CLINICAL STUDY PROTOCOL

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

Sponsor:	Athira Pharma, Inc. 18706 North Creek Parkway Suite 104 Bothell, WA 98011 USA
Protocol No.:	ATH-1017-PD-0201
IND No.:	141768
Investigational Medicinal Product (IMP) Name:	ATH-1017
Development Phase:	Phase 2
Emergency Telephone Number:	(Refer to the study contacts page)
SAE Reporting FAX Number/Email:	[redacted]
Date of Final Protocol:	05-NOV-2021
Version:	3.00

This clinical study will be conducted in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6), the protocol and with other applicable regulatory requirements.

SIGNATURE PAGE – SPONSOR

Declaration of Sponsor or Responsible Medical Expert

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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical, and scientific principles governing clinical research in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6 R2), the ethical principles outlined in the Declaration of Helsinki, the protocol and with other applicable regulatory requirements applicable to this clinical study.

Sponsor Signatory [redacted]

[redacted]

Date (dd mmm yyyy)

SIGNATURE PAGE – INVESTIGATOR

Declaration of the Principal Investigator

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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical, and scientific principles governing clinical research in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6 R2), the ethical principles outlined in the Declaration of Helsinki, the protocol and with other applicable regulatory requirements applicable to this clinical study.

Principal Investigator

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6 R2), the ethical principles outlined in the Declaration of Helsinki and with other regulatory requirements applicable to this clinical study.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name Athira Pharma Inc. and/or ATH-1017 in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without prior written consent of Athira Pharma Inc.

Signature of Site Principal Investigator	Date (dd mmm yyyy)
Printed Name of Site Principal Investigator	

Institution
Name:_____

LIST OF STUDY STAFF

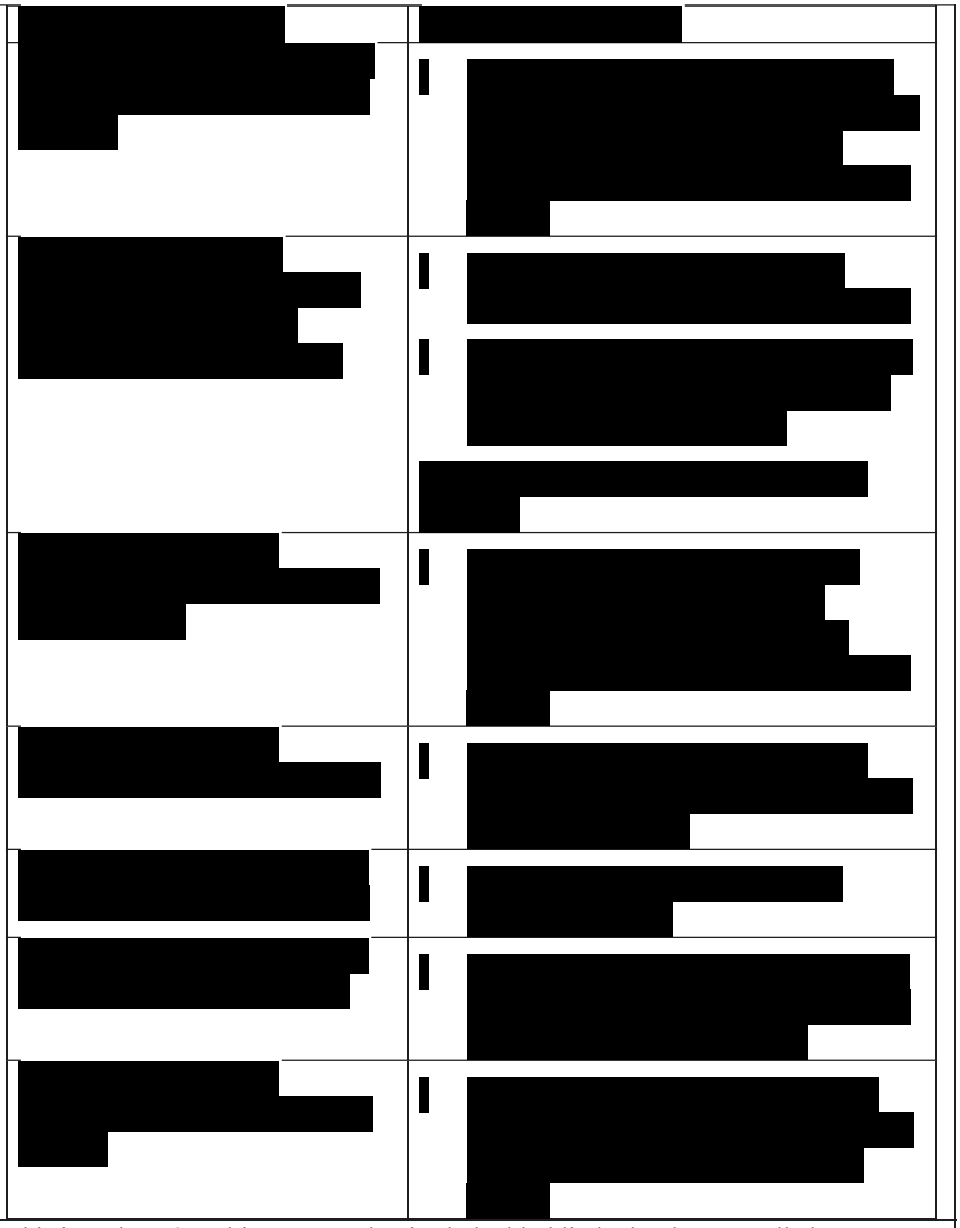
Sponsor:	Athira Pharma, Inc. 18706 North Creek Parkway Suite 104 Bothell, WA 98011 USA
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

PROTOCOL SYNOPSIS

Protocol 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
Development Phase:	Phase 2
Sponsor:	Athira Pharma, Inc.
Type of Study	Interventional
Study Centers:	The study will be conducted at a total of approximately 15 centers in the USA
Study Objectives and Endpoints:	

Primary Objectives	**Primary Endpoints**
To evaluate the clinical effects of ATH-1017 in subjects with Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB)	The Global Statistical Test (GST) (O'Brien, 1984) that combines the scores from cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale 13-item version [ADASCog_{13}]) and event-related potential (ERP) P300 latency, change from baseline at Week 26 compared 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-Cog_{13} 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]

	
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, 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 subcutaneous (SC) injection once-daily (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 Table 1 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-Cog$_{13}$, [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 at clinic visits (pre- and/or post-dose timepoints) as specified in Table 1. 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). Blood draws will take place at scheduled clinic visits for analysis of plasma concentrations of ATH-1017 (pro-drug) and ATH-1001 (active metabolite).
Treatments Administered:	Subjects will be randomized to one of 3 treatment groups: • ATH-1017, 40 mg, OD, SC • ATH-1017, 70 mg, OD, SC • Placebo, OD, SC An interim analysis of pharmacodynamics (ERP P300 latency) and safety is planned for when at least 30 subjects have completed their Week 2 assessment. Subjects subsequently recruited may be randomized to only 1 of the 2 doses of ATH-1017 (either 40 mg or 70 mg, OD, SC) in a 2:1 ratio (ATH-1017:placebo); subjects already enrolled in the study will continue on their treatment as originally assigned. All personnel involved in the management and conduct of the study will remain blinded to dose assignments.
Investigational Medicinal Products:	Active Treatment: ATH-1017 will be presented in identical prefilled 1 mL syringes of 40 mg/mL and 70 mg/mL Placebo: Placebo prefilled 1 mL syringes matching active treatment
Number of Subjects:	The study will randomize approximately 75 subjects in a 1:1:1 ratio to either ATH-1017 40 mg, ATH-1017 70 mg, or placebo

Duration of Treatment:	The study will consist of up to 28 days of screening (Day -32 through Day -4) and a Pre-baseline period of up to 8 days (Day -10 to Day -3), 26 weeks of double-blind treatment, and a 4-week safety follow-up. Note: if 28 days is not sufficient to complete the screening period, an extension can be discussed with the Medical Monitor.
Study Population:	**Inclusion** 1. Age 40 to 85 years, inclusive at the time of signing the informed consent. 2. Subjects with a confirmed diagnosis of PDD (Emre, 2007), or DLB (McKeith, 2017), preferably documented by subject medical records; caregiver reports with examples are acceptable. 3. MOCA score 11 to 23 inclusive at the Screening visit. 4. Body mass index of between ≥ 16 and ≤ 35 kg/m^2 for females and between ≥ 18 and ≤ 35 kg/m^2 for males at Screening. 5. Female subjects of child-bearing potential must not be pregnant (i.e., a negative urine pregnancy result is required prior to randomization) and must not be breastfeeding. 6. Male and female subjects of child-bearing potential and their partners must agree to use a double-barrier method of contraception during the study, including the follow-up period, unless the partner is not of childbearing potential. Female subjects of non-childbearing potential (i.e., permanently sterilized, postmenopausal) are eligible for participation. 7. Reliable and capable support person/caregiver, who is willing to accept responsibility for supervising the treatment or, if required, administering study drug, and assessing the condition of the subject throughout the study in accordance with all protocol requirements. The support person/caregiver must see the subject at least once-daily for dose administration and/or observation. 8. Subject capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. If the subject is incapable of giving informed consent in the judgment of the investigator then consent may be provided by a legally acceptable representative. 9. Written informed consent from a) the subject or legally acceptable representative and b) caregiver/support person has been obtained prior to any study-related procedures, including prior to initiating screening procedures to evaluate eligibility for the study. 10. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (e.g., Written Authorization for Use and Release of Health and Research Study Information). 11. Subjects and caregivers/support persons are able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits. 12. Subjects must be in generally good health as assessed by the investigator from medical history and physical/neurological examination, vital signs, ECG, and standard laboratory tests.

	Exclusion 1. Subjects at modified Hoehn-Yahr stage 5. 2. History of significant neurological disease other than PDD or DLB that may affect cognition, or concurrent neurological disease diagnosed at the time of onset of dementia. 3. Subject has had neurosurgical procedure for treatment of PD (such as deep brain stimulation implant), or if such procedure is anticipated or planned during the study period. 4. History of brain MRI scan indicative of any other significant abnormality, which would explain a dementing process other than PDD or DLB. Note: a new MRI scan is required if not done at or since the initial diagnosis of PD; a repeat MRI scan is required if there have been intervening changes to the subject's clinical presentation in the past 12 months. CT scan is acceptable for subjects fitted with a non-MRI-safe cardiac pacemaker, or other relevant medical reason, with Medical Monitor approval. 5. History of unexplained loss of consciousness, or epileptic fits (unless febrile). 6. Inability 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. 7. Diagnosis with current symptoms of severe major depressive disorder (GDS score [15-item scale] > 7 at Screening). In discussion with the Medical Monitor, subjects with a GDS score between 8 and 10 inclusive can be considered for study participation if the increased score is driven by specific domains related to the pandemic and its restrictions, rather than by major depression. 8. Significant suicide risk as defined by suicidal ideation based on the C-SSRS within the last 12 months, at Screening and on Day 1 (i.e., a 'yes' response to Question 4 or 5, or any specific behaviors). 9. Significant psychosis (according to the Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5; American Psychiatric Association, 2013]) interfering with the ability of the subject to complete study procedures in the judgment of the investigator, for reasons such as requirement to reduce previously stable dopaminergic therapy. 10. Moderate or severe substance abuse disorder (according to DSM-5, American Psychiatric Association, 2013). 11. Untreated conditions, including hypothyroidism, diabetes mellitus, hypo- or hypertension, if clinically relevant in the judgment of the investigator. If treated, must be stably treated and symptom-free for at least 2 months before Screening. 12. Abnormal serum electrolytes (potassium, sodium, magnesium) of clinical significance. If treated, must be stably treated for at least 30 days before Screening. 13. Active, acute, or chronic infectious disease of any type.

	14. Myocardial infarction or unstable angina within the last 6 months or history of more than one myocardial infarction within 5 years before Screening. 15. Clinically significant (in the judgment of the investigator) cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (note: pacemaker is acceptable). 16. Subject has either hypertension not controlled by anti-hypertensives (supine mean diastolic blood pressure > 95 mmHg from 3 sequential measurements), or symptomatic hypotension in the judgment of the investigator. 17. Clinically significant ECG abnormality at Screening as judged by the investigator, including but not limited to a confirmed corrected QT interval using Fridericia's formula (QTcF) value ≥ 450 msec for males and ≥ 470 msec for females. For QTcF readings that are borderline, and in those where the T and U waves are superimposed or connected, a manual reading should be considered to determine eligibility, in discussion with the Medical Monitor. In subjects with a QRS value > 120 msec, those with a QTcF value < 500 msec may be eligible following discussion with the Medical Monitor. 18. Positive results of serology screening for hepatitis B (hepatitis B surface antigen [HBsAg]), hepatitis C (anti-hepatitis C virus [HCV] antibodies) or human immunodeficiency virus (HIV) (antibodies type 1 and 2); past history of positive results with hepatitis B or hepatitis C may be eligible if fully recovered and asymptomatic, following discussion with the Medical Monitor and prior approval is required. 19. Chronic kidney disease with estimated glomerular filtration rate (eGFR) < 45 mL/min using the Cockcroft and Gault formula, with age, sex and weight considered; subjects with moderate to severe impairment (eGFR between 44 and 30 mL/min, inclusive) may be eligible following discussion with the Medical Monitor and prior approval is required. 20. Hepatic impairment with alanine aminotransferase or aspartate aminotransferase > 2 times the upper limit of normal, or Child-Pugh class B and C. 21. Malignant tumor within 3 years before Screening, except for the following conditions that are stable in the judgment of the investigator: a) Adequately treated squamous and basal cell carcinoma, or squamous and basal cell carcinoma in situ b) Prostate carcinoma in situ c) Fully-excised (biopsy-proven) melanoma in-situ; Medical Monitor prior approval is required. 22. Clinically significant (in the judgment of the investigator) unintentional weight loss within 12 months of Screening. 23. The consumption of grapefruit or grapefruit-containing products is prohibited beginning 7 days prior to the first dose of study medication (Day 1) and during the study.

24. Food supplements and nutraceuticals with potential effects on cognition, such as Axona and medium-chain triglyceride, are prohibited beginning 7 days prior to the first dose of study medication (Day 1) and for the duration of the study.

25. Tetrahydrocannabinol (THC) is prohibited beginning 4 weeks prior to the first dose of study medication (Day 1) and for the duration of the study. Cannabidiol (CBD) without THC is allowed but not on the clinical visit days, except for topical applications.

26. Prohibited prior and concomitant medications are excluded within 4 weeks prior to Screening. All allowed medications should remain stable in terms of dose and regimen throughout the study; for medications affecting cognition, the doses should be stable for at least 4 weeks before Screening and throughout the study, unless otherwise noted. If the permissibility of a specific medication is in question, please contact the Medical Monitor prior to randomization (refer to Appendix 1: List of Prohibited Medications; note: this is not an exhaustive list):

    a) Selegiline and trihexyphenidyl in any form or dosage.
    b) Memantine in any form, combination, or dosage.
    c) Donepezil at 23 mg.
    d) Antipsychotics: low doses (in the judgment of the investigator) are allowed if the subject has received a stable dose before Screening. If these medications are taken on a PRN basis they should not be taken the morning before any cognitive testing.
    e) Tryptophan supplements.
    f) Tricyclic antidepressants, irreversible monoamine oxidase B inhibitors, and S-ketamine; all other antidepressants are allowed only if the subject has received a stable dose for at least 3 months before Screening.
    g) Anxiolytics at high doses; low doses of benzodiazepines are allowed in the judgment of the investigator, but not the night before any cognitive assessments.
    h) Sedative hypnotics; Zolpidem is allowed.
    i) Barbiturates (unless given in low doses for benign tremor)
    j) Nicotine therapy (including patches), varenicline (Chantix), or similar therapeutic agent.
    k) Peripherally acting drugs with effects on cholinergic neurotransmission, e.g., oxybutinin. Solifenacin is allowed if the subject has received a stable dose for at least 3 months before Screening.
    l) Systemic immunosuppressants if taken in clinically immunosuppressive doses in the judgment of the investigator; inhaled steroids, otics, opthalmologics, topical applications, and intra-articular injections are allowed.
    m) Antiepileptic medication.
    n) Chronic intake of opioid-containing analgesics; PRN use is allowed (but not within 72 hours before any cognitive assessment).

	o) Sedating H_1 antihistamines; non-sedating H_1 antihistamines are allowed and preferred. p) Systemic moderate to strong cytochrome P450 3A4 inhibitors or inducers; topical applications are allowed. 27. Current enrollment in an investigational drug or device study, or have participated in another clinical trial with an investigational drug within 4 weeks of Screening, or 5 half-lives, whichever is longer, or within 6 months of Screening if an investigational drug for PD or cognition impairment. 28. Subject has known allergy to any component of the investigational medicinal product or an allergy to latex. 29. The subject has a condition or is in a situation which, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's compliance or participation in the study.
Statistical Methods:	**General Statistical Methods and Types of Analysis:** Clinical effect analyses will be based on the modified intent-to-treat (MITT) Population, consisting of all randomized subjects who took at least one dose of the study medication and who completed both an ADAS-Cog_{13} score and ERP P300 latency assessment during Baseline and at least one post-baseline visit. The primary clinical effect endpoint is the GST (combining the ADAS-Cog_{13} score and the ERP P300 latency) change from baseline at Week 26 relative to the placebo group. The primary analysis will use a mixed model for repeated measures (MMRM) with change from baseline as the outcome variable, and terms for baseline, baseline by time interaction, and baseline by time by treatment interaction in the model. Additional terms will be included for GBA genotype, and site (with smaller sites grouped). Least squares means and treatment differences will be estimated from the MMRM model. An interim analysis of the ERP-P300 and safety data is planned when at least 30 subjects have completed the Week 2 visit. Safety analyses will be based on the Safety Population consisting of all randomized subjects who received at least one dose of the study medication. All safety parameters will be summarized descriptively. **Sample Size Considerations:** A total sample size of 75 evaluable subjects (25 per treatment arm) was chosen empirically; no formal sample size calculation was applied.

Figure 1 Study Schema

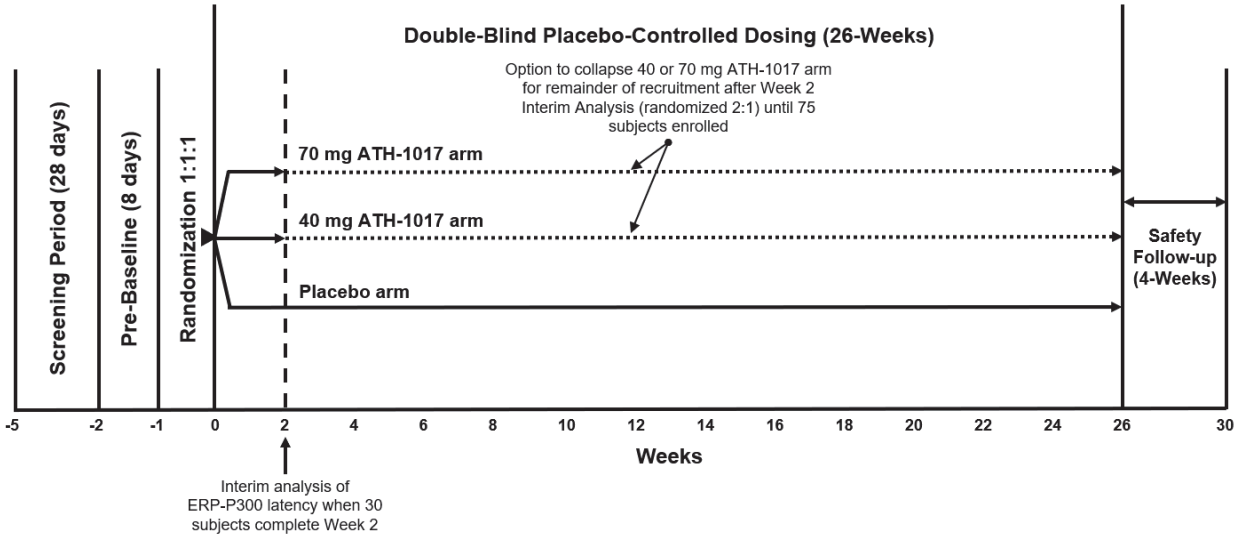


Table 1 Schedule of Assessments

				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									
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]											
ADAS-Cog13 *				X	X		X		X	X	
[redacted]											

				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)
[redacted]											
ERP P300 [o]: Pre-dose			X (no dosing)	X	X		X			X	X (no dosing)
Post-dose				X	X		X			X	
[redacted]											

ADAS-Cog13 = 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; NMSS = Non-Motor Symptom Scale; 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]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog$_{13}$	Alzheimer's Disease Assessment Scale-Cognitive Subscale, 13-item version
[redacted]	[redacted]
AE	Adverse event
AKT	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APP/PS1	Amyloid precursor protein/presenilin 1
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
CBC	Complete blood count
CBD	Cannabidiol
[redacted]	[redacted]
COVID-19	Coronavirus disease – 2019
[redacted]	[redacted]
CPK	Creatine phosphokinase
CRO	Contract research organization
CYP3A4	Cytochrome P450 3A4
C_{max}	Maximum concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
C-SSRS	Columbia-suicide severity rating scale
CT	Computerized tomography
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
eGFR	Estimated glomerular filtration rate
ERP	Event-related potentials

ET	Early termination
FSH	Follicle-stimulating hormone
fT3	Free tri-iodothyronine
fT4	Free thyroxine
FWER	Family-wise error rate
GBA	Glucocerebrosidase
GCP	Good Clinical Practice
GDS	Geriatric depression scale
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
HGF	Hepatic growth factor
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
LAR	Legally authorized representative
LBD	Lewy body dementia
LTP	Long-term potentiation
MAO-B	Monoamine oxidase B
MAPK	Mitogen-activated protein kinase
MCT	Medium-chain triglyceride
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MET	MET receptor tyrosine kinase
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
[redacted]	[redacted]
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging

NMDA	N-methyl D-aspartate
[redacted]	[redacted]
OD	Once-daily
OLEX	Open-label extension
P	Phosphorylated
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
PRN	As needed
PT	Prothrombin time
qEEG	Quantitative electroencephalogram
QTcF	Corrected QT interval using Fridericia's formula
RAC1	Ras-related C3 botulinum toxin substrate 1
RAF	Rapidly accelerated fibrosarcoma (protein)
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SOP	Standard operating procedure
STAT3	Signal transducer and activator of transcription 3
SUSAR	Suspected unexpected serious adverse reaction
THC	Tetrahydrocannabinol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US(A)	United States (of America)
VAS	Visual analog scale
WBC	White blood cells

1 INTRODUCTION

ATH-1017 is an experimental treatment for dementia, including Alzheimer's disease (AD) dementia, Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB). ATH-1017 is formulated as a sterile solution for subcutaneous (SC) injection. ATH-1017 is a prodrug, which is rapidly converted to the active metabolite ATH-1001 in the plasma after SC injection. ATH-1017 was developed as a water-soluble prodrug of ATH-1001 to allow SC dosing in aqueous vehicles. The active metabolite ATH-1001 acts as an agonist of the hepatic growth factor (HGF) receptor and its tyrosine kinase, MET in the brain. The HGF/MET system presents a new therapeutic target to treat neurodegeneration and restore cognitive function in AD, PDD, and DLB.

1.1 Background

Parkinson's disease (PD) is a common neurodegenerative disease characterized by a movement disorder consisting of bradykinesia, rest tremor, and rigidity, along with postural instability, a range of other more-subtle motor features, and many non-motor features (Kalia, 2015). The clinical diagnosis of PD follows validated criteria (Postuma, 2015). Globally, PD prevalence ranges from 1 to 2 per 1000, and is increasing with age; 1% of the population over 60 years suffers from PD (Tysnes, 2017); the prevalence of PD has more than doubled between 1990 and 2016 (Rocca, 2018). There is a significant correlation between quality of life scores and non-motor symptoms (Duncan, 2014). At least 75% of PD patients who survive for more than 10 years will develop dementia. In addition, mild cognitive impairment (MCI) is common even at disease onset, and is associated with a shorter time to dementia (Aarsland, 2010a; Hely, 2008). At presentation, 25% of individuals with PD exhibit mild cognitive impairment (Aarsland, 2010b)

PD, PDD, and DLB have been grouped under an umbrella term referred to as Lewy body disorders (Lippa, 2007), characterized by Lewy body pathology at autopsy; however, there are no definite pathological criteria that separate PD, DLB, and PDD from each other (McKeith, 2004). The earliest signs of DLB and PDD differ but reflect the same biological changes in the brain and over time they may develop similar symptoms, collectively known as Lewy body dementia (LBD) (McKeith, 2004; McKeith, 2017). In general, DLB and PDD are clinically distinguished by the sequence of their symptoms. If dementia occurs before, concurrently, or within 1 year of motor parkinsonism, DLB is diagnosed; if dementia occurs more than 1 year after an established PD diagnosis, then PDD is diagnosed (Emre, 2007).

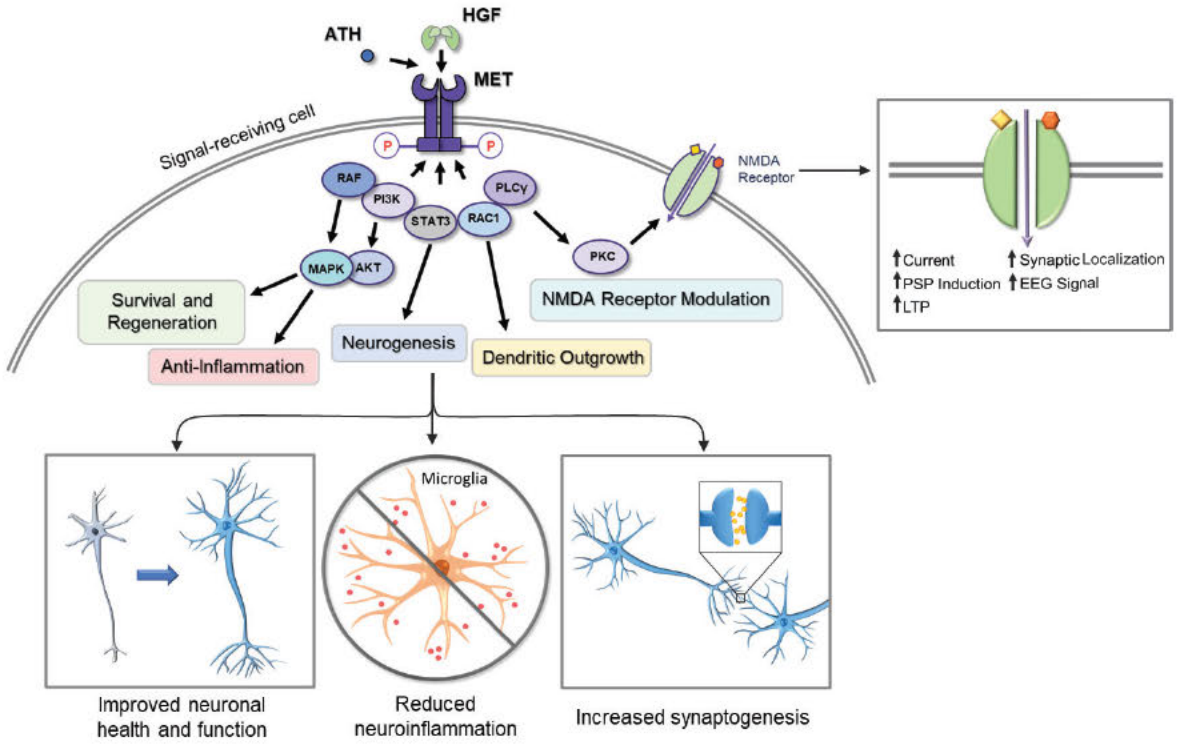
PDD and DLB are progressive disorders, following roughly the same stages as AD dementia, with considerable variability from patient to patient. Virtually every individual with PD experiences some degree of cognitive deficit, ranging from mild cognitive impairment to dementia. Patients diagnosed with PDD have a substantially reduced life expectancy compared to persons in the general population (Buter, 2008).

Current treatments for PDD are mostly derived from those utilized in AD, with cholinesterase inhibitors and Memantine being 2 of the main approaches, and in some cases in combination with antipsychotic drugs (Szeto, 2016). There are no treatments to slow or stop neuro-degeneration, the main underlying condition contributing to progressive deterioration in dementia symptoms.

Growing evidence suggests that complex central nervous system (CNS) disorders, like AD, PDD, and DLB are unlikely to be caused by a single route of pathology; they are likely the result of a multifactorial interplay related to genetics, age, and environment. Pharmacological stimulation of a critical neurotrophic factor system (HGF/MET) may stop neurodegeneration and promote neuro-regeneration. Neurotrophic factors represent a promising therapeutic target for the treatment of dementia caused by neurodegeneration, including AD, PDD, and DLB by protecting existing neurons, promoting synaptogenesis, stimulating neuronal growth, and inducing regenerative mechanisms. Pharmacological stimulation of neurotrophic systems has the potential to treat all stages of AD, PDD, and DLB by directly targeting neurodegeneration, improving cognition, and addressing multiple aspects of the disease, by decreasing inflammation and improving cerebral blood flow (Funakoshi, 2011). The therapeutic promise of neurotrophic factors in neurodegenerative disorders is hampered by the lack of efficient and non-invasive delivery to the brain. Gene therapy strategies, primarily using adeno-associated viral vectors, have been developed and clinically evaluated for therapeutic potential in AD and PDD patients. These strategies are largely hindered by challenges related to gene delivery and transduction with limited brain exposure, uncontrollable dose over long-term treatment, and potential immune complications (Piguet, 2017). Therefore, a small molecule approach capable of passing the blood brain barrier and entering all regions of the brain, presents a superior therapeutic strategy for targeting neurotrophic factors to treat neurodegenerative disorders.

ATH-1017 represents a new approach to treat AD, PDD, and DLB in a systemic approach. The mechanism of action of ATH-1017 is augmentation of HGF function and facilitation of signal transduction through MET phosphorylation (Figure 2).

Figure 2 Mechanism of ATH-1017



AKT = protein kinase B; EEG = electroencephalogram; HGF = hepatic growth factor; LTP = long-term potentiation; MAPK = mitogen-activated protein kinase; MET = MET receptor tyrosine kinase; NMDA = N-methyl D-aspartate; P = phosphorylated; PI3K = phosphoinositide 3-kinase; PKC = protein kinase C; PLCγ = phospholipase C-gamma; RAC1 = Ras-related C3 botulinum toxin substrate 1; RAF = rapidly accelerated fibrosarcoma (RAF) kinase; STAT3 = signal transducer and activator of transcription 3.

After SC injection, the prodrug ATH-1017 is rapidly converted to the active metabolite ATH-1001, which binds to HGF and enhances MET activation. Interaction of the ligand HGF with its receptor MET induces MET phosphorylation (activation) and recruitment of effector proteins that potentiate downstream signaling through the PI3K/AKT and RAS/RAF/MAPK pathways, among others (Organ, 2011). In the CNS, HGF/MET activity has neuroprotective and neurotrophic effects and modulates neurogenesis and neuronal maturation (Ebens, 1996; Maina, 1999; Shang, 2011). As a critical regulator of inflammation, HGF/MET activity reduces the expression of the pro-inflammatory cytokine interleukin-6 and promotes expression of the anti-inflammatory interleukin -10 (Molnarfi, 2015). HGF/MET activity also leads to protein kinase C (PKC)-mediated potentiation of N-methyl D-aspartate (NMDA) receptor current, synaptic localization of NMDA receptors, and long-term potentiation (Tyndall, 2007), processes important for memory formation.

1.2 Rationale for the Clinical Study

The Sponsor has completed a Phase 1a/b study of ATH-1017 in which preliminary safety and tolerability, pharmacokinetics (PK), and pharmacodynamics based on quantitative electroencephalogram (qEEG) and event-related potentials (ERP P300) was established in young healthy and elderly healthy subjects, and elderly subjects with mild to moderate AD/MCI (Study NDX-1017-0101; see Sections 6.3.1.1 and 6.3.1.2 also). Quantitative EEG was employed in both preclinical and clinical studies providing a translatable biomarker of neuronal network activity, as a function of pharmacological intervention. The qEEG analysis, combined with pharmacokinetic-pharmacodynamic (PK-PD) modeling, and preclinical behavioral study results, have supported the identification of an active clinical dose range in humans (see Section 3.2). Additionally, in an ERP auditory oddball paradigm, ATH-1017 treatment in AD subjects significantly reduced ERP P300 latency after 8 days of treatment when compared to placebo (refer to the Investigator's Brochure). This finding suggests ATH-1017 treatment has potential effects on cognitive processing and working memory access in AD.

A Phase 2 study, ATH-1017-AD-0201, was subsequently initiated as a randomized, placebo-controlled, 26-week, multi-center trial, powered to provide primary evidence on the safety and efficacy of ATH-1017 at 2 dose levels (40 and 70 mg, SC, once daily [OD]) in the treatment of mild to moderate AD, followed by an optional open-label extension (OLEX) protocol.

A second Phase 2 study, ATH-1017-AD-0202, was designed to provide evidence for the functional translational biomarker ERP P300 latency as being predictive of pro-cognitive effects induced by ATH-1017 therapy. In addition, the study will determine time to onset and degree of maintenance of P300 latency reduction over 26 weeks. Eligible subjects receive OD SC injections of ATH-1017 at 1 of 2 dose levels (40 mg or 70 mg) or placebo, over a 26-week double-blind period, followed by an optional OLEX protocol.

This study (ATH-1017-PD-0201) is designed to demonstrate the effect of ATH-1017 on ERP P300 latency, as well as cognitive and functional effects in subjects with PDD or DLB, and to establish long-term safety information. Eligible participants will receive OD 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.

1.3 Risk-Benefit Assessment

Whilst qEEG and ERP P300 results in humans are indicative of CNS penetration and target engagement, efficacy in subjects with PDD or DLB (in terms of cognitive, functional, or behavioral improvement) has not been established. Therefore, the benefits to study subjects of participating in this clinical trial are not yet known.

In clinical studies of ATH-1017, single SC administration of 2, 6, 20, 40, 60, and 90 mg in healthy young subjects, and multiple administration of 20, 40, 60, and 80 mg (SC, OD, over 9 consecutive days) in healthy elderly subjects, and 40 mg (SC, OD, over 9 consecutive days) in AD subjects were safe and well tolerated. Injection site reactions included pain, pruritus, and/or erythema, were mild in nature, and resolved without specific therapy. A potential risk for hepatotoxicity identified in nonclinical studies has not been observed in human studies but will be closely monitored in this study. To date, no CNS-specific adverse events have been observed in humans.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives	**Primary Endpoints**
To evaluate the clinical effects of ATH-1017 in subjects with PDD or DLB	The Global Statistical Test (GST) (O'Brien, 1984) that combines the scores from cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale 13-item version [$ADASCog_{13}$]) and ERP P300 latency, change from baseline at Week 26 compared 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	• $ADAS\text{-}Cog_{13}$ 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]
[redacted]	[redacted]
[redacted]	[redacted]

3 OVERALL DESIGN AND PLAN OF THE STUDY

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, 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 Table 1 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-Cog$_{13}$, and [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 Table 1.

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).

Blood draws will take place at scheduled clinic visits for analysis of plasma concentrations of ATH-1017 (pro-drug) and ATH-1001 (active metabolite) (see Table 1 for Schedule of Assessments).

3.1 Justification for Study Design

The study is designed as a safety and proof of concept study of ATH-1017 in PDD and DLB subjects using a double-blind, placebo-controlled, parallel-arm treatment duration of 26 weeks. The target population is based on clinical diagnostic criteria of PDD (Emre, 2007) or DLB (McKeith, 2017) in combination with severity assessments and the inclusion/exclusion criteria.

Any rational assessment of cognitive change can only be performed using a double-blind, placebo-controlled, randomized study design. A study duration of 26 weeks is in keeping with the rivastigmine trial (Emre, 2004) that led to US FDA approval for the use of rivastigmine in PDD subjects.

Clinical effects in the target patient population are assessed by improvement in cognition and global as well as functional variables comparing treatment to placebo. The GST combines the endpoints ADAS-Cog_{13} (i.e., cognition) and change in ERP P300 latency into a single primary endpoint, allowing an unbiased assessment of the overall treatment effects of ATH-1017 in this complex disorder. The inclusion of an additional assessment of ERP P300 at a pre-Baseline visit in addition to corresponding baseline assessments pre-dose at the Baseline/ Day 1 visit of the study is intended to reduce possible variability of the baseline measure for this functional variable.

As well as providing pharmacodynamic data on the effect of ATH-1017 on ERP P300 latency in this patient population, this study will provide data on clinical effects using validated outcome scales for cognitive function, executive memory function, activities of daily living, motor function, and behavioral changes.

The safety assessments for the study are generally accepted measures for ensuring safety of subjects during a double-blind clinical trial. In addition, subject safety will be closely monitored and stopping criteria implemented (see Section 5.8).

The PK sampling schedule is considered appropriate given the information available. The rationale for dose selection is discussed in Section 3.2.

3.2 Justification for Dose

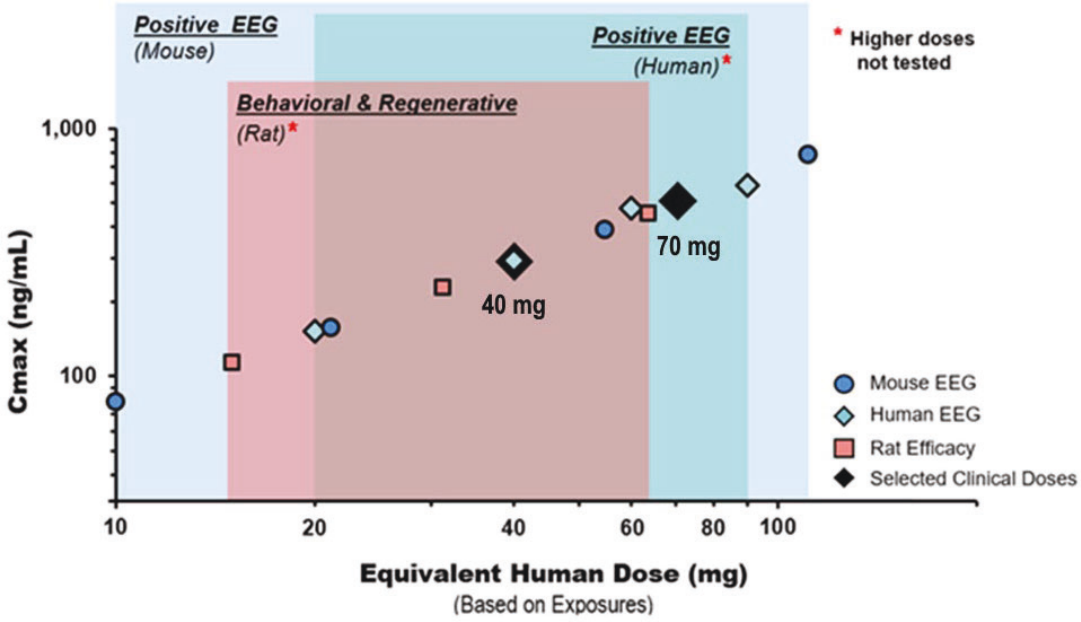
The dose selection for this clinical study is based on safety, PK, and PK-PD modeling of ATH-1017's treatment effect in nonclinical studies in animal models, a qEEG study in amyloid precursor protein/presenilin 1 (APP/PS1) mice, and the qEEG and ERP P300 results of a completed Phase 1a/b study.

In the randomized placebo-controlled Phase 1a/b study (Study NDX-1017-0101), ATH-1017 was evaluated for safety, PK, and pharmacodynamics in a total of 88 subjects (of whom 65 were

exposed to active study drug), including healthy young, healthy elderly, and AD subjects. ATH-1017 was evaluated over a wide dose range (2 to 90 mg) to understand the safety profile and pharmacodynamic effects based on qEEG and ERP assessment. The observed qEEG effects (i.e., gamma power induction) are thought to be linked to the mechanism of action of ATH-1017, indicative of CNS penetration and target engagement. PK-PD modeling has been employed to guide dose selection, considering data from a nonclinical qEEG study in APP/PS1 mice, nonclinical efficacy studies in animal models (i.e., scopolamine-induced amnesia in rat and aged dementia rat), and the Phase 1a/b human clinical study. The results were compared based on equivalent PK exposures to inform dose selection for further clinical studies.

As summarized in Figure 3, the active pharmacodynamic dose range in humans (20 to 90 mg) overlaps with exposures that lead to qEEG gamma induction as well as improved behavioral measures and regenerative effects in nonclinical studies. Higher doses in humans and animal efficacy studies have not been tested, therefore the upper limit of the pharmacodynamic dose range is not defined. The PK profile is highly consistent across multiple species including rat, mouse, dog, and human, further supporting the utility of PK-PD modeling in guiding dose selection. The use of qEEG as a translational biomarker to guide dose optimization in clinical trials of ATH-1017 allowed for efficient selection of doses that fall within the cross-species pharmacodynamic dose range.

Figure 3 Dose selection based on PK-PD modeling



The doses selected for the proposed study are 40 mg (SC, OD) and 70 mg (SC, OD). Both the 40 mg and 70 mg doses are covered by the current pharmacodynamic active dose range (20 mg to 90 mg) defined by human qEEG studies, while the upper boundary is not yet determined. Equivalent dose exposure levels (C_{max}-based) have been tested in nonclinical studies and showed

positive qEEG effects and functional improvement. The safety and tolerability of both doses are supported by the Phase 1a/b results. The 40 mg dose has been evaluated in 8 healthy young subjects (SC, single dose; 6 active versus 2 placebo), 8 healthy elderly subjects (SC, OD, over 9 days; 6 active versus 2 placebo), and 11 AD subjects (SC, OD, over 9 days; 7 active versus 4 placebo), with consistent and dose-linear PK, and good safety across all 3 cohorts. The normalization of ERP P300 in AD subjects treated with 40 mg ATH-1017 suggests a treatment-dependent promotion of synaptic activity, and further suggests a therapeutic potential of ATH-1017 at the 40 mg dose level.

In reference to the 40 mg dose, a high dose range is defined based on pharmacodynamics and safety, including dose levels between 60 mg and 90 mg. In the healthy subject single-dose studies, there was a dose-dependent increase in the qEEG signal (i.e., gamma power induction) across 20 mg and 90 mg. The most notable effects in gamma power induction were observed in the high dose groups including 60 mg (SC; 6 treated versus 2 placebo) and 90 mg (SC; 6 treated versus 2 placebo). The 90 mg dose demonstrated a statistically significant effect in the frontal area of the brain when compared to placebo ($p < 0.05$; n=6 treated versus n=6 placebo). In healthy elderly subject studies, the 80 mg dose was evaluated over 9 days (SC, OD; 4 active versus 1 placebo), with PK results in keeping with dose-linearity, and supportive safety data. The 70 mg dose is therefore selected in reference to the high dose range defined as 60 mg to 90 mg.

The selection of the 40 mg and 70 mg doses is supported by the 26-week Good Laboratory Practice (GLP) toxicology studies in rats and dogs.

In summary, the selected doses of 40 mg and 70 mg cover the nonclinical effects and the clinical pharmacodynamic range, were well-tolerated in humans based on safety data from the Phase 1a/b study, and are covered by the 26-week GLP nonclinical toxicology studies in animals at equivalent doses (please refer to the ATH-1017 Investigator's Brochure for further details). The doses of ATH-1017 used for evaluation of clinical effects and safety in this study will support selection of an appropriate dose for registration of ATH-1017 as a potential treatment for subjects with PDD or DLB).

4 STUDY POPULATION

All subjects must meet all the inclusion criteria and none of the exclusion criteria.

Protocol exemptions related to enrollment criteria are only allowed with prior investigator, Medical Monitor, and Sponsor approval, supported by documented agreement from the IRB/IEC.

4.1 Number of Subjects

The study will randomize approximately 75 subjects in a 1:1:1 ratio to ATH-1017 40 mg, ATH-1017 70 mg, and placebo groups.

4.2 Inclusion Criteria

1. Age 40 to 85 years, inclusive at the time of signing the informed consent.
2. Subjects with a confirmed diagnosis of PDD (Emre, 2007), or DLB (McKeith, 2017), preferably documented by subject medical records; caregiver reports with examples are acceptable.
3. MOCA score 11 to 23 inclusive at the Screening visit.
4. Body mass index (BMI) of between ≥ 16 and ≤ 35 kg/m^2 for females and between ≥ 18 and ≤ 35 kg/m^2 for males at Screening.
5. Female subjects of child-bearing potential must not be pregnant (i.e., a negative urine pregnancy result is required prior to randomization) and must not be breastfeeding.
6. Male and female subjects of child-bearing potential and their partners must agree to use a double-barrier method of contraception during the study, including the follow-up period, unless the partner is not of childbearing potential. Female subjects of non-childbearing potential (i.e., permanently sterilized, postmenopausal) are eligible for participation.
7. Reliable and capable support person/caregiver, who is willing to accept responsibility for supervising the treatment or, if required, administering study drug, and assessing the condition of the subject throughout the study in accordance with all protocol requirements. The support person/caregiver must see the subject at least once-daily for dose administration and/or observation.
8. Subject capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. If the subject is incapable of giving informed consent in the judgment of the investigator then consent may be provided by a legally acceptable representative.
9. Written informed consent from a) subject or legally acceptable representative and b) caregiver/support person has been obtained prior to any study-related procedures, including prior to initiating screening procedures to evaluate eligibility for the study.

10. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (e.g., Written Authorization for Use and Release of Health and Research Study Information).
11. Subjects and caregivers/support persons are able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits.
12. Subjects must be in generally good health as assessed by the investigator from medical history and physical/neurological examination, vital signs, ECG, and standard laboratory tests.

4.3 Exclusion Criteria

1. Subjects at modified Hoehn-Yahr stage 5.
2. History of significant neurologic disease, other than PDD or DLB that may affect cognition, or concurrent neurological disease diagnosed at the time of onset of dementia.
3. Subject has had neurosurgical procedure for treatment of PD (such as deep brain stimulation implant), or if such procedure is anticipated or planned during the study period.
4. History of brain magnetic resonance imaging (MRI) scan indicative of any other significant abnormality, which would explain a dementing process other than PDD or DLB. Note: a new MRI scan is required if not done at or since the initial diagnosis of PD; a repeat MRI scan is required if there have been intervening changes to the subject's clinical presentation in the past 12 months. CT scan is acceptable for subjects fitted with a non-MRI-safe cardiac pacemaker, or other relevant medical reason, with Medical Monitor approval.
5. History of unexplained loss of consciousness, or epileptic fits (unless febrile).
6. Inability 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.
7. Diagnosis with current symptoms of severe major depressive disorder (GDS score [15-item scale] > 7 at Screening). In discussion with the Medical Monitor, subjects with a GDS score between 8 and 10 inclusive can be considered for study participation if the increased score is driven by specific domains related to the pandemic and its restrictions, rather than by major depression.
8. Significant suicide risk as defined by suicidal ideation based on the C-SSRS within the last 12 months, at Screening and on Day 1 (i.e., a 'yes' response to Question 4 or 5, or any specific behaviors).
9. Significant psychosis (according to the Diagnostic and Statistical Manual of Mental Disorders, [5th edition; DSM-5; American Psychiatric Association, 2013]) interfering with

the ability of the subject to complete study procedures in the judgment of the investigator, for reasons such as requirement to reduce previously stable dopaminergic therapy.

10. Moderate or severe substance abuse disorder (according to DSM-5; American Psychiatric Association, 2013).
11. Untreated conditions, including hypothyroidism, diabetes mellitus, hypo- or hypertension, if clinically relevant in the judgment of the investigator. If treated, must be stably treated and symptom-free for at least 2 months before Screening.
12. Abnormal serum electrolytes (potassium, sodium, magnesium) of clinical significance. If treated, must be stably treated for at least 30 days before Screening.
13. Active, acute, or chronic infectious disease of any type.
14. Myocardial infarction or unstable angina within the last 6 months or history of more than one myocardial infarction within 5 years before Screening.
15. Clinically significant (in the judgment of the investigator) cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (note: pacemaker is acceptable).
16. Subject has either hypertension not controlled by anti-hypertensives (supine mean diastolic blood pressure > 95 mmHg from 3 sequential measurements), or symptomatic hypotension in the judgment of the investigator.
17. Clinically significant ECG abnormality at Screening as judged by the investigator, including but not limited to a confirmed corrected QT interval using Fridericia's formula (QTcF) value ≥ 450 msec for males and ≥ 470 msec for females. For QTcF readings that are borderline, and in those where the T and U waves are superimposed or connected, a manual reading should be considered to determine eligibility, in discussion with the Medical Monitor. In subjects with a QRS value > 120 msec, those with a QTcF value < 500 msec may be eligible following discussion with the Medical Monitor.
18. Positive results of serology screening for hepatitis B (hepatitis B surface antigen [HBsAg]), hepatitis C (anti-hepatitis C virus [HCV] antibodies) or human immunodeficiency virus (HIV) (antibodies type 1 and 2); past history of positive results with hepatitis B or hepatitis C may be eligible if fully recovered and asymptomatic, following discussion with the Medical Monitor and prior approval is required.
19. Chronic kidney disease with estimated glomerular filtration rate (eGFR) < 45 mL/min using the Cockcroft and Gault formula, with age, sex and weight considered; subjects with moderate to severe impairment (eGFR between 44 and 30 mL/min, inclusive) may be eligible following discussion with the Medical Monitor and prior approval is required.
20. Hepatic impairment with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal, or Child-Pugh class B and C.

21. Malignant tumor within 3 years before Screening, except for the following conditions that are stable in the judgment of the investigator:
    a) Adequately treated squamous and basal cell carcinoma, or squamous and basal cell carcinoma in situ
    b) Prostate carcinoma in situ
    c) Fully-excised (biopsy-proven) melanoma in-situ; Medical Monitor prior approval is required.
22. Clinically significant (in the judgment of the investigator) unintentional weight loss within 12 months of Screening.
23. The consumption of grapefruit or grapefruit-containing products is prohibited beginning 7 days prior to the first dose of study medication (Day 1) and during the study.
24. Food supplements and nutraceuticals with potential effects on cognition, such as Axona and medium chain triglyceride (MCT), are prohibited beginning 7 days prior to the first dose of study medication (Day 1) and for the duration of the study.
25. Tetrahydrocannabinol (THC) is prohibited beginning 4 weeks prior to the first dose of study medication (Day 1) and for the duration of the study. Cannabidiol (CBD) without THC is allowed but not on the clinical visit days, except for topical applications.
26. Prohibited prior and concomitant medications are excluded within 4 weeks prior to Screening. All allowed medications should remain stable in terms of dose and regimen throughout the study; for medications affecting cognition, the doses should be stable for at least 4 weeks before Screening and throughout the study, unless otherwise noted. If the permissibility of a specific medication is in question, please contact the Medical Monitor prior to randomization (refer to Appendix 1: List of Prohibited Medications; note: this is not an exhaustive list):
    a) Selegiline and trihexyphenidyl in any form or dosage.
    b) Memantine in any form, combination, or dosage.
    c) Donepezil at 23 mg.
    d) Antipsychotics: low doses (in the judgment of the investigator) are allowed if the subject has received a stable dose before Screening. If these medications are taken on a PRN basis they should not be taken the morning before any cognitive testing.
    e) Tryptophan supplements.
    f) Tricyclic antidepressants, irreversible monoamine oxidase B (MAO-B) inhibitors, and S-ketamine; all other antidepressants are allowed only if the subject has received a stable dose for at least 3 months before Screening.

g) Anxiolytics at high doses; low doses of benzodiazepines are allowed in the judgment of the investigator, but not the night before any cognitive assessments.

h) Sedative hypnotics; Zolpidem is allowed.

i) Barbiturates (unless given in low doses for benign tremor).

j) Nicotine therapy (including patches), varenicline (Chantix), or similar therapeutic agent.

k) Peripherally acting drugs with effects on cholinergic neurotransmission, e.g., oxybutinin. Solifenacin is allowed if the subject has received a stable dose for at least 3 months before Screening.

l) Systemic immunosuppressants if taken in clinically immunosuppressive doses in the judgment of the investigator; inhaled steroids, otics, opthalmologics, skin creams, and intra-articular injections are allowed.

m) Antiepileptic medication.

n) Chronic intake of opioid-containing analgesics; PRN use is allowed (but not within 72 hours before any cognitive assessment).

o) Sedating H_1 antihistamines; non-sedating H_1 antihistamines are allowed and preferred.

p) Systemic moderate to strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers; topical applications are allowed.

27. Current enrollment in an investigational drug or device study, or have participated in another clinical trial with an investigational drug within 4 weeks of Screening, or 5 half-lives, whichever is longer, or within 6 months of Screening if an investigational drug for PD or cognition impairment.
28. Subject has known allergy to any component of the investigational medicinal product (IMP) or an allergy to latex.
29. The subject has a condition or is in a situation which, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's compliance or participation in the study.

4.4 Caregiver / Support Person Eligibility and Responsibility

For the purpose of this study, all subjects must have a suitable designated caregiver/support person who must meet the following eligibility criteria:

1. Understand and agree with the potential risks and benefits to subjects as well as the nature of all procedures and restrictions associated with this study
2. Understand, agree to, and sign a separate caregiver/support person's ICF
3. Willing to receive caregiver training related to the conduct of this study

4. Willing and able to administer and/or supervise the administration of all study drugs
5. Willing and able to evaluate the subject's tolerability to study drugs and any associated AEs
6. Able to communicate by phone/email/text message or in person between clinic visits
7. Able to accompany the subject to all clinic visits
8. Available for scheduled weekly phone calls from site personnel
9. Has frequent and sufficient contact with the subject to be able to provide accurate information regarding the subject's cognitive, behavioral and functional abilities at study visits (which require caregiver/support person input for scale completion)

Site personnel will instruct the caregiver / support person about:

- Study drug administration and disposal of empty syringes
- Study drug storage requirements
- The nature of expected AEs
- How to report AEs
- Scheduled weekly phone calls from site personnel

A consistent caregiver/support person is necessary for the conduct of the study. If an unforeseen change in caregiver/support person occurs during the course of study, please inform your assigned Study Monitor immediately. The replacement caregiver/support person must meet all requirements as outlined in the protocol and discussed with the Contract Research Organization (CRO) and/or Sponsor.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened unless the investigator feels that rescreening would be appropriate, the reason for rescreening has been discussed with the Medical Monitor, and Sponsor approval has been obtained. Individuals who are rescreened will receive a new screening number. (Note: clinical

laboratory test results, ECGs, and vital signs may be repeated during Screening if outside the normal range and not considered clinically significant).

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Identity of the Medicinal Products

The products that will be used in this study are outlined in Table 2.

Table 2 Identity of Investigational Products

Study Drug Name	Formulation	Strength	Route	Manufacturer
ATH-1017 40 mg	Injection	40 mg/mL	SC	Patheon
ATH-1017 70 mg	Injection	70 mg/mL	SC	Patheon
Placebo	Injection	NA	SC	Patheon

NA = not applicable; SC = subcutaneous

Pre-filled syringes of active IMP at 40 mg will contain 1.0 mL of 40 mg/mL ATH-1017 in a solution of 10 mM sodium phosphate and 0.5% sodium chloride. Pre-filled syringes of active IMP at 70 mg will contain 1.0 mL of 70 mg/mL ATH-1017 in a solution of 10 mM sodium phosphate. Each pre-filled syringe of placebo will contain 1.0 mL of a solution of 10 mM sodium phosphate and 1.1% sodium chloride. All IMPs are adjusted to pH of approximately 7.6.

5.2 Supply, Packaging, Labeling, and Storage

IMP (ATH-1017 and placebo) will be provided as blinded subject kits and will be labeled according to applicable local and regulatory requirements.

IMP will be stored under refrigerated conditions (between 2°C and 8°C) at study sites in a securely locked area, accessible to authorized persons only. Once dispensed, study subjects may store the product under refrigerated conditions (between 2°C and 8°C) or ambient conditions (between 15°C and 25°C, as supported by stability data).

5.3 Drug Accountability, Dispensing, and Destruction

Randomization and dispensation will be controlled by an interactive response technology (IRT) system. Dispensation will occur every 2 weeks, or as needed, at the study site or by direct-to-patient shipment. Larger provision of study drug will be permitted to accommodate personal need, e.g., vacation. Study subjects will be provided with sharps containers for proper disposal of used IMP.

The caregiver/support person will supervise or record daily administration of IMP. Each site will ship any product materials (kits and sharps containers) to a central location for destruction or will destruct on-site. Reconciliation of IMP will be managed at each study site.

5.4 Subject Identification and Randomization

5.4.1 Screening Numbers

All screened subjects are assigned a unique Screening Number. The Screening Numbers identify subjects from time of Screening until time of randomization. Enrolled subjects who drop out of the clinical study before randomization will retain their Screening Number.

5.4.2 Randomization Numbers

Prior to dosing on Day 1, subjects will be assigned a randomization number generated by an IRT system; the randomization numbers will subsequently be incorporated into the Electronic Data Capture (EDC) system.

Once a randomization number has been allocated to 1 subject, it may not be assigned to another subject.

5.5 Administration of Investigational Medicinal Products

Training on safe and effective use of prefilled syringes will be provided to study subjects and caregivers by site staff. Practice syringes (filled with placebo) in kits and injection pads will be provided to each site. Capable subjects will be allowed to self- administer upon judgment of site staff; those not capable will require caregiver-assisted administration after deemed capable by site staff. If stored at refrigerated conditions, pre-filled syringes should be kept at room temperature for at least 30 minutes after taking out of the refrigerator before administering the injection. The first dose will be administered on Day 1 (Visit 2b) at the clinic site; site staff will be expected to observe dose administration on day of study visit to ensure safe and effective use. Subjects will remain at the clinic site for 2-hour clinical observation (± 15 minutes). The subject may be discharged from the clinic following the 2-hour observation period provided they have no systemic AEs. Should there be AEs of a systemic nature, they should be observed an additional 2 hours. They should in all cases be discharged only after approval of the investigator. Subsequent visits do not have a specified period of observation but in all cases subjects must be discharged by the investigator.

Should self-administration or caregiver-assisted administration not be judged adequate a suitable caregiver must be identified, otherwise subject discontinuation will be required.

5.6 Compliance with Investigational Medicinal Products

IMP compliance will be determined from daily records of IMP administration recorded by the caregiver/support person. If a subject demonstrates consistent poor compliance during the study (< 80%), the investigator should evaluate whether the subject should be discontinued from the study, in discussion with the Medical Monitor. Subjects who are off drug for ≥ 14 consecutive days may be prematurely discontinued from the study, in discussion with the Medical Monitor.

The study centers will keep an accurate drug disposition record that specifies the subject kit ID number, number of kits dispensed to each subject, and the date of dispensation.

5.7 Blinding and Breaking the Blind

The clinical study will be performed in a double-blind manner.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the Principal Investigator in collaboration with the Sponsor and Medical Monitor. The applicable CRO standard operating procedure (SOP) will be followed for blind breaking procedures.

An interim analysis is planned when at least 30 subjects have completed the Week 2 visit (see Section 8.7). Adequate measures will be defined in the final statistical analysis plan (SAP) and implemented with the aim to maintain the blind for all involved in actual study conduct at the Sponsor, the CRO, or any vendor.

After database lock, the overall randomization code will be broken only for reporting purposes.

5.8 Stopping Criteria

For all subjects, at any time during the study, study treatment should be discontinued and the subject will be withdrawn immediately if any of the following criteria/AEs are recorded:

- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 8 × upper limit of normal (ULN)
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN, or international normalized ratio [INR] > 1.5
- ALT or AST > 3 × ULN with symptoms (the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%)
- AEs:
  - Any SAE confirmed as probably or definitely related to the IMP
  - Any AE of severe intensity confirmed as probably or definitely related to the IMP and associated with clinically significant findings
    (Note: causality as determined by the Sponsor)

- ECG criterion:
  - QTcF > 500 msec (if prolonged QTcF interval is observed during the study, then a minimum of 2 repeat ECGs should be obtained over a brief period. The mean of the 3 ECGs will be used to determine this stopping criterion).

For QTcF readings that are borderline, or difficult to interpret due to e.g., presence of a branch bundle block, or in those where the T and U waves are superimposed or connected, a manual, local reading using the same ECG device should be considered to determine applicability of this ECG stopping criterion, in discussion with the Medical Monitor. Baseline conditions should be taken into account when considering the ECG stopping criterion (see Section 4.3, exclusion criterion #17).

In addition, if any of the above criteria are met, the event must be reported and discussed with the Medical Monitor.

5.9 Treatment of Overdose

Overdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is above the maximum recommended dose according to the protocol for the study treatment (see Section 6.4.1.1 for reporting of overdose). This also takes into account cumulative effects due to overdose.

There is no prior knowledge of clinical symptoms occurring with ATH-1017 overdose. In case of suspected or reported overdose, treatment of any clinical signs will be symptomatic.

5.10 Treatment after the End of the Study

Access to study treatment will be limited to the period of study participation.

Upon discontinuation of double-blind treatment, subjects will return to their original medication; tapering off study medication is not required.

The investigator will determine whether additional care is needed after the subject completes or discontinues from the study.

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Screening Assessments

6.1.1 Montreal Cognitive Assessment (MOCA)

The MOCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.

The total possible score is 30 points; a final total score of 26 and above is considered normal.

The MOCA is administered at Screening only; a score of 11 to 23 inclusive is required to meet the subject eligibility criterion.

6.2 Clinical Effect Variables

As specified by each assessment scale, a qualified, trained and certified rater will administer questionnaires to the study subject and/or dedicated support person/caregiver. Rater training and certification (as applicable) will occur, and if necessary be repeated, in a standardized manner.

[redacted] ADAS-Cog13, [redacted] assessments should be done in the same time frame at all visits, in the morning.

6.2.1 Cognitive Variables

[redacted]

6.2.1.2 Alzheimer's Disease Assessment Scale – Cognitive Subscale, 13-Item Version (ADAS-Cog13)

The ADAS-Cog13 is designed to measure cognitive symptom change in subjects with MCI as well as AD (Mohs, 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.

Due to known circadian fluctuations of cognitive capacity (Hilt, 2015), ADAS-Cog$_{13}$ will be assessed in the morning at approximately the same time of day as the baseline assessment for all applicable visits.

ADAS-Cog$_{13}$ assessments will be performed pre-dose at Visit 2b (Baseline/Day 1), and post-dose at approximately 1 hour (± 30 minutes) at Visit 3 (Week 2), Visit 5 (Week 12), Visit 7 (Week 20), and Visit 8/ET (Week 26).

[redacted]

[redacted]

6.2.2.6 [redacted]

[redacted]

6.3 Pharmacodynamic Variables

Pharmacodynamic variables will consist of ERP P300 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, 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, 2011).

To assess the P300 wave (latency and amplitude), the subject is in a semi-sitting position, eyes closed, and has to perform a task related to auditory stimuli. The stimulus consists of an oddball paradigm with 2 sound stimuli. Stimuli are presented through headphones and auditory stimulation for P300 will be assessed in a recording lasting up to 10 minutes.

ERP P300 will be performed at the Pre-baseline visit (Visit 2a, Day -10 to Day -3, no dosing). ERP P300 data should be uploaded for quality check immediately after the completion of the Pre-baseline visit (Visit 2a).

At Baseline/Day 1 (Visit 2b), ERP P300 will be performed at pre-dose following the completion of baseline assessments of [redacted],ADAS-Cog$_{13}$, and [redacted] up to 1.5 hour before dose in clinic. EEG will be assessed post-dose at approximately 2 (±1) hours after IMP dosing.

At Visits 3, 5, and 8, ERP P300 will be performed at pre-dose up to 1 hour before dose in clinic. ERP P300 will be assessed post-dose following the completion of [redacted] ADAS-Cog$_{13}$, [redacted] assessments, at approximately 2 (±1) hours after IMP dosing.

ERP P300 will also be performed at the Safety follow-up visit (Visit 9, no dosing).

6.4 Safety Variables

6.4.1 Adverse Events

AE reporting will begin at Screening (Visit 1) and will continue until the end of the study (28 days from last dose of IMP, Visit 9 – Safety Follow-up). AEs will be reported by the subject (or, when appropriate, by a caregiver, support person, or the subject's legally authorized representative).

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 6.4.1.5).

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 (eg, 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: pre-existing conditions will be recorded as part of the subject's medical history).

6.4.1.2 Recording of Adverse Events

AEs should be collected and recorded for each subject from signing informed consent until the end of their participation in the study, i.e., from Screening until the subject has discontinued or completed the study, including the post-treatment Safety Follow-up period at the timepoints specified in the Schedule of Assessments (Table 1). AEs identified after signing the ICF and before dosing will be recorded as pre-treatment AEs. If AEs occur, the first concern will be the safety of the study subjects.

AEs may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be recorded together with the investigator's assessment of the seriousness of the AE and causal relationship to IMP and/or study procedure on an AE electronic case report form (eCRF).

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor and/or CRO. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom.

6.4.1.3 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. The subject 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 3 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.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**

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 requirements.

Table 3 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 fulfill 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 re-administered 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.

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 inpatient 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 fulfills 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.

6.4.1.4 Reporting of Serious Adverse Events

Prompt (within 24 hours) notification by the investigator to the Sponsor's designated Drug Safety and Pharmacovigilance vendor, i.e., MMS, of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

The investigator will review each SAE and evaluate the intensity and the causal relationship of the event to IMP/study procedure. All SAEs will be recorded from signing of informed consent until completion of the Safety Follow-up. SAEs occurring after the Safety Follow-up Visit and coming to the attention of the investigator must be reported only if there is (in the opinion of the investigator) reasonable causal relationship with the IMP.

The investigator is responsible for updating the EDC and providing notification to MMS Drug Safety and Pharmacovigilance of any SAE, whether deemed IMP-related or not, that a subject experiences during their participation in study within 24 hours of becoming aware of the event to:

[redacted]

MMS Drug Safety and Pharmacovigilance is responsible for providing notification to the Sponsor of any SAE as soon as they become aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Identifiable subject
- Identifiable event (including causality assessment)
- Identifiable IMP

- Identifiable reporter

MMS Drug Safety and Pharmacovigilance will request clarification of omitted or discrepant information from the initial notification. The Principal Investigator or an authorized designee is responsible for faxing or emailing the requested information to MMS Drug Safety and Pharmacovigilance within 24 hours of the request.

It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of appropriate completion of an SAE Report Form. Additional information (copies of laboratory reports, consultant reports, copies of discharge summaries, etc.) should be provided on request to MMS Drug Safety and Pharmacovigilance. If an SAE Report Form is faxed or emailed, then the Principal Investigator must sign and date the form.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report Form within the designated reporting time frames. Contacts for SAE reporting can be found on the protocol title page

All SAE reports submitted by the investigator will be reviewed by the study Sponsor and assessed for meeting criteria of suspected unexpected serious adverse reactions (SUSARs). All SUSARs will be reported by the Sponsor to competent national authorities and investigators according to local regulatory requirements and Sponsor policy.

An investigator who receives an individual case safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

6.4.1.5 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. If a subject is lost to follow-up and has not answered any phone calls from the site (at least 3 calls), a final proof of contact via certified letter is required (see Section 7.5).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor and/or CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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.

The investigator will attempt to collect pregnancy information on (i) any female participant or (ii) male participant's female partner (after obtaining the necessary signed informed consent) who becomes pregnant while participating in this study.

The investigator will record pregnancy information on the appropriate form and submit it to MMS Drug Safety and Pharmacovigilance within 24 hours of learning of the pregnancy. The pregnant participant /female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

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

6.4.3 Clinical Laboratory Assessments

The following laboratory variables will be determined as outlined in Table 4 below:

Table 4 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 as described in Section 5.8.

A medical alert for potential Hy's laws cases (possible drug-induced liver injury) will be issued based on laboratory values and supported by Medical Monitor interpretation. Investigators, the Sponsor, Medical Monitor, and MMS (the Sponsor's designated vendor for Drug Safety and Pharmacovigilance) will immediately be notified when the above criteria have been met through a central laboratory alert. The AE eCRF should be completed within 3 business days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Medical Monitor and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

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

Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the subject signs the ICF for the study until 4 weeks after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

Any clinically significant abnormalities from Screening labs must be discussed with the Medical Monitor to confirm eligibility of the subject. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the safety follow-up visit, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized.

6.4.4 Vital Signs

Vital signs will be assessed pre-dose at the timepoints detailed in the Schedule of Assessments (Table 1). 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.

Orthostatic blood pressure will be recorded as specified in Table 1. 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

Weight will be measured at Screening (for calculation of BMI as part of the eligibility criteria), at Baseline/Day 1 (Visit 2b), Visit 5 (Week 12), Visit 8 (Week 26), and Visit 9 (Safety follow-up).

6.4.6 12-Lead Electrocardiogram

Standard safety 12-lead ECGs will be performed at Screening, at pre-dose and 30 (± 15) minutes post-dose on Day 1 and 30 (± 15) minutes post-dose at all other visits. All ECGs will be performed in triplicate, as detailed in the Schedule of Assessments (Table 1).

The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. 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, and QTcF.

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

Physical and neurological examination will be performed by the investigator or designee at the timepoints detailed in the Schedule of Assessments (Table 1).

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).

Body weight (kg) and height (meters) will be assessed at Screening. Body weight and height will be used to calculate BMI using the following formula: weight (kg)/[height (m)]^2.

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.

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

The C-SSRS will be performed at Screening, Baseline/Day 1 (Visit 2b), Visit 3 (Week 2), Visit 4 (Week 6), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), Visit 8/ET, and Visit 9 (Safety follow-up) (Week 30) (Table 1). 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. If items 1 to 5 of the C-SSRS have a positive response and are of clinical concern, as judged by the investigator during the study, the Medical Monitor must be contacted.

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, 1986). The total score range is 0 to 15, with a higher score indicating more severity. A GDS score of ≤ 7 is required at Screening. In discussion with the Medical Monitor, subjects with a GDS score between 8 and 10 inclusive can be considered for study participation if the increased score is driven by specific domains related to the pandemic and its restrictions, rather than by major depression.

GDS assessments will be performed at Screening, Visit 2b (Baseline/Day 1), Visit 5 (Week 12), Visit 8/ET (Week 26), and Visit 9 (Safety follow-up).

[redacted]

6.6 Genotyping

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

[redacted]

7 STUDY CONDUCT

- Study procedures and their timing are summarized in the Schedule of Assessments (Table 1).

- Protocol exemptions related to enrollment criteria are only allowed with prior investigator, Medical Monitor, and Sponsor approval, supported by documented agreement from the IRB/IEC.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Screening procedures may be conducted on up to 2 separate dates if necessary to accommodate subject and study center schedule. However, every effort should be made to conduct all procedures as early as possible in the screening period. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Due to the quantitative functional biomarker nature of this study, particular precautions will have to be implemented at each site for the electrophysical assessments, i.e. availability of a dedicated quiet EEG room with controlled lighting and temperature.

7.1 Schedule and Order of Assessments

The study will consist of up to 28 days of Screening (Day -32 through Day -4), a Pre-baseline visit (Visit 2a, Day -10 to Day -3), Baseline (Visit 2b, Day 1, randomization), followed by 26 weeks of double-blind treatment, and a 4-week safety follow-up. Note: if 28 days is not sufficient to complete the screening period, the possibility of an extension can be discussed with the Medical Monitor.

All assessments to be performed during the study are detailed by visit/timepoint in Table 1. For clinical outcome assessments evaluating subject's cognitive condition, the general order should be followed:

(1) [redacted]
(2) ADAS-Cog$_{13}$
(3) [redacted]
(4) ERP P300 assessments

All cognitive assessments including MMSE, ADAS-Cog$_{13}$, and [redacted] shall occur at clinic visits in the morning, in the specified order when applicable.

[redacted]

ADAS-Cog$_{13}$ assessments will be performed pre-dose at Baseline/Day 1 (Visit 2b), and post-dose at approximately 1 hour (± 30 minutes) at Week 2 (Visit 3), Week 12 (Visit 5), Week 20 (Visit 7), and Week 26 (Visit 8).

[redacted]

[redacted]

The order of assessments and timing for all other endpoints [redacted] are flexible.

7.1.1 Unscheduled Visit(s)

An unscheduled visit may be performed at any time during the study as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording should be performed by the investigator. Other procedures and evaluations will be completed as deemed necessary by the investigator and may include (but not limited to) laboratory tests, ECG, vital signs, and physical examination. Please ensure to discuss with the Medical Monitor prior to conducting any unscheduled visit.

7.2 Pandemic Response

In the event of a pandemic that impacts study conduct, the following protocol changes will be implemented should the situation arise (implementation should be discussed on a case-by-case basis, with sponsor approval):

- Visit 1 (Screening), Visit 2 (Pre-baseline, Day -10 to Day -3; Baseline/Day 1), Visit 5 (Week 12), Visit 8 (Week 26), and Visit 9 (Safety follow-up) are considered **essential visits**, and these visits need to be conducted on-site, with proper site arrangements to protect the safety of study participants and site staff, including personal protection equipment, proper spacing between subjects to avoid crowding and allow proper cleaning, transportation arrangements, etc. (full details will be agreed with the CRO and study sites)

- Visit 3 (Week 2), Visit 4 (Week 6), Visit 6 (Week 16), and Visit 7 (Week 20) should be conducted on-site if conditions permit, but flexibility will be allowed upon agreement between sites, CRO, and sponsor. These visits are to be completed according to one of the following options:

    a. On-site visit with proper safety arrangements
    b. Site staff visit to the subject at home
    c. Travel nurse visits the subject at home
    d. Tele-health using phone, video call, or others
    e. Subject goes to local laboratory for biological samples to be taken

Any coronavirus disease – 2019 (COVID-19) vaccinations received before screening and during the study through to the Safety follow-up visit will be recorded, and specific guidance in relation to visits will be provided.

7.3 Concomitant Medications and Treatments

7.3.1 Prohibited Treatments During the Study

Concomitant use of the following drugs is excluded within 4 weeks prior to Screening and for the duration of the study. All allowed medications should remain stable throughout the study; for medications affecting cognition, the doses should be stable for at least 4 weeks before Screening and throughout the study, unless otherwise noted.:

- Selegiline and trihexyphenidyl in any form or dosage.

- Memantine in any form, combination, or dosage.

- Donepezil at 23 mg.

The following drugs are prohibited during the study:

- Psychoactive medications (including antipsychotics, tricyclic antidepressants, anxiolytics or sedative hypnotics, including barbiturates) having significant anticholinergic effects and/or believed to affect cognitive function (for exceptions see Section 7.3.2).

- Nicotine therapy (including patches), varenicline (Chantix), or similar therapeutic agent.
- Peripherally acting drugs with effects on cholinergic neurotransmission, e.g., oxybutinin (for exception see Section 7.3.2).
- Systemic immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses in the judgment of the investigator (for exceptions see Section 7.3.2).
- Antiepileptic medication.
- Chronic intake of opioid containing analgesics; PRN use is allowed (but not within 72 hours before any cognitive assessment).
- Sedating H_1 antihistamines; non-sedating H_1 antihistamines are allowed and preferred.
- Systemic moderate to strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, fluconazole, cimetidine, clarithromycin, erythromycin, troleandomycin) (see Appendix 1: List of Prohibited Medications for non-exhaustive list).
- Systemic moderate to strong CYP3A4 inducers (e.g., carbamazepine, rifabutin, ritonavir, and St. John's wort) (see Appendix 1: List of Prohibited Medications for non-exhaustive list).

Subjects that use prohibited medications listed above during the double-blind treatment period of the study may be discontinued from study drug.

Note: The discontinuation of a subject due to use of a prohibited medication shall be discussed between the investigator, Medical Monitor, and Sponsor. The investigator should contact the Medical Monitor prior to discontinuing a subject for disallowed medications.

See Appendix 1: List of Prohibited Medications for a non-exhaustive list of prohibited medications.

7.3.2 Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

In this study, subjects may be taking a stable dose of acetylcholinesterase inhibitors (e.g., rivastigmine), as long the dose and dosage form have been stable for 3 months prior to Screening and no changes are planned during the study.

Solifenacin is allowed if the subject has received a stable dose for at least 3 months before Screening.

The dosage(s) of other allowed concomitant medications should have been stabilized for at least 4 weeks prior to Screening and should remain constant during the course of the study. For concomitant medications that affect cognition, the dosage(s) must have been stabilized for at least 4 weeks prior to Screening and should remain constant during the course of the study. With the exception of medications listed in the Exclusion Criteria (Section 4.3), in Section 7.3.1, and below, concomitant medications will be allowed at the investigator's discretion. When in doubt, the Medical Monitor should be contacted.

In close communication with the Medical Monitor, low doses of antipsychotics (except clozapine) may be allowed if the subject has received a stable dose for at least 4 weeks before Screening. If these medications are taken on a PRN basis, they should not be taken the morning before any cognitive testing. Pimavanserine and aripiprazole (oral) are allowed.

Low doses (in the judgment of the investigator) of anxiolytics may be given PRN but not the night before any cognitive assessments. Barbiturates are allowed only if given for benign tremor in low doses (in the judgment of the investigator). Zolpidem is allowed.

With the exception of tricyclic antidepressants, irreversible MAO-B inhibitors, and S-ketamine, all other antidepressant medications are allowed.

Immunosuppressants in the form of inhaled steroids, otics, opthalmologics, skin creams, and intra-articular injections are allowed.

Topical application of moderate to strong cytochrome P450 3A4 inhibitors or inducers is allowed.

If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

7.3.3 Other Restrictions

7.3.3.1 Food and Food Supplements

The consumption of grapefruit or grapefruit-containing products is prohibited beginning 7 days prior to the first dose of study medication (Day 1) and during the study.

Food supplements and nutraceuticals with potential effects on cognition, such as Axona, tryptophan supplements, and MCT, are excluded during the study, beginning 7 days prior to the first dose of study medication (Day 1). Tetrahydrocannabinol (THC) is prohibited beginning 4 weeks prior to the first dose of study medication (Day 1) and for the duration of the study.

Cannabidiol (CBD) without THC is allowed but not on the clinical visit days, except for topical applications. CBD use should be recorded as concomitant medication.

7.3.3.2 Contraceptives

Sexually active males and females and their partners must ensure that a double barrier method of contraception is used (i.e., condom plus diaphragm, condom or diaphragm plus spermicide gel or foam) for the duration of the study, including the 4-week safety follow-up period.

7.4 Subject Withdrawal

A subject's participation in the study may be discontinued at any time at the discretion of the investigator and/or Sponsor, in accordance with his/her best professional judgment. However, it is encouraged that the investigator contacts the Sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a subject from the study. Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the Sponsor and will be clearly documented on the appropriate eCRF.

7.4.1 Discontinuation of Study Treatment

All subjects who permanently discontinue study treatment, for whatever reason, will be withdrawn from the study. Upon discontinuation of study drug, subjects will continue with their original treatment; tapering off study medication is not required.

See the schedule of activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed (Table 1).

7.4.2 Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, including protocol deviations

- Subjects must be discontinued from the study and/or receive no further study treatment, if any of the following criteria are met:

    - Any of the stopping criteria described in Section 5.8

    - Any AE or safety finding that may jeopardize the subject's health in the investigator's judgment, and which is considered to be at least possibly related to the study drug.

    - Withdrawal of informed consent by subject/legally authorized representative. In the event that a subject's decision to withdraw from the study is motivated by adverse

event(s) or stated lack of efficacy, these reasons should be recorded as the reason for early termination.

  - Physician decision
  - Non-compliance with study drug
  - Site terminated by sponsor
  - Repeat incapacity of subject and/or caregiver (in the judgment of the investigator) to properly administer study drug despite training and testing
  - Prolonged or definitive loss of caregiver without adequate replacement
  - Nursing home placement

- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- All subjects who prematurely discontinue from the study, i.e., prior to Visit 8 (Week 26), unless the cause is screen failure, should return for an early termination visit and complete all the assessments scheduled for the Week 26 visit (Visit 8); see the schedule of activities (Table 1) for data to be collected.
- Unless the reasons of premature discontinuation prevent further meaningful testing, investigators should make every effort to motivate subjects who discontinue early (and caregiver) to return for a Visit 8 (Week 26) for final assessments

Upon discontinuation of study drug, subjects will continue with their original treatment; tapering off study medication is not required.

7.5 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit

schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls/emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's study records.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.6 Termination of the Clinical Study

The Sponsor designee reserves the right to close the study site(s) or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines

- Inadequate recruitment of participants by the investigator

- Discontinuation of further study treatment development

8 STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the clinical study report.

8.1 Populations for Analysis

8.1.1 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.

8.1.2 Per protocol population

The per protocol population will include all mITT subjects who were medication compliant during the 26 weeks of double-blind treatment (as defined in Section 5.6) and 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 analyzed based on actual treatment received.

8.1.3 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.

8.2 General Considerations

Descriptive statistics for continuous variables will include number of subjects (n), arithmetic mean, standard deviation, median, minimum, maximum and first and third quartile limits unless otherwise noted. Frequency and percentage will be calculated for categorical variables.

Change from baseline is calculated by subtracting the baseline score from the observed value at any subsequent visit. 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.

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.

8.3 Clinical Effect Analyses

8.3.1 Primary Clinical Effect Analysis - GST

The primary hypothesis is that treatment with ATH-1017 will result in a statistically significant reduction in change from baseline in the GST score (O'Brien, 1984) (combining the ADAS-Cog$_{13}$ score and the change from baseline in ERP P300 at Week 26) relative to the placebo group in the mITT population. The primary analysis will test the statistical hypothesis of no difference between placebo and 70 mg ATH-1017 first and then 40 mg ATH-1017 versus placebo.

The primary analysis will use a mixed model with repeated measures (MMRM) to compare the estimated change from baseline between active treatment and placebo in the GST score. This analysis will assess whether or not there is a difference in estimated GST values between treatment groups and placebo at 26 weeks using least squares means estimates from the MMRM model, and will include terms for baseline, baseline by time interaction, and baseline by time by treatment interaction in the model. Additional terms will be included for GBA genotype, and site (with smaller sites grouped), and age. Least squares means and standard errors will be estimated from the MMRM model at Week 26. Further details relating to the primary analysis will be described in the SAP.

8.3.2 Secondary Analysis – ADAS-Cog$_{13}$ and ERP P300

The separate secondary variables of ADAS-Cog$_{13}$ and ERP P300 will be analyzed using the same MMRM model that was used for analysis of the primary endpoint.

[redacted]

8.4 Safety Summaries

The Safety population will be used for analyses of each of the safety endpoints. All concomitant medications will be tabulated according to drug class and preferred term using the World Health Organization Drug dictionary. Clinical laboratory tests, vital signs, physical and neurological examinations, and ECG results will be summarized by number of subjects, frequency rates and by treatment group. The timepoint of each event will also be summarized.

8.4.1 Adverse Events

AEs occurring after the start of study drug dosing on Day 1 will be summarized descriptively for the Safety population. All AEs will be coded according to system organ class and preferred term using a Medical Dictionary for Regulatory Activities dictionary. Summary tables showing the number of subjects and percentage within each category will be generated for each of the following types of AEs:

- All events
- Serious events
- Deaths
- Events leading to study discontinuation
- Events related to study treatment (study drug and injection procedure separately)
- Severe events

8.4.2 Laboratory parameters

Laboratory parameters and vital signs will be summarized by visit. Frequencies of high and low values with respect to the normal range will be displayed, as will shift tables comparing results at each treatment visit.

8.4.3 12-Lead Electrocardiogram

12-lead ECG data (observed and change from baseline) will be listed for each subject by visit. Observed values and change from baseline will be summarized descriptively.

8.4.4 Columbia-Suicide Severity Rating Scale

Results from the C-SSRS questionnaire will be listed and summarized using descriptive statistics by treatment group and visit.

8.4.5 Geriatric Depression Scale

Results from the GDS questionnaire will be listed and summarized using descriptive statistics by treatment group and visit**.**

[redacted]

8.6 Determination 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.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The CRO/Sponsor will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study subject.

Audio recording for certain clinical assessments, including [redacted] MOCA, [redacted] and ADAS-Cog$_{13}$ will be done for quality control purposes. No personal identifying information will be included in the recording.

The investigator is responsible for ensuring that data are properly recorded on each subject's eCRF and related documents in a timely manner. An investigator who has signed the protocol signature page should electronically sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted in a timely manner, or as otherwise specified by the Sponsor, and will be maintained in a central data repository.

Frequent communication between the study site and the CRO/Sponsor is essential to ensure that the safety of the study is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.2 Access to Source Data/Documents

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.

The investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. Data reported or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE, and concomitant medication reporting, raw data collection forms, as well as the results of diagnostic tests such as MRI scans and laboratory tests) designed to record all observations and other pertinent data for each subject receiving IMP.

The investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IRB/IEC to have direct access to all documents pertaining to the study.

9.3 Archiving Study Documents

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.4 Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the investigator abide by the ICH Tripartite Guideline for GCP (E6) and with other applicable regulatory requirements. The clinical study also will be carried out in keeping with national and

local legal requirements (in accordance with United States Investigational New Drug Regulations [21 CFR 56]).

9.5 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor or designee with sufficient, accurate financial information as requested to allow the Sponsor or designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.6 Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject or his/her legally authorized representative (LAR) according to the applicable regulatory and legal requirements. As part of this procedure, the investigator or appropriately qualified designee must explain orally and in writing (when possible) the nature, duration, and purpose of the study and the action of the IMP in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur, and answer all questions regarding the study. The study subject should be informed that their participation is voluntary and that he/she is free to withdraw from the study at any time. If a subject, LAR, and caregiver/support person is not able to review consent in person at the clinic due to travel restrictions, documented oral review by the investigator or appropriately qualified designee with the subject, LAR, and caregiver/support person must occur and be documented in the subject's study records.

Subjects or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center. The investigator or designee will provide the CRO with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; the authorized person obtaining the informed consent must also sign the ICF. One copy will be provided to the subject/LAR and to the caregiver/support person, and the investigator will retain a copy as part of the clinical study records.

If the caregiver/support person is different from the LAR, a specific ICF must be explained and this person be consented to the tasks and duties during the study; since many assessments rely only on the input from the caregiver/support person, it is important they understand fully their role in the trial. The investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the informed consent document(s) may need to be revised to reflect the changes to the protocol. If the informed consent document(s) are revised, they must be reviewed and approved by the responsible IRB/IEC, and signed by all subjects/ LARs/caregiver/support persons subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.7 Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the Sponsor and receive IRB/IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

9.8 Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, Investigator Brochures, and other material) will be stored appropriately to ensure their confidentiality. The investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the investigator. The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject/LAR.

9.9 Publication Policy

By signing the clinical study protocol, the investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent

authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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11 APPENDICES

11.1 Appendix 1: List of Prohibited Medications (Non-exhaustive Examples)

This is not an exhaustive list; if the permissibility of a specific medication is in question, please contact the Medical Monitor.

Category of Prohibited Medications	Examples: General Name (Trade Name)
NMDA receptor antagonists	• Memantine (Namenda) in any form, combination or dosage • Dextromethorphan
High-dose donepezil	• Donepezil (Aricept) at 23 mg
Dopamine receptor antagonists (not antipsychotics)	• Metoclopramide (Reglan)
Peripherally acting anticholinergics (exception: solifenacin [Vesicare] is allowed)	• Fesoterodine (Taviaz) • Oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol) • Tolterodine (Detrol, Detrol LA) • Trospium (Sanctura, Sanctura XR)
Nicotine therapy	• Nicotine patches, gum, sprays, inhalers, lozenges, etc. • Varenicline (Chantix) or similar therapeutic agent
Psychoactive medications having significant anticholinergic effects and/or believed to affect cognitive function including antipsychotics (Exclusion Criterion 26(d)), anti-depressants (tricyclics, irreversible MAO-B inhibitors (Exclusion Criterion 26(f)), anxiolytics (Exclusion Criterion 26(g)) or sedative hypnotics (Exclusion Criteria 26(h) and 26(i))	Antipsychotics (please refer to Exclusion Criterion 26(d) [Section 4.3] for conditions under which antipsychotics may be allowable): • Haloperidol (Haldol, Serenace) • Pimozide (Orap) • Perazine (Peragal, Perazin, Pernazinum, Taxilan) • Perphenazine (Trilafon) • Prochlorperazine (Compazine) • Promethazine (Avomine, Phenergan) • Trifluoperazine (Stelazine) • Clopenthixol (Sordinol) • Tiotixene (Navane, Thixit) • Loxapine (Adasuve, Loxitane) • Amoxapine (Asendin) • Asenapine (Saphris, Sycrest) • Clozapine (Clozaril) • Iloperidone (Fanapt, Fanapta) • Lurasidone (Latuda) • Olanzapine (Zyprexa) • Paliperidone (Invega) • Quetiapine (Seroquel)

Category of Prohibited Medications	Examples: General Name (Trade Name)
	• Risperidone (Risperdal) • Trimipramine (Surmontil) • Ziprasidone (Geodon, Zeldox) Antidepressants (tricyclics and irreversible MAO-B inhibitors): • Selegiline (Eldepryl, Emsam) • Clomipramine (anafranil) • Imipramine (tofranil, Janimine, Praminil) • Desipramine (Norpramin, Pertofrane) • Nortriptiline (Pamelor, Aventyl, Norpress) • Protriptyline (Vivactil) • Amitriptyline (Tryptomer, Elavil, Endep) • Amitripyilinoxide (Amioxid, Ambivalon, Equilibrin) • Amoxapin (Asendin) • Trimipramine (Surmontil) • Doxepin (Adapin, Sinequan) Other: • Trihexyphenidyl (Artane) • Sedating H_1 antihistamines • Chronic opioids • S-ketamine • Anti-epileptics
Moderate or strong CYP3A4 inhibitors	• Boceprevir (Victrelis) • Cimetidine • Clarithromycin (Biaxin, Prevpac) • Conivaptan (Vaprisol) • Diltiazem • Erythromycin • Fluconazole • Indinavir (Crixivan) • Itraconazole (Onmel, Sporanox) • Ketoconazole (Exina, Ketozole, Nizoral) • Lopinavir/ritonavir (Kaletra) • Mibefradil • Nefazodone (Serzone) • Nelfinavir (Viracept) • Posaconazole (Noxafil) • Ritonavir (Norvir) • Saquinavir (Fortovase, Invirase) • Telaprevir (Incivek) • Telithromycin (Ketek)

Category of Prohibited Medications	Examples: General Name (Trade Name)
	• Troleandomycin • Verapamil • Voriconazole (Vfend)
Moderate or strong CYP3A4 inducers	• Avasimibe • Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro, Teril) • Mitotane (Lysodren) • Modafinil *(at doses 400 mg/day and above)* • Nafcillin (Unipen, Nallpen) • Phenobarbital (Solfoton, Luminal) • Phenytoin (Dilantin, Cerebyx, Phenytek, Phenytex) • Primidone (Mysoline) • Rifampin (Rifater, Rimactane, Rifamate, Rifadin) • St. John's wort • Rifabutin (Mycobutin) • Ritonavir (Norvir)
Systemic immunosuppressants	• Tacrolimus • Sirolimus • Cyclophosphamide • Methotrexate • Azathioprine • Prednisone • Prednisolone • Methylprednisolone