safety follow-up
		Screening [a]	Pre-baseline	Baseline							
	Visit:	1	2a	2b	3	4	5	6	7	8/ET [r]	9
	Week:	-5 to -2	-1	1	2	6	12	16	20	26	30
Assessment	Day:	-32 to -4	-10 to -3	1	14 (±7)	42 (±7)	84 (±7)	112 (±7)	140 (±7)	182 (±7)	210 (±7)
Inclusion/ Exclusion		X	X	X							
Informed Consent		X									
Pregnancy Test [c]		X									
Demographics		X									
Medical History		X									
Height and Weight		X		X [b]			X [b]			X [b]	X [b]
Blood [d]		X									
Modified Hoehn-Yahr staging		X									
MOCA		X									
C-SSRS [e] *		X		X	X	X	X	X	X	X	X
GDS *		X		X			X			X	X
Randomization				X							
Drug Dispensing [f]				X	X	X	X	X	X		
Dose of IMP in-clinic [g]				X	X	X	X	X	X	X	
Drug Accountability					X	X	X	X	X	X	
Physical and Neurological Exam [h]		X		X	X	X	X	X	X	X	X
MRI [i]		X									

Assessment		Screening [a]	Pre-baseline	Double-blind placebo-controlled treatment period (26-week)							Safety follow-up
				Baseline							
	Visit:	1	2a	2b	3	4	5	6	7	8/ET [r]	9
	Week:	-5 to -2	-1	1	2	6	12	16	20	26	30
	Day:	-32 to -4	-10 to -3	1	14 (±7)	42 (±7)	84 (±7)	112 (±7)	140 (±7)	182 (±7)	210 (±7)
12-Lead ECG [j]		X		X	X	X	X	X	X	X	X
Vital signs [k]		X		X	X	X	X	X	X	X	X
Safety Labs [l]		X		X	X	X	X	X	X	X	X
AE		X	X	X	X	X	X	X	X	X	X
Conmeds [m]		X	X	X	X	X	X	X	X	X	X
Hearing Test [n]		X									
[redacted]				[redacted]			[redacted]		[redacted]	[redacted]	
ADAS-Cog13 *				X	X		X		X	X	
[redacted]				[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]				[redacted]			[redacted]			[redacted]	
[redacted]							[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]			[redacted]	
[redacted]							[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]			[redacted]	
[redacted]				[redacted]			[redacted]			[redacted]	
ERP P300 °: Pre-dose			X (no dosing)	X	X		X			X	X (no dosing)
Post-dose				X	X		X			X	
[redacted]				[redacted]			[redacted]			[redacted]	
[redacted]				[redacted]						[redacted]	

ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13-item version; [redacted] AE = adverse event; BP = blood pressure; [redacted] CT = computed tomography; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ECG = electrocardiogram; ERP = event-related potential; FSH = follicle-stimulating hormone; fT3 = free tri-iodothyronine; fT4 =free thyroxine; GDS = Geriatric Depression Scale; HR = heart rate; IMP = investigational medicinal product; [redacted] MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; [redacted] PK=pharmacokinetic; SC = subcutaneous; TSH = thyroid-stimulating hormone.

a If 28 days is not sufficient to complete the Screening period, the possibility of an extension can be discussed with the Medical Monitor.

b Only weight collected at Baseline/Day 1 (Visit 2b), Week 12 (Visit 5), Week 26 (Visit 8), and Safety follow-up (Visit 9).

c Urine pregnancy test will be performed for females with child-bearing potential at screening.

d Blood collection for FSH levels (to confirm post-menopausal state in females), serology, genotyping, fT3, fT4, and TSH.

e 'C-SSRS Baseline/Screening' version will be administered at Screening and 'C-SSRS Since Last Visit' version will be administered at all post-Screening visits.

f Dispensing of kits containing study drug will occur every 2 weeks; drug returns will be recorded and compliance calculated. Larger provision of study drug is permitted to accommodate personal need, e.g., vacation; site should check in with subject/caregiver via phone approximately every 2 weeks in cases of larger dispensing. IMP administration by the caregiver will be assessed at Visits 2b through 8, inclusive.

g First SC injection of IMP will be performed at site under supervision; subject should withhold IMP dose on the day of subsequent clinic visits (IMP administration will be done on site under supervision of site staff; training of proper injection techniques for subject/caregiver will be performed as needed); subjects will remain at site for 2 hours ± 15 minutes for safety observation follow up after first SC injection of IMP.

h Physical and neurological exam to be done post-dose at all visits where subjects are dosed.

i MRI (or CT) scan if not done since the initial diagnosis of PD.

j 12-lead ECGs will be performed pre-dose and 30 (± 15) minutes post-dose on Day 1(Visit 2b) and 30 (± 15) minutes post-dose at all other visits. All ECG assessments will be performed in triplicate.

k Vital signs (systolic and diastolic BP, orthostatic BP, HR, respiratory rate, and body temperature) will be performed pre-dose on all visits. Supine BP and HR recordings will be made after the subject has been supine for at least 5 minutes. Orthostatic BP will be recorded as follows: the first blood pressure will be the average of 3 measurements recorded after the subject is supine for 5 minutes; the second blood pressure will be recorded after the subject stood for up to 3 minutes.

l Safety labs include chemistry, hematology, urinalysis, and coagulation.

m Prior and concurrent medications.

n Subject hearing will be tested to establish suitability for ERP assessment (ability to hear or differentiate the 2 different tones necessary for auditory ERP P300 assessment, using the centrally provided ERP equipment); subjects who wear a hearing aid must remove their hearing aid during the Screening auditory test and during ERP P300 recordings.

o ERP P300 will be performed at the Pre-baseline visit (Visit 2a, Day -10 to Day -3, no dosing); pre-dose and post-dose at Baseline/Day 1 (Visit 2b), Week 2 (Visit 3), Week 12 (Visit 5), and Week 26 (Visit 8). ERP P300 data should be uploaded for quality check immediately after the completion of the Pre-baseline visit (Visit 2a). ERP P300 will also be performed at Safety follow-up (Visit 9, no dosing).

- Pre-dose ERP P300 assessments will be performed immediately preceding IMP dose but can be up to 1 hour before dose in clinic.
- Post-dose ERP P300 assessments will be performed at approximately 2 (± 1) hours after dose.

[redacted]

r Subjects who terminate prior to Visit 9 are to complete same assessments as Visit 8/ET (early termination). For clinical outcome assessments, if completed the assessment within 4 weeks of the ET visit they do not need to be repeated; all safety outcomes and drug accountability should be performed regardless of interval.

* At Baseline/Day 1 (Visit 2b), [redacted] ADAS-Cog$_{13}$, [redacted] will be performed pre-dose. For visits after Baseline (except for Safety follow-up when dosing is not applicable), all cognitive assessments will be performed post-dose, in the order of [redacted] ADAS-Cog$_{13}$, [redacted] assessments, with ADAS-Cog$_{13}$ performed at approximately 1 hour (± 30 minutes) post dose. [redacted] C-SSRS and GDS may be completed any time at applicable visits.

Appendix 3. Imputation of Partial Dates

Table 4. Imputation Rules for Partial Dates – Adverse Events

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y are prior to first study drug dose	First day of indicated month
		M and Y is same as first study drug dose	Date of first study drug dose
		M and Y are after first study drug dose	First day of indicated month
	M and D	Y is prior to first study drug dose	01 Jan of indicated year
		Y is same as first study drug dose	Date of first study drug dose
		Y is after first study drug dose	01 Jan of indicated year
	M, D, and Y	-	assumed to be TEAE
End Date	D only	M and Y are prior to last study drug dose	Last day of indicated month
		M and Y is same as last study drug dose	Date of last observation
		M and Y are after last study drug dose	First day of indicated month
	M and D	Y is prior to last study drug dose	31 Dec of indicated year
		Y is same as last study drug dose	Date of last observation
		Y is after last study drug dose	01 Jan of indicated year
	M, D, and Y	-	TEAE is ongoing
	-	Estimated end date is before a complete or imputed AE start date	Last day of the month of AE start date

D = day; M = month; Y= year; TEAE = treatment-emergent adverse event
Note: The imputation of end date must be later than start date

Table 5. Imputation Rules for Partial Dates – Prior and Concomitant Medications

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first study drug dosing	Date of first study drug dose
		M and/or Y not the same as M and Y of first study drug dosing	First day of indicated month
	M and D	Y same as Y of first study drug dosing	Date of first study drug dose
		Y not the same as Y of first study drug dosing	01 Jan of indicated year
	M, D, and Y	none – date completely missing	Date of first study drug dose
End Date	D only	M and Y same as M and Y of last study drug dosing	Date of last study drug dose
		M and/or Y not the same as M and Y of last study drug dosing	Last day of indicated month
	M and D	Y same as Y of last study drug dosing	Date of last study drug dose
		Y not the same as Y of last study drug dosing	31 Dec of indicated year
	M, D, and Y	none – date completely missing	Date of last study drug dose

D = day; M = month; Y= year

Appendix 4. Summary of Efficacy Analyses

Table 6. Analyses of Efficacy Parameters

Parameter	Population	Statistical Method	Missing Data	Interpretation	Table Number
GST Score	mITT	t-test/MMRM	NA	Primary analysis	Table 14.2.3.1
CFB ADAS-Cog13 score	mITT	t-test/MMRM	NA	Secondary analysis	Table 14.2.3.2
CFB ERP P300 latency	mITT	t-test/MMRM	NA	Secondary analysis	Table 14.2.3.3

mITT = Modified intent-to-treat; MMRM = Mixed Model Repeated Measures; CFB = change from baseline