Clinical Study Protocol

A Randomized, Placebo-Controlled, Double-Blind Study of ATH-1017 Treatment in Subjects with Mild to Moderate Alzheimer's Disease

Sponsor:	Athira Pharma, Inc. 18706 North Creek Parkway Suite 104 Bothell, WA 98011 USA
Protocol No.:	ATH-1017-AD-0201
IND No.:	135103
Investigational Medicinal Product (IMP) Name:	Fosgonimeton (ATH-1017)
Development Phase:	Phase 2/3
Emergency Telephone Number:	(Refer to the study contacts page)
SAE Reporting FAX Number/Email:	[redacted]
Date of Final Protocol:	21-MAR-2024
Version	8

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 Mild to Moderate Alzheimer's Disease

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 Mild to Moderate Alzheimer's Disease

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.

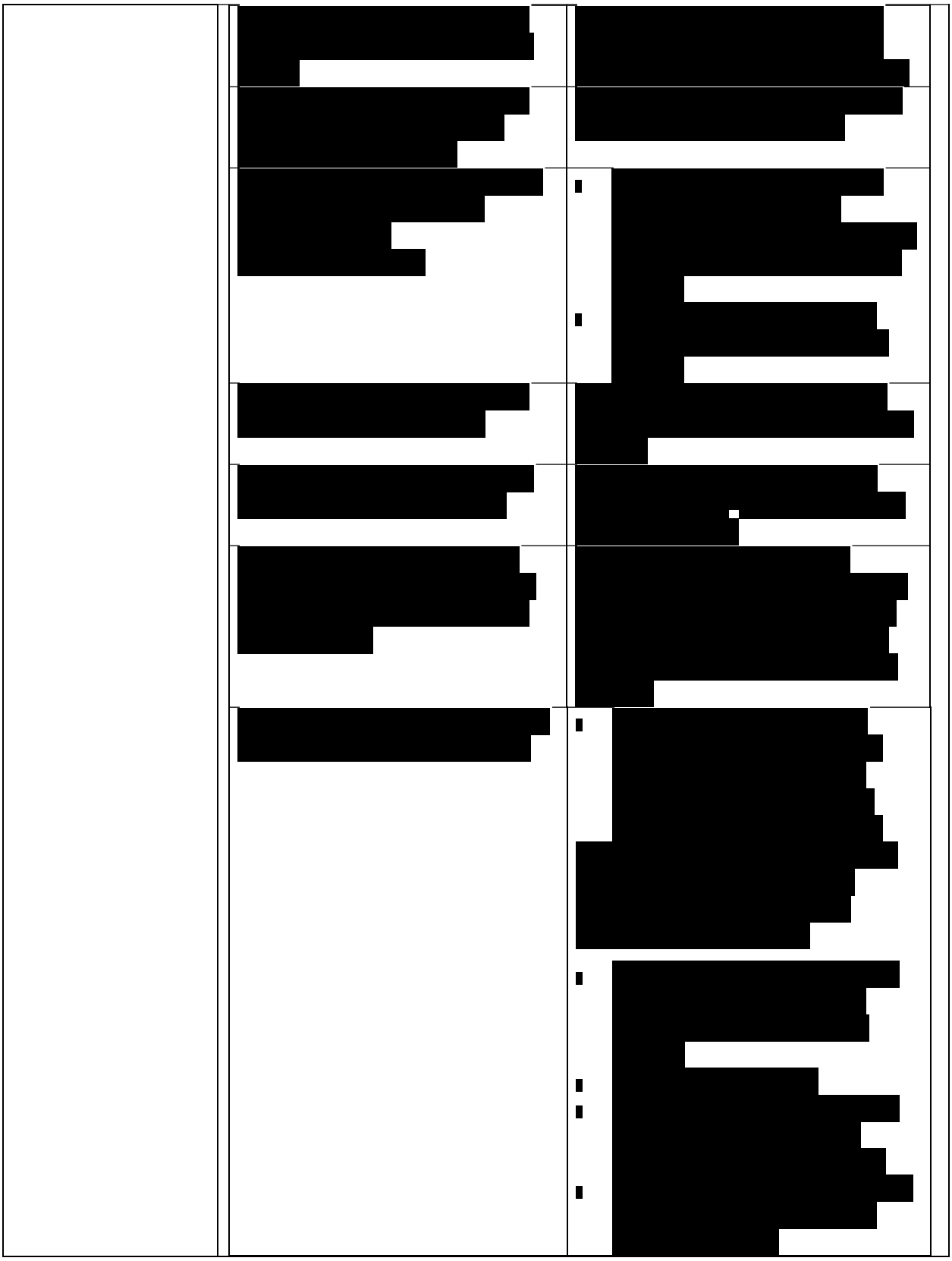
Signature of Site Principal Investigator	Date (DD MMM YYYY)
Printed Name of Site Principal Investigator	

Institution
Name:_____

PROTOCOL SYNOPSIS

Protocol Title:	A Randomized, Placebo-Controlled, Double-Blind Study of ATH-1017 Treatment in Subjects with Mild to Moderate Alzheimer's Disease
Study Number:	ATH-1017-AD-0201
Development Phase:	Phase 2/3
Sponsor:	Athira Pharma, Inc.
Type of Study	Interventional
Study Centers:	The study will be conducted at a total of approximately 70 centers in the US
Study Objectives and Endpoints:	

Primary Efficacy Objectives	**Primary Efficacy Endpoint***
To evaluate the clinical efficacy of ATH-1017 in subjects not on background acetylcholinesterase inhibitors (AChEIs)	The Global Statistical Test (GST) score (O'Brien, 1984) is a composite of cognition and function, calculated as the average of two change from baseline z-scores; the z-scores are calculated for the change from baseline scores for cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog_{11}]) and function (Alzheimer's Disease Cooperative Study – Activities of Daily Living, 23-item version [ADCS-ADL23] score) at Week 26
Key Secondary Efficacy Objectives	**Key Secondary Efficacy Endpoints***
To evaluate the clinical efficacy of ATH-1017 in subjects not on background AChEIs separately on: (1) cognition and (2) activities of daily living	• ADAS-Cog_{11} score: change from baseline at Week 26 • ADCS-ADL23 score: change from baseline at Week 26
To determine the effect of ATH-1017 on plasma neurofilament light chain (NfL) levels in subjects not on background AChEIs (a biomarker of neurodegeneration with literature support for being a biomarker of Alzheimer's disease [AD] progression)	Change from baseline in NfL concentration at Week 26
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



	[redacted] change from baseline at Week 20

Safety Objective	Safety Endpoints
To determine the safety and tolerability of ATH-1017	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)

* The comparison between ATH-1017 40 mg/once daily (qd) and placebo in subjects not on background AChEIs will serve as the primary efficacy comparison for the primary and key secondary endpoints. [redacted]

Study Design:	This is a Phase 2/3 multicenter**,** randomized, double-blind, placebo-controlled, parallel-group study comparing ATH-1017 treatment with placebo in subjects with a clinical diagnosis of mild to moderate AD, diagnosed on a 'probable' level according to the National Institute on Aging – Alzheimer's Association (NIA-AA; McKhann, 2011). The study will be conducted at a total of approximately 70 centers in the US. 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. Prior to protocol version 7, subjects meeting all inclusion/exclusion criteria were randomized in a ratio of 1:1:1 to 3 parallel arms, either to treatment (ATH-1017 40 mg/qd or ATH-1017 70 mg/qd or placebo. As of protocol version 7, randomization to ATH-1017 70 mg/qd was discontinued, and all subjects will be randomized in a ratio of 1:1 to 2 parallel arms, either to receive ATH-1017 40 mg/qd or placebo. Subjects randomized to ATH-1017 70 mg/qd prior to protocol version 7 will continue their regimen until either study completion or early termination. During randomization, subjects will be stratified by screening Mini-Mental State Examination (MMSE) severity: mild (MMSE: 20-24) versus moderate (MMSE: 14-19). All eligible subjects will be tested for apolipoprotein E (ApoE) genotype. Study drugs will be administered by subcutaneous (SC) injection qd preferably during daytime. Subjects should not take more than one dose within 8 hours. The first SC injection of study drug will be performed at 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 randomized 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 trial at Week 30 (see Table 1 for Schedule of Assessments). On Day 1, after completion of the first dose, subjects will remain on-site 2 hours for post-treatment clinical observation subject to the conditions in Section 5.5 of the protocol. As marked circadian fluctuations of cognitive performance have been observed in AD (Hilt, 2015), ADAS-Cog_{11}, [redacted] assessments should occur at clinic visits in the morning at approximately the same time they were performed during the initial Baseline assessment. [redacted] 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. Subjects enrolled at participating sites may seamlessly enroll onto the open-label extension (OLEX) study (ATH-1017-0203) following Visit 8, subject to meeting all eligibility criteria for that study. For subjects who do not enroll into the OLEX, the end of study is defined as either the Safety Follow-up (Visit 9/Week 30) or the date of an early termination (ET) visit for those subjects who terminate prior to Visit 8. Subjects who terminate prior to Visit 8 are to complete the same assessments as Visit 8 at the ET visit. An independent Data Safety Monitoring Board will conduct periodic review and assessments of unblinded safety data (AEs, labs, ECG, etc.) throughout the study to ensure the safety of study subjects. Blood draws will take place at scheduled clinic visits for analysis of blood-based biomarkers and for plasma concentrations of ATH-1017 and ATH-1001. An open-label extension will be offered to eligible subjects at participating sites.
Treatments Administered:	Subjects will be randomized to one of 2 treatment groups: • ATH-1017, 40 mg, qd, SC • Placebo, qd, SC Prior to version 7 of this protocol, subjects were also randomized to a 70 mg dose group. Randomization to the 70 mg dose group was discontinued, however, subjects already randomized to receive ATH-1017 70 mg/qd will continue the following regimen until completion or early termination of the study: • ATH-1017, 70 mg, qd, SC
Investigational Medicinal Products:	Treatment: ATH-1017 will be presented in prefilled 1 mL syringes of 40 mg/mL or 70 mg/mL (prior to version 7) Placebo: Placebo prefilled 1 mL syringes to match treatment

Number of Subjects:

The study was originally designed to enroll approximately 300 subjects in a 1:1:1 ratio to ATH-1017 40 mg/qd, ATH-1017 70 mg/qd, and placebo groups (Protocol versions 1-3). In version 4, the sample size was increased to 420 subjects in order to increase statistical power. After the ATH-1017-AD-0202 ACT-AD readout, the protocol was amended (version 5) to: stop enrollment of subjects receiving AChEIs and perform an independent, unblinded interim analysis with a pre-specified sample size re-estimation (SSR) procedure following a test for futility, based on conditional power (CP) using the promising zone approach (Mehta and Pocock, 2011). Prior to version 5, approximately 200 subjects who were receiving AChEIs were already enrolled in the trial.

The interim analysis was conducted on approximately 100 subjects not receiving AChEIs who had completed participation in the trial or terminated early, and the results indicated that a pre-specified sample size re-estimation of up to 275 subjects was well powered to meet the primary endpoint of the study.

The primary purpose of version 6 of the protocol was to add ADAS-Cog_{11} at screening, elevated NfL to be a secondary endpoint, and this did not impact the number of subjects to be enrolled.

In protocol version 7, randomization to the 70 mg dose group was discontinued. In order to provide 85% power with two-sided 0.05 testing, a sample size of 298 subjects will be randomized in a 1:1 ratio between the two treatment groups, ATH-1017 40 mg/qd or placebo, for a total of approximately 149 subjects per treatment group who are not receiving AChEIs. Approximately 60 subjects not on background AChEIs have already been randomized to ATH-1017 70 mg/qd; these subjects will complete the study as planned. Therefore, the maximum total enrollment for this study will be approximately 558 subjects as outlined in the table below.

Number of Subjects Planned for Enrollment

Number of Subjects						
Receiving AChEIs			Not Receiving AChEIs			
Plc	ATH-1017 40 mg/qd	ATH-1017 70 mg/qd	Plc	ATH-1017 40 mg/qd	ATH-1017 70 mg/qd	Total
~200			~149	~149	~60[a]	~558

AChEI = acetylcholinesterase inhibitor; Plc = placebo; qd = once daily.

[a] Approximate number of subjects who were randomized to ATH-1017 70 mg/qd prior to version 7.

Duration of Treatment:

The study will consist of up to 28 days of screening (Day -28 through Day -1) followed by 26 weeks of randomized 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.

Study Population:	**Inclusion** 1. Age 55 to 85 years, inclusive at the time of signing the informed consent. 2. Mild-to-moderate AD dementia subjects a) MMSE score 14 to 24 inclusive at Screening b) Clinical Dementia Rating (CDR) Scale global score of 1 or 2 at Screening 3. Clinical diagnosis of dementia, due probably to AD, by Revised National Institute on Aging-Alzheimer's Association criteria (McKhann, 2011): a) Magnetic resonance imaging (MRI) or computerized tomography (CT) scan (for subjects with non-MRI-safe cardiac pacemaker, or other relevant medical reason, with Medical Monitor approval) performed within 12 months before Screening, with findings consistent with the diagnosis of dementia due to AD without any other significant comorbid central nervous system pathologies. If such scan is unavailable or older than 12 months, it should be repeated to ascertain the diagnosis before randomization. b) Documented clinical decline within 12 months before Screening and onset of symptoms at least 12 months before Screening (preferably subject medical records; caregiver reports with examples are acceptable). 4. Formal education of 8 or more years; exceptions may be made for subjects with less than 8 years of education at the discretion of the investigator. 5. Body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2 at Screening; subjects with BMI outside the allowed BMI range but ≥ 16 and ≤ 37 kg/m^2 may enroll only with prior agreement of the Sponsor. 6. Male subjects 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. Only 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 and have approximately 4 to 6 hours daytime contact with the subject for at least 4 days/week. 8. Treatment-free (subjects not receiving AChEI treatment), defined as: a) Treatment-naïve, OR b) Subjects who received an AChEI in the past and discontinued at least 4 weeks prior to Screening. 9. 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. 10. 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 procedures to evaluate eligibility for the study. 11. 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). 12. 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. 13. 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. History of significant neurologic disease, other than AD, that may affect cognition, or concurrent with the onset of dementia. 2. Subject has atypical variant presentation of AD, if known from medical history, particularly non-amnestic AD. 3. History of brain MRI scan indicative of any other significant abnormality, including but not limited to multiple (> 10) microhemorrhages, severe white matter hyperintensities, history or evidence of a single prior hemorrhage > 1 cm^3, multiple (> 3) lacunar infarcts or evidence of a single prior infarct > 1 cm^3, evidence of a cerebral contusion, encephalomalacia, aneurysms, vascular malformations, subdural hematoma, or space-occupying lesions (e.g., brain tumors). If a known meningioma has been stable for > 1 year and the subject has no history of any type of convulsions, this can be allowable after consultation with the Medical Monitor. Note: a new MRI scan is required if the scan was performed > 12 months prior to Screening; 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 non-MRI-safe cardiac pacemaker or other relevant medical reason, with Medical Monitor approval. 4. Diagnosis with current symptoms of severe major depressive disorder even without psychotic features. Any subject with formalized delusions or hallucinations should be excluded. 5. 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.

	6. 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 behaviours). 7. History within 2 years of Screening, or current diagnosis of psychosis (American Psychiatric Association [APA], 2000) or moderate substance abuse disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) (APA, 2013). 8. Untreated conditions, including vitamin B_{12} or folate deficiency, 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 6 months before Screening. 9. Abnormal serum electrolytes (potassium, sodium, magnesium) of clinical significance. If treated, must be stably treated for at least 30 days before Screening. 10. Active, acute, or chronic infectious disease of any type. 11. Myocardial infarction or unstable angina within the last 6 months or history of more than one myocardial infarction within 5 years before Screening. 12. Clinically significant (in the judgment of the investigator) cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (note: pacemaker is acceptable). 13. Subject has either hypertension (supine diastolic blood pressure > 95 mmHg), or symptomatic hypotension in the judgment of the investigator. 14. Clinically significant ECG abnormality at Screening, 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, 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 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. 15. Positive results of serology screening for hepatitis B (hepatitis B surface antigen), hepatitis C (anti-hepatitis C virus antibodies) or human immunodeficiency virus (antibodies type 1 and 2); subjects with a history of positive results for cured hepatitis B or hepatitis C may be eligible following discussion with the Medical Monitor and prior approval is required. 16. 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.

	17. Hepatic impairment with alanine aminotransferase or aspartate aminotransferase > 2 times the upper limit of normal, or Child-Pugh class B and C. 18. Malignant tumor within 3 years before Screening, except for the following conditions that are stable in the judgement 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; prior Medical Monitor approval is required. 19. Clinically significant (in the judgment of the investigator) unintentional weight loss within 12 months of Screening. 20. 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. 21. 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. 22. 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. 23. Prohibited prior and concomitant medications are excluded within 4 weeks prior to Screening. All allowed medications should remain stable throughout the study for medications negatively affecting cognition, the doses should be stable for at least 4 weeks before Screening and throughout the study, unless otherwise noted. (This is not an exhaustive list; 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 also]): a) Memantine in any form, combination, or dosage b) Acetylcholinesterase inhibitors in any dosage form c) Antipsychotics; antipsychotics in low doses (in the judgment of the investigator) are allowed only if given for sleep disturbances, agitation and/or aggression, and only if the subject has received a stable dose for at least 3 months before Screening. If these medications are taken on a PRN basis, they should not be taken the night before any cognitive testing d) Tricyclic antidepressants, monoamine oxidase 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 e) Anxiolytics at high doses; low doses of benzodiazepines are allowed in the judgment of the investigator, but not the night before any cognitive assessments f) Sedative hypnotics; Zolpidem is allowed g) Barbiturates (unless given in low doses for benign tremor)

	h) Nicotine therapy (including patches), varenicline (Chantix), or similar therapeutic agent i) Peripherally acting drugs with effects on cholinergic neurotransmission. Solifenacin is allowed if the subject has received a stable dose for at least 3 months before Screening j) Systemic immunosuppressants if taken in clinically immunosuppressive doses in the judgment of the investigator (note: immunosuppressant use for allergy or other inflammation, e.g., inhaled steroids, otics, ophthalmologics, skin creams, and intra-articular injections are allowed) k) Antiepileptic medication if taken for control of seizures. Other uses, e.g., neuropathy and restless legs, are allowed l) Chronic intake of opioid-containing analgesics; PRN use is allowed (but not within 72 hours before any cognitive assessment) m) Sedating H_1 antihistamines; non-sedating H_1 antihistamines are allowed and preferred n) Systemic moderate to strong cytochrome P450 3A4 inhibitors or inducers; topical applications are allowed 24. 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 AD investigational drug. 25. The subject has received active amyloid or tau immunization (i.e., vaccination for Alzheimer's disease) at any time, or passive immunization (i.e., monoclonal antibodies for Alzheimer's disease) within 6 months of Screening. FDA approved vaccinations or monoclonal antibodies for other indications are allowed. 26. Subject has known allergy to any component of the investigational medicinal product. 27. 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:** The intent-to-treat (ITT) Population will consist of all randomized subjects regardless of whether or not the subject received study medication. The modified ITT (mITT) Population is a subset of the ITT Population and will consist of all randomized subjects who took at least one dose of the study medication and who, during at least one post-baseline visit, completed both an ADAS-Cog_{11} and ADCS-ADL23 assessment, as well as at baseline. Statistical tests will use a hierarchical gatekeeping procedure to account for multiplicity, with two-sided tests at 0.05 (Dmitrienko, 2013). The primary analysis population is comprised of all members of the mITT, who were not taking AChEIs during the trial and were randomized to either ATH-1017 40 mg/qd or placebo. The primary efficacy endpoint is the GST score (a composite of cognition and function, calculated as the average of two change from baseline z-scores; the z-scores

	are calculated for the change from baseline scores for cognition [ADAS-Cog$_{11}$] and function [ADCS-ADL23]) compared to the placebo group at Week 26. The primary analysis will use a mixed model for repeated measures (MMRM) with GST score as the outcome variable, and terms for baseline value, visit, treatment, visit by treatment interaction, ApoE4 carrier status, pooled site as a factor (with geographically similar sites grouped and a group of sites using Spanish for clinical assessments), baseline age (continuous), and the baseline MMSE stratification factor. Least squares means and treatment differences will be estimated from the MMRM model. Statistical testing to the key secondary efficacy endpoints continues only if the null hypothesis for the primary efficacy endpoint is rejected. If the null hypothesis for GST score is rejected, then the key secondary endpoints of change from baseline in ADAS-Cog$_{11}$ and ADCS-ADL23 scores will be analyzed using an MMRM as described for the primary analysis. If both of these null hypotheses are also rejected, then the key secondary efficacy endpoint of change from baseline in NfL concentration will also be analyzed using an MMRM as described for the primary analysis. Safety analyses will be based on the Safety Population consisting of all randomized subjects who received at least one dose of any study medication. All safety parameters will be summarized descriptively. **Sample Size Considerations:** The sample size for the trial was chosen to provide 85% power for the primary endpoint. The following treatment effect premises were made to support sample size calculations: • Change from Baseline to Week 26 in ADAS-Cog$_{11}$: Mean treatment difference (standard deviation): 1.8 (6). • Change from Baseline to Week 26 in ADCS-ADL23: Mean treatment difference (standard deviation): 2.7 (9). The sample size of 149 evaluable subjects (subjects in the primary analysis population, comprised of mITT subjects randomized to either 40 mg/qd or placebo, and not on background AChEIs) per trial arm would yield at least 85% power with a two-sided 0.05 level. A positive outcome will be achieved in the trial if a significant treatment effect based on the primary endpoint is established and power calculations were based on successfully meeting the GST score endpoint. In view of the overall number of subjects already enrolled prior to version 7 of this protocol, including those receiving background AChEI therapy (200 subjects), and those already randomized to the 70 mg treatment group not receiving AChEI therapy (60 subjects), the maximum number of subjects to be enrolled would be approximately 558.

Table 1 Schedule of Assessments

		Screening[a]	Randomized placebo-controlled treatment period (26-week)							Safety Follow-up[p]
	Visit:	1	2	3	4	5	6	7	8/ET[o]	9
	Week:	-4 to -1	1	2	6	12	16	20	26	30
Assessment	Day:	-28 to -1	1	14 (±7)	42 (±7)	84 (±7)	112 (±7)	140 (±7)	182 (±7)	210 (±7)
Inclusion/Exclusion		X	X							
Informed Consent		X								
Demographics		X								
Medical History		X								
Height and Weight		X	X[b]			X[b]			X[b]	X[b]
Blood[c]		X								
C-SSRS[d, q]		X	X	X	X	X	X	X	X	X
GDS		X	X			X			X	X
MMSE[q]		X	[redacted]							
CDR		X								
Randomization			X							
Drug Dispensing[e]			X	X	X	X	X	X		
Dose of IMP in-clinic[f]			X	X	X	X	X	X	X	
Drug Accountability				X	X	X	X	X	X	
Physical and Neurological Exam[g]		X	X	X	X	X	X	X	X	X
MRI[h]		X								
12-Lead ECG[i]		X	X	X	X	X	X	X	X	X
Vital signs[j]		X	X	X	X	X	X	X	X	X
Safety Labs[k]		X	X	X	X	X	X	X	X	X
AE		X	X	X	X	X	X	X	X	X
Conmeds[l]		X	X	X	X	X	X	X	X	X
ADAS-Cog11[q]		X	X	X	X	X		X	X	X
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]	
ADCS-ADL23[q]			X			X		X	X	
[redacted]			[redacted]			[redacted]			[redacted]	
PK (plasma)[m, q]			X			X			X	
Plasma Sample Collection (biomarker analyses)[n]			X			X			X	
[redacted]			[redacted]						[redacted]	
[redacted]			[redacted]						[redacted]	
[redacted]			[redacted]						[redacted]	

ADCS-ADL23 = Alzheimer's Disease Cooperative Study-Activities of Daily Living, 23-item version; ADAS-Cog11 = Alzheimer's Disease Assessment Scale-Cognitive Subscale; [redacted] AE = adverse event; CDR = Clinical Dementia Rating Scale; [redacted] C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted] GDS = Geriatric Depression Scale; IMP = investigational medicinal product; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; [redacted]

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 2), Week 12 (Visit 5), Week 26 (Visit 8), and Safety follow-up (Visit 9).
c. Blood collection for FSH levels (to confirm post-menopausal state in females), serology, ApoE genotyping, folate, Vitamin B12, fT3, fT4, and TSH.
d. '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.
e. Dispensing of kits containing study drug will occur every 2 weeks, at the study site or as needed by direct-to-patient shipment; larger provision of study drug is permitted to accommodate personal need, e.g., vacation; drug returns will be recorded, and compliance calculated. IP administration by subject or caregiver will be assessed at Visits 2 through 7, inclusive.
f. First SC injection of IMP will be performed at site under supervision. Subjects will remain at site for 2 hours ± 15 minutes for safety observation follow up. They may be discharged from the clinic at this time absent any systemic AEs (but not for local site reaction). Should they have systemic AEs, they should remain under observation for an additional 2 hours and may be discharged at that time with investigator's clearance. Subjects should withhold IMP dose on the day of subsequent clinic visits whereupon IMP administration will be done on site under supervision of site staff. There is no specified in-clinic observation period for these subsequent visits but will require investigator discharge from the clinic. It is recommended to contact the subject/caregiver by phone at appropriate intervals to support dosing compliance and injection techniques.
g. Physical and Neurological Exam should be done post-dose on all visits when dosing applies
h. MRI (or CT for subjects with non-MRI-safe cardiac pacemaker, or other relevant medical reason, with Medical Monitor approval) scan must have been performed within 12 months before Screening. If such scan is unavailable or older than 12 months, it should be repeated to ascertain the diagnosis before randomization.
i. 12-lead ECGs will be performed pre-dose and 30 (± 15) minutes post-dose on Day 1 and 30 (± 15) minutes post-dose at all other visits. All ECG assessments will be performed in triplicate sequentially.
j. Vital signs 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.
k. Safety labs include chemistry, hematology, and urinalysis.
l. Prior or concurrent medications.
m. PK plasma samples will be collected at pre-dose and post-dose on Baseline/Day 1 (Visit 2); pre-dose and post-dose at Week 12 (Visit 5) and Week 26 (Visit 8). The pre-dose PK sample is collected any time before dosing. The post-dose PK sample is collected anytime between 30 minutes and 120 minutes after dosing as practical. The actual time of dosing and of PK sampling will be recorded.
n. Plasma samples will be collected for biomarker analysis. Prior to version 7 this was optional for subjects.
o. Subjects who terminate prior to Visit 9 are to complete same assessments as Visit 8/ET (early termination). For clinical outcome assessments if completed 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.
p. Safety follow-up visit to be performed for subjects who do not roll over into the optional open-label extension (OLEX) study; subjects who roll over into the OLEX study will complete the safety follow-up visit at the end of the OLEX study.
q. At Baseline/Day 1 (Visit 2), MMSE should be done first before all other assessments pre-dose. ADAS-Cog11, [redacted] will be performed pre-dose; [redacted]. For visits after the baseline (except for safety follow-up when

dosing is not applicable), all clinical outcome assessments will be performed post-dose. [redacted]

ADAS-Cog11 [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog$_{11}$	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS-ADL23	Alzheimer's Disease Cooperative Study-Activities of Daily Living, 23-Item Version
[redacted]	[redacted]
AE	Adverse event
AEC	Absolute eosinophil count
AKT	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CBC	Complete blood count
CBD	Cannabidiol
CDR	Clinical dementia rating scale
C_{max}	Maximum concentration
CNS	Central nervous system
[redacted]	[redacted]
CP	Conditional power
CPK	Creatine phosphokinase
CRO	Contract research organization
C-SSRS	Columbia-suicide severity rating scale
CT	Computerized tomography
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
EQ-5D-5L	EuroQol group 5-dimension 5 level questionnaire

ERP	Event-related potentials
ET	Early termination
FSH	Follicle-stimulating hormone
fT3	Free tri-iodothyronine
fT4	Free thyroxine
GCP	Good clinical practice
GDS	Geriatric depression scale
[redacted]	[redacted]
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
GST	Global statistical test
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HGF	Hepatic growth factor
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
iSAP	Interim Statistical Analysis Plan
ISR	Injection site reaction
ITT	Intent-to-treat
LAR	Legally authorized representative
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MCT	Medium-chain triglyceride
MET	MET receptor tyrosine kinase
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NfL	Neurofilament light chain

NIA-AA	National Institute on Aging – Alzheimer's Association
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
OLEX	Open-label extension
P	Phosphorylated
PD	Pharmacodynamic(s)
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PKC	Protein kinase C
Plc	Placebo
PLCγ	Phospholipase C-gamma
PM	Plasma membrane
PRN	As needed
PSP	Post-synaptic potential
PT	Prothrombin time
[redacted]	[redacted]
qEEG	Quantitative electroencephalogram
qd	Once daily
QTcF	Corrected QT interval using Fridericia's formula
RAC1	Ras-related C3 botulinum toxin substrate 1
RAF	Rapidly accelerated fibrosarcoma (protein)
RAS	Rat sarcoma (protein)
RBC	Red blood cells
[redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SOP	Standard operating procedure
SSR	Sample size re-estimation
STAT3	Signal transducer and activator of transcription 3
THC	Tetrahydrocannabinol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US(A)	United States (of America)
[redacted]	[redacted]
WBC	White blood cells
[redacted]	[redacted]

1 INTRODUCTION

Fosgonimeton (ATH-1017) is an experimental Alzheimer's disease (AD) treatment, 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 a positive modulator at the hepatic growth factor (HGF) and its tyrosine kinase, MET, receptor system. Central nervous system (CNS) MET expression is crucial in maintaining the healthy adult brain (Hawrylycz, 2015), and is reduced in AD particularly in the hippocampus and frontal cortex (Hamasaki, 2014). The HGF/MET system presents a new therapeutic target to treat neurodegeneration and restore cognitive function in AD and other neurodegenerative disorders.

1.1 Background

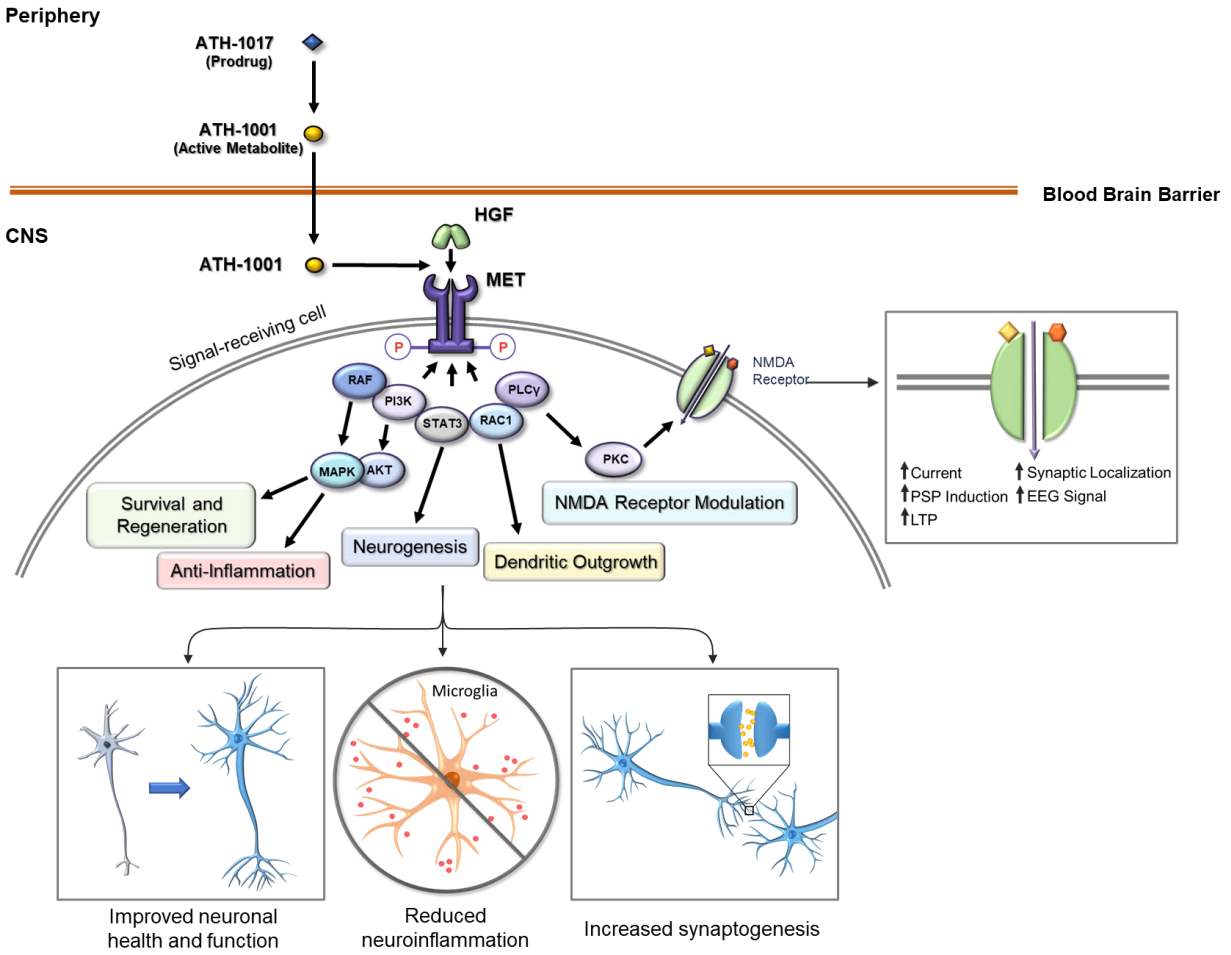
Dementia of the Alzheimer's type (hereafter referred to as AD) is the most common form of dementia and the largest unmet medical need in neurology (Citron, 2010). AD can be further classified based on age of onset and genetic risks. Individuals under age 65 have early-onset AD, and many of whom have a dominant genetic mutation (i.e., familial AD with known mutations in the following genes: amyloid precursor protein, presenilin-1, and presenilin-2). Late-onset AD patients have an age of onset at 65 years and older, who typically have no dominant genetic risks (i.e., sporadic AD), with disease onset involving a complex interplay of aging, Apolipoprotein E (ApoE)-ε4 genotype, environmental, and lifestyle risk factors. The late-onset sporadic cases account for about 95% of the total AD population. Although age is the biggest risk factor, AD is not a part of normal aging.

Growing evidence suggests that complex CNS disorders, like AD, 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 AD and other dementias, and drugs that stimulate neurotrophic systems have the potential to address neurodegeneration and improve cognition by protecting existing neurons, promoting connectivity, inducing neuro-regenerative mechanisms, as well as addressing multiple aspects of the AD pathology, 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 Parkinson's disease 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 in a systemic approach. The mechanism of action of ATH-1017 via its active metabolite is augmentation of HGF function and facilitation of signal transduction through MET phosphorylation (Figure 1).

Figure 1 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; PM = plasma membrane; PSP = post-synaptic potential; 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 in plasma 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 (PD) based on quantitative electroencephalogram (qEEG) and event-related potentials (ERP) was established. 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 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 11 AD subjects with 40 mg/once daily (qd) SC significantly reduced P300 latency (p=0.027) after 8 days of treatment when compared to placebo (Hua, 2022). This finding suggests ATH-1017 treatment has potentially beneficial effects on cognitive processing and working memory access in AD.

The sponsor has completed a Phase 2 study (ATH-1017-AD-0202 [ACT-AD]) study of ATH-1017 in 77 mild to moderate Alzheimer's subjects over 6 months of treatment. The results of the study suggested ATH-1017 had positive effects on measures of cognition, function and neurodegeneration in subjects taking ATH-1017 alone compared to placebo at 26 weeks (data on file).

This study (ATH-1017-AD-0201) is designed to demonstrate efficacy in mild to moderate AD subjects and establish long-term safety information. Eligible subjects prior to version 7 will receive qd SC injections of ATH-1017 (40 mg or 70 mg) or placebo, over a 26-week randomized period, followed by a 4-week safety follow-up. Subjects who complete the study will have the option to roll over into a long-term open-label extension study.

Based on the results of the ATH-1017-AD-0202 ACT-AD study, as of version 5 of this protocol no additional subjects on acetylcholinesterase inhibitor (AChEI) therapy will be enrolled, and, as of version 7 of this protocol, subjects are no longer randomized to receive 70 mg of ATH-1017, since 40 mg/qd is the dose intended for further development. The 70 mg/qd dose was tested in the ATH-1017-AD-0202 study; clinical and biomarker endpoints did not consistently favor 70 mg/qd when compared to 40 mg/qd. While ATH-1017 has demonstrated a favorable safety

profile in all completed and ongoing studies to date, there appears to be better tolerability in the 40 mg cohort when compared to 70 mg. By discontinuing the 70 mg cohort, with no further plans to develop the 70 mg formulation, it will also decrease the burden on clinical trial healthcare resources (e.g., clinical site utilization, availability of eligible subjects, caregiver commitments), and subjects will be randomized to ATH-1017 40 mg/qd or placebo, in a 1:1 ratio. Subjects already randomized to receive the 70 mg dose will complete the study as planned. The primary analysis population will include modified intent-to-treat (mITT) subjects randomized to ATH-1017 40 mg/qd or placebo who are not receiving AChEI treatment (see Sections 8.1.1 and 8.1.3 for details). The comparison between ATH-1017 70 mg/qd and placebo, between ATH-1017 70 mg/qd and ATH-1017 40 mg/qd, and between pooled ATH-1017 (70 mg/qd + 40 mg/qd subjects) and placebo will be treated as exploratory comparisons. In addition, exploratory analyses for the effect of ATH-1017 in the presence of background AChEIs will be performed for subjects who enrolled prior to protocol version 5.

1.3 Risk-Benefit Assessment

Whilst qEEG and ERP results in humans are indicative of CNS penetration and target engagement, ATH-1017 efficacy in subjects with AD (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 human 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, qd, over 9 consecutive days) in healthy elderly subjects, and 40 mg (SC, qd, over 9 consecutive days) in AD subjects were safe and well tolerated.

Injection site reactions (ISRs), eosinophilia, and transaminase elevations are considered as nonserious adverse drug reactions to ATH-1017.

Injection site reactions have been observed commonly in clinical trials and are characterized by localized symptoms including swelling, erythema, pruritus, pain, and/or irritation around the injection site. They have usually been mild, appear during the first weeks of injections, though in some cases ISRs may appear later. Most ISRs were mild and recovered shortly without treatment, while some were more persistent.

Transient absolute eosinophil count (AEC) elevations without signs of clonality and without associated clinical symptoms have been observed in subjects. The majority of these elevations stayed below $3 \times 10^3/\mu L$ and resolved without intervention during continued IMP administration. Very few subjects experienced elevations above $5 \times 10^3/\mu L$. No AEs potentially associated with eosinophilia were reported. None of the subjects fulfilled the criteria for a hyper-eosinophilic syndrome. All AEC elevations have resolved without sequela, and the vast majority of subjects continued in the trials.

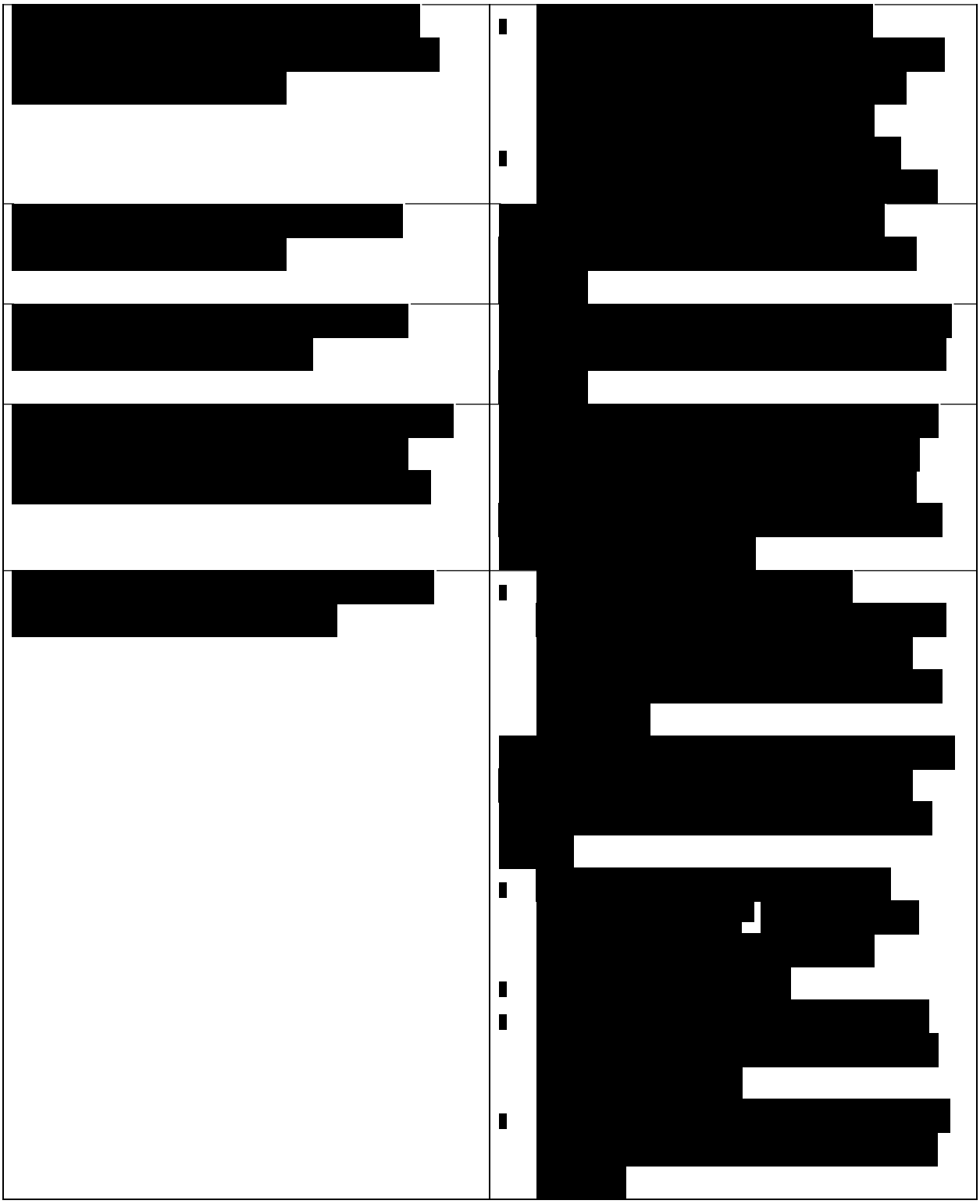
Non-clinical data identified a potential risk for hepatotoxicity and will be closely monitored in this study. The sponsor reviewed clinical data from the Phase 1 trial ATH-1017-0103, and 6 healthy subjects in the 140 mg cohort had elevated transaminases. Repeat testing showed resolution towards normal in all subjects, with no reports of associated complications. No serious events of transaminase elevations have been reported and there have been no cases meeting Hy's Law criteria.

In the completed translational Phase 2 study (ATH-1017-AD-0202), an apparent and unexpected pharmacodynamic drug-drug interaction (DDI) with background AChEIs was observed. The suspected pharmacodynamic DDI did not affect safety in ATH-1017-AD-202 or the present study. A pre-specified ERP P300L analysis, and post-hoc unadjusted summary statistical analysis, as well as post-hoc Mini-Mental State Examination (MMSE) data collected during the study and during an open-label extension, consistently suggest favorable effects of ATH-1017 in the "no AChEI" group. In addition, analysis of biomarkers in the Phase 2 study showed statistically significant reduction in Neurofilament light chain (NfL) concentration, a well-established biomarker of neurodegeneration, among subjects not using AChEIs, and congruent trends in improvement in all other blood-based biomarkers.

The safety of ATH-1017 is monitored by an independent unblinded Data Safety Monitoring Board (DSMB), which continues to recommend that Study ATH-1017-AD-0201 continue without modification. ATH-1017 has demonstrated a favorable safety profile in all completed and ongoing studies to date.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	**Primary Efficacy Endpoint***
To evaluate the clinical efficacy of ATH-1017 in subjects not on background acetylcholinesterase inhibitors (AChEIs)	The Global Statistical Test (GST) score (O'Brien, 1984) is a composite of cognition and function, calculated as the average of two change from baseline z scores; the z-scores are calculated for the change from baseline scores for cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog_{11}]) and function (Alzheimer's Disease Cooperative Study – Activities of Daily Living, 23-item version [ADCS-ADL23] score) at Week 26
Key Secondary Efficacy Objectives	**Key Secondary Efficacy Endpoints***
To evaluate the clinical efficacy of ATH-1017 in subjects not on background AChEIs separately on: (1) cognition and (2) activities of daily living	• ADAS-Cog_{11} score: change from baseline at Week 26 • ADCS-ADL23 score: change from baseline at Week 26
To determine the effect of ATH-1017 on plasma neurofilament light chain (NfL) levels in subjects not on background AChEIs (a biomarker of neurodegeneration with literature support for being a biomarker for Alzheimer's disease [AD] progression)	Change from baseline in the NfL concentration at Week 26
[redacted]	[redacted]



[redacted]	[redacted]
Safety Objective	**Safety Endpoints**
To determine the safety and tolerability of ATH-1017	Analysis of 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)

* The comparison between ATH-1017 40 mg/qd and placebo in subjects not on background AChEIs will serve as the primary efficacy comparison for the primary and key secondary endpoints. [redacted]

3 OVERALL DESIGN AND PLAN OF THE STUDY

This is a Phase 2/3 multicenter**,** randomized, double-blind, placebo-controlled, parallel-group study comparing ATH-1017 treatment with placebo in subjects with a clinical diagnosis of mild to moderate AD, diagnosed on a 'probable' level according to the National Institute on Aging – Alzheimer's Association (NIA-AA; McKhann, 2011). The study will be conducted at a total of approximately 70 centers in the US. 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. Up to protocol version 7, subjects meeting all inclusion/exclusion criteria were randomized in a ratio of 1:1:1 to 3 parallel arms, either to treatment (ATH-1017 40 mg/qd or ATH-1017 70 mg/qd) or placebo group. As of protocol version 7, randomization to ATH-1017 70 mg/qd was discontinued, and subjects will be randomized in a ratio of 1:1 to 2 parallel arms, either to receive ATH-1017 40 mg/qd or placebo. Subjects randomized to ATH-1017 70 mg/qd prior to protocol version 7 will continue that treatment regimen until either study completion or early termination (ET).

During randomization, subjects will be stratified by screening MMSE severity: mild (MMSE: 20-24) versus moderate (MMSE: 14-19). All eligible subjects will be tested for ApoE genotype.

Study drugs will be administered by SC injection qd preferably during daytime. Subjects should not take more than one dose within 8 hours. The first SC injection of study drug will be performed at 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 randomized 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 trial at Week 30 (see Table 1 for schedule of assessments). On Day 1, after completion of the first dose, subjects will remain on-site 2 hours (±15 minutes) for post-treatment clinical observation subject to the conditions in Section 5.5. As marked circadian fluctuations of cognitive performance have been observed in AD (Hilt, 2015), ADAS-Cog$_{11}$, [redacted] assessments should occur at clinic visits in the morning at approximately the same time they were performed during the initial Baseline [redacted] ubjects 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. Subjects enrolled at participating sites may seamlessly enroll onto the open label extension (OLEX) study (ATH-1017-0203) following Visit 8, subject to meeting all eligibility criteria for that study. For

subjects who do not enroll into the OLEX, the end of study is defined as either the Safety Follow-up (Visit 9/Week 30) or the date of an ET visit for those subjects who terminate prior to Visit 8. Subjects who terminate prior to Visit 8 are to complete the same assessments as Visit 8 at the ET visit.

An independent Data Safety Monitoring Board (DSMB) will conduct periodic review and assessments of unblinded safety data (AEs, labs, ECG, etc.) throughout the study to ensure the safety of study subjects (see Section 7.2).

Blood draws will take place at scheduled clinic visits (Day 1, Week 12, and Week 26) for analysis of blood-based biomarkers (optional prior to version 7 of the protocol), and for plasma concentrations of ATH-1017 and ATH-1001 (see Table 1 for schedule of assessments).

An open-label extension will be offered to eligible subjects at participating sites.

3.1 Justification for Study Design

The study is designed to demonstrate efficacy and safety of ATH-1017 in mild to moderate AD subjects, with double-blind, parallel-arm treatment duration of 26 weeks, and based on clinical diagnostic criteria of AD (McKhann, 2011) and the inclusion/exclusion criteria. An option to roll over into a long-term open-label extension study will be available to subjects who complete this study; the purpose of the open-label extension is to continue to collect long-term safety.

Clinical efficacy in the target patient population is demonstrated by improvement in cognition and global/function assessments comparing treatment to placebo. Based on the results of the ATH-1017-AD-0202 ACT-AD study, only subjects not receiving AChEI treatment will be included in the primary analysis population. Following protocol version 7, only subjects randomized to either ATH-1017 40 mg/qd or placebo will be included in the primary analysis population. The Global Statistical Test (GST) score combines the change from baseline scores from efficacy endpoints ADAS-Cog_{11} (i.e., cognition) and ADCS-ADL23 (i.e., function) into a single primary efficacy endpoint, allowing an assessment of the overall treatment effects of ATH-1017 in this complex disorder. Assessment of NfL, a biomarker of neurodegeneration, will provide objective data to support the clinical evaluations of benefit.

As well as providing efficacy data using validated outcome scales for cognitive function, executive memory function, activities of daily living, and behavioral changes, this study will collect pharmaco-economic data using validated scales for caregiver burden and healthcare resource utilization.

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). This study will employ an independent DSMB who will conduct periodic review and assessments of unblinded safety data (AEs, labs, ECG, etc.) throughout the study.

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

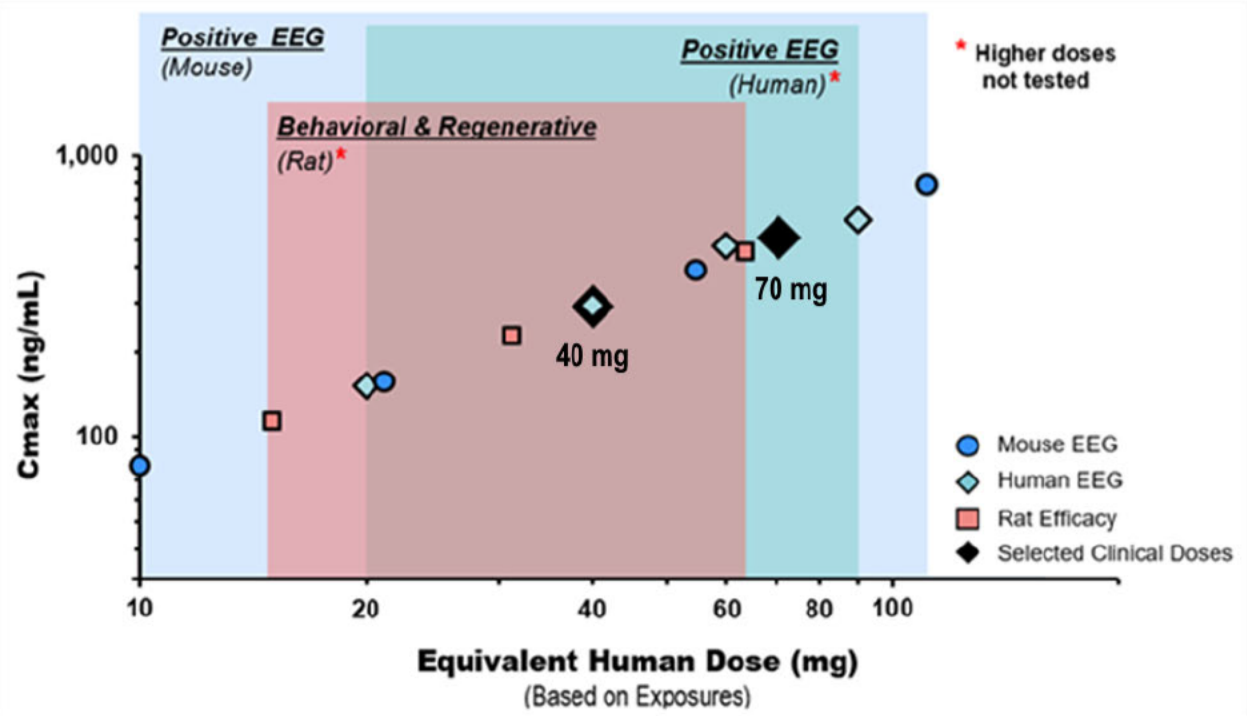
3.2 Justification for Dose

The dose selection for this clinical study is based on safety, PK, and PK-PD modeling of ATH-1017's treatment effect in qEEG and nonclinical studies in animal models, together with the qEEG and ERP P300 results of a completed Phase 1a/b study.

In the randomized placebo-controlled Phase 1a/b study, ATH-1017 has been evaluated for safety, PK, and PD 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 to understand the safety profile and PD 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 nonclinical qEEG studies in mouse, nonclinical efficacy studies in animal models (i.e., scopolamine-induced amnesia in rat and aged dementia rat), and Phase 1a/b human clinical study. The results were compared based on equivalent PK exposures, based on C_{max}, to inform dose selection for the next proposed study. Given the mode of action of ATH-1017 is via pulsatile activation of a growth factor system, the PD of ATH-1017 are primarily driven by concentration (C_{max}). Upon activation, MET phosphorylation persists for some time before the active complex is internalized, and either degraded or dephosphorylated and recycled back to the membrane. This pulsatile method of ATH-1017 (prodrug) administration is aligned with the natural regulatory mechanisms of HGF/MET activity and suggests a steady-state level of ATH-1001 (active metabolite) exposure is not necessary for a therapeutic effect.

As summarized in Figure 2, the active PD 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 PD 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 PD range.

Figure 2 Dose selection based on PK-PD modeling



The doses selected for the proposed study were 40 mg (SC, qd) and 70 mg (SC, qd). Both the 40 mg and 70 mg doses are covered by the current PD 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, qd, over 9 days; 6 active versus 2 placebo), and 11 AD subjects (SC, qd, 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 PD 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, qd; 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 6- and 9-month 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 PD range, were well-tolerated in humans based on safety data from the Phase 1a/b study and are covered by the 6- and 9-month GLP nonclinical toxicology studies in animals at equivalent doses.

Based on the results of the ATH-1017-AD-0202 ACT-AD study, no additional subjects on AChEI therapy will be enrolled (version 5) and, as of version 7, subjects will no longer be randomized to receive 70 mg of ATH-1017. The ATH-1017 70 mg/qd dose is not intended for further clinical development. The 70 mg/qd dose was tested in the ATH-1017-AD-0202 study, where there was no clear suggestion of added clinical benefit of 70 mg/qd when compared to 40 mg/qd. In addition, there appears to be better tolerability in the 40 mg cohort when compared to 70 mg. By discontinuing the 70 mg cohort, with no further plans to develop the 70 mg formulation, it will also decrease the burden on clinical trial healthcare resources (e.g., clinical site utilization, availability of eligible subjects, caregiver commitments). Subsequently, as of version 7, subjects will be randomized to ATH-1017 40 mg/qd or placebo, in a 1:1 ratio. Subjects already randomized to receive the 70 mg dose will complete the study as planned. The doses of ATH-1017 used for evaluation of efficacy and safety in this study will support selection of an appropriate dose for registration of ATH-1017 as a potential treatment for mild to moderate AD.

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 and Sponsor approval, supported by documented agreement from the IRB/IEC.

4.1 Number of Subjects

The study was originally designed to enroll approximately 300 subjects in a 1:1:1 ratio to ATH-1017 40 mg/qd, ATH-1017 70 mg/qd, and placebo groups (Protocol versions 1-3). In version 4, the sample size was increased to 420 subjects in order to increase statistical power. After the ATH-1017-AD-202 ACT-AD read out (data on file, peer-reviewed publication is in preparation), the protocol was amended (version 5) to: stop enrollment of subjects receiving AChEIs, and perform an independent, unblinded interim analysis with a pre-specified sample size re-estimation (SSR) procedure following a test for futility based on conditional power (CP), using the promising zone approach (Mehta and Pocock, 2011). Prior to version 5, approximately 200 subjects who were receiving AChEIs were already enrolled in the trial.

The interim analysis was conducted on approximately 100 subjects not receiving AChEIs who completed participation in the trial (either completion of Week 26 assessments or terminated early). The results indicated that a pre-specified sample size of up to 275 subjects was well powered to meet the primary endpoint of the study. The primary purpose of version 6 of the protocol was to add ADAS-Cog_{11} at screening, and to elevate NfL to be a secondary endpoint. These changes did not impact the number of subjects to be enrolled.

With version 7 of this protocol, randomization to the 70 mg dose group was discontinued. In order to provide 85% power with two-sided 0.05 testing, a sample size of 149 subjects will be randomized in a 1:1 ratio to each of the two treatment groups, ATH-1017 40 mg/qd or placebo, for a total of approximately 298 subjects who are not receiving AChEIs. Approximately 60 subjects have already been randomized to ATH-1017 70 mg/qd; these subjects will complete the study as planned. Therefore, the maximum total enrollment for this study will be approximately 558 subjects as outlined in Table 2 below.

Table 2 Number of Subjects Planned for Enrollment

Number of Subjects						
Receiving AChEIs			Not Receiving AChEIs			
Plc	ATH-1017 40 mg/qd	ATH-1017 70 mg/qd	Plc	ATH-1017 40 mg/qd	ATH-1017 70 mg/qd	Total
~200			~149	~149	~60[a]	~558

AChEI = acetylcholinesterase inhibitor; Plc = placebo; qd = once daily.

[a] Approximate number of subjects who were randomized to ATH-1017 70 mg/qd prior to version 7.

4.2 Inclusion Criteria

1. Age 55 to 85 years, inclusive at the time of signing the informed consent.
2. Mild-to-moderate AD dementia subjects:
   a) MMSE score 14 to 24 inclusive at Screening
   b) Clinical Dementia Rating (CDR) Scale global score of 1 or 2 at Screening
3. Clinical diagnosis of dementia, due probably to AD, by Revised National Institute on Aging -Alzheimer's Association criteria (McKhann, 2011):
   a) Magnetic resonance imaging (MRI) or computerized tomography (CT) scan (for subjects with non-MRI-safe cardiac pacemaker, or other relevant medical reason, with Medical Monitor approval) performed within 12 months before Screening, with findings consistent with the diagnosis of dementia due to AD without any other significant comorbid CNS pathologies. If such scan is unavailable or older than 12 months, it should be repeated to ascertain the diagnosis before randomization.
   b) Documented clinical decline within 12 months before Screening and onset of symptoms at least 12 months before Screening (preferably subject medical records; caregiver reports with examples are acceptable)
4. Formal education of 8 or more years; exceptions may be made for subjects with less than 8 years of education at the discretion of the investigator.
5. Body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2 at Screening; subjects with BMI outside the allowed BMI range but ≥ 16 and ≤ 37 kg/m^2 may enroll only with prior agreement of the Sponsor.
6. Male subjects 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. Only female subjects of nonchildbearing 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 and have approximately 4 to 6 hours daytime contact with the subject for at least 4 days/week.

8. Treatment-free (subjects not receiving AChEI treatment), defined as:
   a) Treatment-naïve, OR
   b) Subjects who received an AChEI in the past and discontinued at least 4 weeks prior to Screening
9. 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.
10. Written informed consent from the 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.
11. 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).
12. 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.
13. 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. History of significant neurologic disease, other than AD, that may affect cognition, or concurrent with the onset of dementia.
2. Subject has atypical variant presentation of AD, if known from medical history, particularly non-amnestic AD.
3. History of brain MRI scan indicative of any other significant abnormality, including but not limited to multiple (> 10) microhemorrhages, severe white matter hyperintensities, history or evidence of a single prior hemorrhage > 1 cm^3, multiple (> 3) lacunar infarcts or evidence of a single prior infarct > 1 cm^3, evidence of a cerebral contusion, encephalomalacia, aneurysms, vascular malformations, subdural hematoma, or space-occupying lesions (e.g., brain tumors). If a known meningioma has been stable for > 1 year and the subject has no history of any type of convulsions, this can be allowable after consultation with the Medical

Monitor. Note: a new MRI scan is required if the scan was performed > 12 months prior to Screening; 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 non-MRI-safe cardiac pacemaker or other relevant medical reason, with Medical Monitor approval.

4. Diagnosis with current symptoms of severe major depressive disorder even without psychotic features. Any subject with formalized delusions or hallucinations are excluded.
5. Geriatric Depression Scale (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.
6. Significant suicide risk as defined by suicidal ideation based on the Columbia-Suicide Severity Rating Scale (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 behaviours).
7. History within 2 years of Screening, or current diagnosis of psychosis (American Psychiatric Association [APA], 2000) or moderate substance abuse disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) (APA, 2013).
8. Untreated conditions, including vitamin B_{12} or folate deficiency, 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 6 months before Screening.
9. Abnormal serum electrolytes (potassium, sodium, magnesium) of clinical significance. If treated, must be stably treated for at least 30 days before Screening.
10. Active, acute, or chronic infectious disease of any type.
11. Myocardial infarction or unstable angina within the last 6 months or history of more than one myocardial infarction within 5 years before Screening.
12. Clinically significant (in the judgment of the investigator) cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (note: pacemaker is acceptable).
13. Subject has either hypertension (supine diastolic blood pressure > 95 mmHg), or symptomatic hypotension in the judgment of the investigator.
14. Clinically significant ECG abnormality at Screening, 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, 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 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.

15. 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); subjects with a history of positive results for cured hepatitis B or hepatitis C may be eligible following discussion with the Medical Monitor and prior approval is required.
16. 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.
17. Hepatic impairment with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal, or Child-Pugh class B and C.
18. Malignant tumor within 3 years before Screening, except for the following conditions that are stable in the judgement 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; prior Medical Monitor approval is required.
19. Clinically significant (in the judgment of the investigator) unintentional weight loss within 12 months of Screening.
20. 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.
21. 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.
22. 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.
23. Prohibited prior and concomitant medications are excluded within 4 weeks prior to Screening. All allowed medications should remain stable throughout the study; for medications negatively affecting cognition, the doses should be stable for at least 4 weeks before Screening and throughout the study, unless otherwise noted. This is not an exhaustive

list; 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 also):

a) Memantine in any form, combination, or dosage

b) Acetylcholinesterase inhibitors in any dosage form

c) Antipsychotics; antipsychotics in low doses (in the judgment of the investigator) are allowed only if given for sleep disturbances, agitation and/or aggression, and only if the subject has received a stable dose for at least 3 months before Screening. If these medications are taken on a PRN basis, they should not be taken the night before any cognitive testing.

d) Tricyclic antidepressants, monoamine oxidase 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

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

f) Sedative hypnotics; Zolpidem is allowed

g) Barbiturates (unless given in low doses for benign tremor)

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

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

j) Systemic immunosuppressants if taken in clinically immunosuppressive doses in the judgment of the investigator (note: immunosuppressant use for allergy or other inflammation, e.g., inhaled steroids, otics, ophthalmologics, skin creams, and intra-articular injections are allowed)

k) Antiepileptic medication if taken for control of seizures. Other uses, e.g., neuropathy and restless legs, are allowed

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

m) Sedating H_1 antihistamines; non-sedating H1 antihistamines are allowed and preferred

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

24. 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 AD investigational drug.

25. The subject has received active amyloid or tau immunization at any time (i.e., vaccination for Alzheimer's disease), or passive immunization (i.e., monoclonal antibodies for Alzheimer's disease) within 6 months of Screening. FDA approved vaccinations or monoclonal antibodies for other indications are allowed.
26. Subject has known allergy to any component of the investigational medicinal product (IMP).
27. 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 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 and has discussed the reason for this with the Medical Monitor. 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 Investigational Medicinal Products

The products that will be used in this study are outlined in Table 3.

Table 3 Identity of Investigational Medicinal Products

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

NA = not applicable; SC = subcutaneous

[a] Subjects were only randomized to this dose prior to version 7 of the protocol.

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% NaCl. 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% NaCl. Placebo pre-filled syringes will be fully matching. 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) during storage 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 at the study site or as needed by direct-to-patient shipment. For visits greater than 2 weeks apart, additional study drug kits may be assigned. 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. A stratified permuted block randomization procedure will be used (stratification will be by screening MMSE severity: mild (MMSE: 20-24) versus moderate (MMSE: 14-19).

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 judgement 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 2) 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 absent any systemic AEs at the 2-hour timepoint. 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 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 Sponsor. However, subjects who are off drug for ≥ 14 consecutive days may be prematurely discontinued from the study, in discussion with the Sponsor.

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 Contract Research Organization (CRO) standard operating procedure (SOP) will be followed for blind breaking procedures.

An unblinded interim analysis was performed for this study by an independent DMC. Sponsor staff involved in the conduct of the trial remain blinded. Details of the interim analysis were pre-specified in the interim Statistical Analysis Plan (iSAP, dated September 2022). After database lock, the overall randomization code will be broken for final analysis and 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 if any of the following criteria/AEs do not resolve in a satisfactory time frame per investigator judgment:

- ALT or AST > 8 × upper limit of normal (ULN)
- ALT or AST > 5 × ULN for more than 2 weeks
- 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 AE of severe intensity and related causality
  - Any SAE of related causality

  (Note: causality as determined by the Sponsor)
- Other clinical laboratory criteria:

  - Creatine phosphokinase (CPK) ≥ 3 × ULN (that cannot be attributed to causes other than the study treatment, i.e., vigorous exercise)
  - Serum creatinine > 1.5 × ULN
  - A decrease from baseline in hemoglobin concentration > 2 g/dL
  - Absolute neutrophil count < 1,000/µL
  - Platelets < 50,000/µL
- Vital sign criteria:

  - Hypotension (systolic blood pressure [SBP] < 90 mmHg and symptomatic). If hypotension is observed during the study and the subject is symptomatic, then a minimum of 2 repeat blood pressure measurements should be obtained approximately 5 minutes apart. The mean of the 3 SBP measurements will be used to determine stopping criteria.
  - Tachycardia defined as heart rate (HR) > 120 beats per minute (bpm) lasting longer than 30 minutes or with impaired consciousness
- ECG criterion:

  - QTcF > 500 msec (if prolonged QTcF interval is observed during the study, then a minimum of 2 sets of repeat ECGs in triplicate should be obtained over a brief period. The mean of the 3 sets of ECGs will be used to determine 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. The conditions of determining eligibility should be taken into account when considering the ECG stopping criterion.

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

The responsibilities of the independent DSMB will be defined in a DSMB Charter and shall include making recommendations regarding continuation of any dose groups (as described in Section 7.3), and of the study itself.

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.

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 in this study and (if subjects decide to participate and are eligible) for the duration of their participation in the optional open-label extension study.

Subjects who decide not to roll over into the open-label extension study upon discontinuation of randomized treatment may continue with their original treatment following consultation with their primary care physician; 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 Mini–Mental State Examination (MMSE)

The Mini–Mental State Examination (MMSE) (Folstein, 1975) is a widely used test of overall cognitive function, assessing memory, orientation, and praxis in a short series of tests. The score is from 0 to 30 with 30 being the best possible and 0 being the worst possible score. The MMSE is administered at Screening with a score of 14 to 24 inclusive for subject eligibility and at Baseline.

6.1.2 Clinical Dementia Rating Scale (CDR)

The Clinical Dementia Rating Scale (Hughes, 1982) is a global rating of the function of AD subjects assessed in 6 categories: memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care. It is based on a semi-structured interview conducted with the subject and caregiver. Each category has scores from 0 (no symptoms) to 3 (severe) from which the overall CDR global score is derived. The CDR is administered at the Screening visit with a score of 1 or 2 required for subject eligibility.

6.2 Efficacy 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]

6.2.1 Primary Efficacy Variable: Composite of Cognition and Function

6.2.1.1 Global Statistical Test (GST) Score

A composite approach will be used to facilitate the assessment of an overall change in disease status/trajectory in the trial. The GST score will be defined as a single outcome variable based on standardizing and then combining individual patient-level change from baseline cognition (ADAS-Cog$_{11}$; Section 6.2.2.1) and functional (ADCS-ADL23; Section 6.2.3.2) scores. The GST score will be determined for each patient at each time point and the resulting scores will define the efficacy outcome variable to be used in the primary efficacy analysis. Full details will be provided in the Study SAP.

6.2.2 Cognitive Variables

6.2.2.1 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog$_{11}$)

The ADAS-Cog$_{11}$ is designed to measure cognitive symptom change in subjects with AD (Rosen, 1984). The standard 11 items are 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 test includes 7 performance items and 4 clinician-rated items, with a total score ranging from 0 (no impairment) to 70 (severe impairment). Therefore, higher scores indicate more severe cognitive impairment.

Due to known circadian fluctuations of cognitive capacity (Hilt, 2015), ADAS-Cog$_{11}$ will be assessed in the morning at approximately the same time of day as the baseline assessment for all applicable visits.

ADAS-Cog$_{11}$ assessments will be performed at Screening and pre-dose at Visit 2 (Baseline/Day 1), and post-dose at approximately 1 hour (± 30 minutes) at Visit 3 (Week 2), Visit 4 (Week 6), Visit 5 (Week 12), Visit 7 (Week 20), Visit 8/ET (Week 26), and Visit 9 (Safety follow-up; no dosing).

6.2.3 Disease Condition

[redacted]

6.2.3.2 Alzheimer's Disease Cooperative Study – Activities of Daily Living, 23-item Version (ADCS-ADL23)

The ADCS-ADL23 (Galasko, 1997) is a 23-item assessment of functional impairment in terms of activities of daily living administered to the support person/caregiver. It comprises 23 questions about the subject's involvement and level of performance across items representing daily living. The questions range from basic to instrumental activities of daily living. Each item is rated from the highest level of independent performance to complete loss. The total score range is from 0 to 78, with lower scores indicating greater functional impairment. ADCS-ADL23 assessments will be performed at any time during Visit 2 (Baseline/Day 1), post-dose at Visit 5 (Week 12), Visit 7 (Week 20) and post-dose at Visit 8/ET (Week 26).

[redacted]

[redacted]

[redacted]

6.3 Safety Variables

6.3.1 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 6.3.1.5).

6.3.1.1 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), 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
- New condition detected or diagnosed after Screening even though it may have been present in the medical history before the start of the study
- 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.

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events not meeting the definition of AE include:

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

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

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

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

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

6.3.1.2 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 subject identifiers, with the exception of the subject 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.

In the event that a moderate or severe injection site reaction is reported, the site will take photographs of the affected area for subjects consenting to photographs.

6.3.1.3 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. 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 4 should be selected based on medical judgment, considering the definitions below and all contributing factors. In this study AEs will be considered related to IMP/study procedure if causality is ascribed as either related, probably related, or possibly related.

Table 4 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 readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

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

Seriousness

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

- Results in death.

- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation in existing hospitalization; in general, hospitalization signifies that the subject 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.

6.3.1.4 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 subjects 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) a reasonable causal relationship with the IMP.

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

The 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

The 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 the 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 SAE Report Form. Additional information (copy of lab reports, consultant reports, copy of discharge summaries, etc.) should be provided on request of MMS Drug Safety and Pharmacovigilance.

If a new SAE Report Form is faxed or emailed, then the Principal Investigator must sign and date the form. In rare circumstances, and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE Report Form sent by email [redacted] or Fax [redacted]. 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 (ICSR) 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.

6.3.1.5 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 7.7).

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.

6.3.2 Pregnancy

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. Only female subjects of non-childbearing potential (i.e., permanently sterilized, postmenopausal) are eligible for participation.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the MMS Drug Safety and Pharmacovigilance within 24 hours of learning of the partner's pregnancy. The 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

6.3.3 Clinical Laboratory Assessments

The following laboratory variables will be determined as outlined in Table 5 below:

Table 5 Clinical Laboratory Assessments

Test	Parameters	
Hematology	CBC HbA1c Hemoglobin Hematocrit Erythrocytes (RBC)	Leukocytes (WBC) Differential WBC Platelets
Biochemistry	Sodium Potassium Magnesium FSH (post-menopausal females only) Calcium Chloride Glucose Creatinine ALP AST	GGT CPK Total bilirubin Total protein Albumin Total Cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides Vitamin B_{12} [a]

	ALT	Folate [a] TSH, fT3 and fT4 [a]
Coagulation	INR PT	aPTT
Serology	HBsAg HCV	HIV type 1 or type 2
Urinalysis	pH glucose ketones specific gravity	nitrite protein bilirubin blood

CBC = complete blood count; RBC = red blood cells; WBC = white blood cells; AST = aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; aPTT = activated partial thromboplastin time; fT3 = free tri-iodothyronine; fT4 = free thyroxine; TSH = thyroid-stimulating hormone

[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 per stopping criteria described in Section 5.8.

A medical alert for potential Hy's law cases (possible drug-induced liver injury) will be issued based on lab values and supported by Medical Monitor interpretation. Investigators, the Sponsor, Medical Monitor [redacted], and MMS (Sponsor's designated CRO for Drug Safety and Pharmacovigilance [redacted]) 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.

6.3.4 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 systolic blood pressure of ≥ 20 mmHg, or in diastolic blood pressure of ≥ 10 mmHg will be considered abnormal.

6.3.5 Weight

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

6.3.6 12-Lead Electrocardiogram

Standard safety 12-lead ECGs will be performed 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 sequentially, 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. 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, in discussion with the Medical Monitor.

6.3.7 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, and neurological systems).

Body weight (kg) and height (meters) will be assessed at Screening. Body weight and height will be used to calculate body mass index 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.

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

The C-SSRS will be performed at Screening, Baseline/Day 1, Visit 3 (Week 2), Visit 4 (Week 6), Visit 5 (Week 12), Visit 7 (Week 20), Visit 8/ET, and Visit 9 (Safety follow-up) (Week 26) (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.

6.3.9 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, Baseline/Day 1, Visit 5 (Week 12), Visit 8/ET (Week 26), and Visit 9 (Safety follow-up).

6.4 Pharmacokinetic Variables

Blood will be collected for PK analyses at the timepoints detailed in Table 1. The actual time of PK sampling will be recorded.

Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual. In brief, blood will be processed, and plasma analyzed by a validated method for concentrations of ATH-1017 and ATH-1001. PK parameters will be calculated from the plasma concentration-actual time profiles. The noncompartmental analysis, if feasible, will be performed using WinNonlin version 7.0. Plasma concentrations may also be used for population PK analysis, the results of which will be reported separately.

6.5 Genotyping

Blood sample(s) will be collected at Screening for analysis of ApoE genotype.

6.6 Plasma Sample Collection (Biomarker Analyses)

Collection of samples for blood-based biomarkers is also part of this study, with sample results analyzed as described in Sections 8.3.2 and 8.3.3 (further biomarkers may be analyzed in addition to those specified). Plasma samples for biomarkers will be collected pre-dose at Baseline (Day 1), Week 12 (Visit 5), and at the last scheduled visit (Week 26) from all subjects in this study (Table 1).

[redacted] analysis will be performed to determine impact of ATH-1017 treatment on biomarkers thought to relate to AD progression and/or pathology, as well as to evaluate their association with observed clinical responses.

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 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.

7.1 Schedule and Order of Assessments

The study will consist of up to 28 days of Screening (Day -28 through Day -1) followed by 26 weeks of randomized 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:

[redacted]

(2) ADAS-Cog$_{11}$

[redacted]

[redacted]

At Baseline/Day 1 (Visit 2), MMSE should be done first before all other assessments pre-dose.

MMSE assessments will be performed first before all other clinical outcome assessments post-dose at approximately 30 minutes (± 15 minutes) at Week 20 (Visit 7) and Week 26 (Visit 8).

ADAS-Cog$_{11}$ [redacted] assessments should occur at clinic visits in the morning at approximately the same time they were performed during the initial Baseline/Day 1 assessment. ADAS-Cog$_{11}$ [redacted] assessments will be performed pre-dose at Baseline/Day 1 (Visit 2), and post-dose at approximately 1 hour (± 30 minutes) at Week 2 (Visit 3), Week 6 (Visit 4) Week 12 (Visit 5), Week 20 (Visit 7), and Week 26 (Visit 8); and additionally at Safety follow up (visit 9; no dosing).

[redacted]

PK plasma samples will be collected at pre-dose and post-dose at Baseline/Day 1 (Visit 2); pre-dose and post-dose at Week 12 (Visit 5) and Week 26 (Visit 8). The pre-dose PK sample is collected any time before dosing. The post-dose PK sample is collected anytime between 30 minutes and 120 minutes after dosing as practical. The actual time of dosing and of PK sampling will be recorded.

The order of assessments for all other endpoints is 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):

- Visits 1 (Screening), 2 (Baseline/Day 1), 5 (Week 12), 8 (Week 26), and 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 subjects 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)

- Visits 3 (Week 2), 4 (Week 6), 6 (Week 16), and 7 (Week 20) should be conducted onsite 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

7.3 Data Safety Monitoring Board

An independent DSMB will conduct periodic review and assessments of unblinded safety data (AEs, labs, ECG, etc.) throughout the study to ensure the safety of study subjects. Based on unblinded safety data review, the DSMB may recommend terminating the study.

The DSMB is composed of at least a study-independent non-Sponsor physician and a study-independent statistician. Additional members have been included and ad hoc members may also be invited depending on the safety findings and required scope of expertise.

Details regarding the DSMB are included in the DSMB charter, including committee membership, data review procedures, frequency of review, and communication between the DSMB and others.

7.4 Supportive Care Measures for Potential Adverse Events

If a subject experiences an AE relating to eosinophilia or an ISR, the investigator will take the appropriate follow-up action to manage clinical symptoms and monitor subject safety (Table 6).

Table 6 Supportive Care Measures and Follow-up of Potential Adverse Events

Adverse Event	Action Required
Eosinophilia	
AEC < 3000/µL	Continue IP as per protocol.
AEC > 3000/µL	Arrange repeat measurement within 2 weeks and continue IP. • If further increase of AEC on 2 repeat tests, consult with Medical Monitor and Sponsor. ○ Consider hold of IP for 2 weeks. • If trend is stable or downward on 2 repeat tests, continue IP and standard testing schedule as per protocol.
AEC increase associated with other hematologic signs or symptoms	Consult with Medical Monitor and Sponsor promptly and follow local SOP for SAE/Emergency as appropriate. • Consider hold of IP for 2 weeks.

Injection Site Reaction	
Mild ISR	Consider treatment with topical hydrocortisone 1% and/or non-sedating antihistamines up to twice daily, as needed.
Moderate ISR	Immediately apply prescription strength ointment/cream (e.g., Triamcinolone, 0.1% Betamethasone, 0.05% Clobetasol, and/or non-sedating antihistamines) up to twice daily, as needed.

AEC = absolute eosinophil count; IP = investigational product; SAE = serious adverse event; SOP = standard operating procedure.

7.5 Concomitant Medications and Treatments

7.5.1 Prohibited Treatments During 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.

Use of the following drugs is excluded within 4 weeks prior to Screening:

- Memantine in any form, combination, or dosage
- Any AChEI in any dosage form

The following drugs are prohibited during the study:

- Memantine in any form, combination, or dosage
- Any AChEI in any dosage form
- 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 7.5.2).
- Nicotine therapy (including patches), varenicline (Chantix), or similar therapeutic agent
- Peripherally acting drugs with effects on cholinergic neurotransmission. Solifenacin is allowed if the subject has received a stable dose for at least 3 months before Screening
- Systemic immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses in the judgment of the investigator (for exceptions see Section 7.5.2)
- Antiepileptic medication if taken for control of seizures. Other uses e.g., neuropathy and restless legs, are allowed

- 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); topical applications are allowed (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); topical applications are allowed (see Appendix 1: List of Prohibited Medications for non-exhaustive list)

Subjects that use prohibited medications listed above during the randomized 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.

7.5.2 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

The dosage(s) of 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 negatively 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 7.5.1, 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 only if given for sleep disturbances, agitation and/or aggression, and only if the subject has received a stable dose for at least 3 months before Screening. If these medications are taken on a PRN basis, they should not be taken the night before any cognitive testing.

Low doses (in the judgement 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, monoamine oxidase inhibitors, and S-ketamine, all other antidepressant medications are allowed.

Immunosuppressant use for allergy or other inflammation, e.g., inhaled steroids, otics, ophthalmologics, skin creams, and intra-articular injections are allowed.

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

7.5.3 Other Restrictions

7.5.3.1 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 and MCT, are excluded during the study, beginning 7 days prior to the first dose of study medication (Day 1). THC is prohibited beginning 4 weeks prior to the first dose of study medication (Day 1) and for the duration of the study. CBD without THC is allowed but not on the clinical visit days except for topical applications. CBD use should be recorded as concomitant medication.

7.5.3.2 Contraceptives

Sexually active males with female 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.

7.6 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 contact 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.

7.6.1 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 may continue with their original treatment following consultation with their primary care physician; 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).

7.6.2 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 ET 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 an ET visit for final assessments.

Upon discontinuation of study drug, subjects may continue with their original treatment following consultation with their primary care physician; tapering off study medication is not required.

7.7 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.

7.8 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 subjects 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 ITT Population

The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether or not the subject received test article. A subject is considered randomized when the test article assignment (i.e., completes a randomization transaction) is provided. Analyses will be based on the randomized treatment assignment.

8.1.2 MITT Population

The modified intent-to-treat (mITT) population is a subset of the ITT population, which will include all randomized subjects who took at least one dose of the study medication and who, during at least one post-baseline visit, completed both an ADAS-Cog_{11} and ADCS-ADL23 assessment, as well as at baseline. Analyses will be based on the randomized treatment assignment.

8.1.3 Primary Analysis Population

The primary analysis population is comprised of all members of the mITT population who were not taking AChEIs during the trial, and were randomized to either ATH-1017 40 mg/qd or placebo. Analyses will be based on the randomized treatment assignment.

8.1.4 Per Protocol Population

The per protocol population will include all primary analysis subjects who took the assigned medication, completed both an ADAS-Cog_{11} and ADCS-ADL-23 assessment during at least one post-baseline visit as well as at baseline, and did not have any major protocol deviations that are deemed to potentially interfere with efficacy as evaluated at a classification meeting prior to unblinding. Analyses will be based on the actual treatment received.

8.1.5 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 measurement prior to first dose is defined as the baseline value. For efficacy measures, baseline is defined as either the measurement on Day 1, or else the last measurement before Day 1 if there is no Day 1 measurement. If no test article is received, baseline is defined as the value closest to but prior to randomization.

Statistical tests for the primary and secondary efficacy endpoints will use a hierarchical gatekeeping procedure to account for multiplicity, with two-sided tests at 0.05 (Dmitrienko, 2013).

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 Statistical Analyses

8.3.1 Primary Efficacy Analysis - GST Score

The primary efficacy hypothesis is that treatment with ATH-1017 40 mg/qd will result in a statistically significant reduction in the Global Statistical Test score (GST; O'Brien, 1984) compared to the placebo group at Week 26 in the primary analysis population (Section 8.1.3). The primary analysis will test the statistical null hypothesis of no difference between ATH-1017 40 mg/qd and placebo.

The primary analysis will use a mixed model for repeated measures (MMRM) to compare treatment and placebo in the GST score, which is a composite of cognition and function, calculated as the average of two change from baseline z-scores; the z-scores are calculated for the change from baseline scores for cognition (ADAS-Cog$_{11}$) and function (ADCS-ADL23). This analysis will assess whether there is a difference in mean GST scores between treatment and placebo at 26 weeks using least squares means estimates from the MMRM model, which will include terms for baseline value, visit, treatment, visit by treatment interaction, ApoE4 carrier status, pooled site as a factor (with geographically similar sites grouped and a group of sites using Spanish for clinical assessments), baseline age (continuous), and the baseline MMSE stratification factor. 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. Statistical testing to the key secondary efficacy endpoints only continues if the null hypothesis for the primary endpoint is rejected.

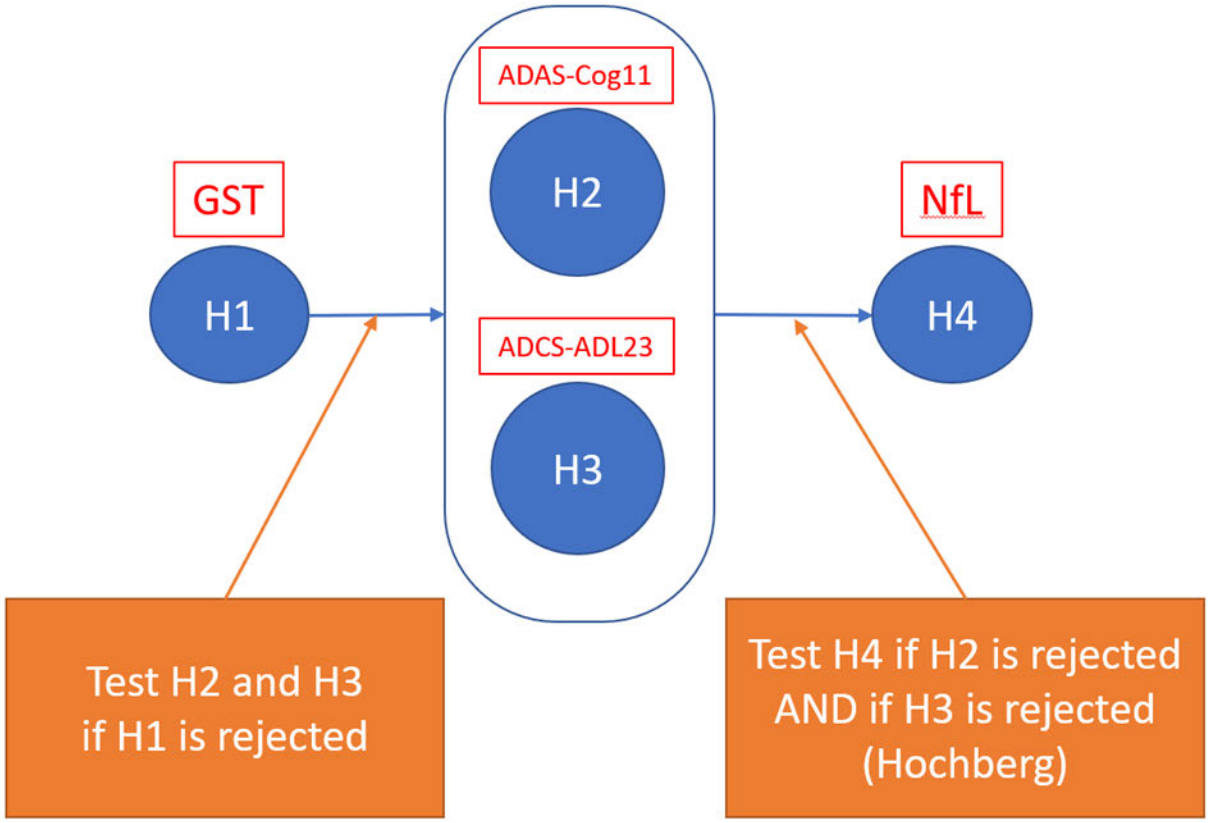
8.3.2 Key Secondary Efficacy Analysis – ADAS-Cog$_{11}$, ADCS-ADL23, and Biomarkers (NfL)

If the null hypothesis for GST score is rejected, then the key secondary endpoints of change from baseline in ADAS-Cog$_{11}$ and ADCS-ADL23 will be analyzed (Refer to the SAP for details),

using an MMRM as described for the primary analysis. These individual endpoints will be tested using the Hochberg procedure. If both of these null hypotheses are also rejected after the Hochberg-based multiplicity adjustment, then the key secondary efficacy endpoint of change from baseline in NfL concentration will also be analyzed using an MMRM as described for the primary analysis.

The statistical testing hierarchy for the study is presented in Figure 3. This strategy controls the overall Type I error rate for the primary and key secondary efficacy endpoints.

Figure 3 Hierarchical Statistical Gatekeeping Strategy



ADAS-Cog$_{11}$ = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL23 = Alzheimer's Disease Cooperative Study-Activities of Daily Living, 23-Item Version; GST = Global statistical test score; NfL = Neurofilament light chain.
The null hypothesis of no effect is presented for each comparison of ATH-1017 40 mg/qd versus placebo as follows: H1 = GST score; H2 = ADAS-Cog$_{11}$ score; H3 = ADCS-ADL23 score; H4 = NfL.

[redacted]

[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 at 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 percent 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 scheduled and unscheduled 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**.**

8.5 Pharmacokinetic Analyses

PK and pharmacogenetics analyses will be described in a separate document.

8.6 Determination of Sample Size

The sample size for the trial was chosen to provide 85% power for the primary endpoint. The following 40 mg/qd treatment effect premises were made to support sample size calculations:

- Change from Baseline to Week 26 in ADAS-Cog$_{11}$: Mean treatment difference (standard deviation): 1.8 (6).
- Change from Baseline to Week 26 in ADCS-ADL23: Mean treatment difference (standard deviation): 2.7 (9).

The sample size of 149 evaluable subjects (subjects in the primary analysis population) per trial arm would yield at least 85% power with a two-sided 0.05 level. The power calculations were performed using a simulation-based approach with 10,000 simulation runs based on the parameters listed above (in addition, it was assumed that the endpoint-specific statistics follow a multivariate normal distribution with a correlation coefficient of 0.5). Power was estimated as the fraction of the simulation runs where the primary endpoint was significant at a two-sided 0.05 level.

In view of the overall number of subjects already enrolled prior to version 7 of this protocol, including those receiving background AChEI therapy (200 subjects), and those already randomized to the 70 mg treatment group not receiving AChEI therapy (60 subjects), the maximum number of subjects to be enrolled would be approximately 558.

8.7 Interim Analysis

An interim analysis was planned for this study to allow the possibility of stopping for futility, or to potentially increase sample size to achieve a target study power. The SSR procedure was based on the Promising Zone Design (Mehta and Pocock, 2011). The interim analysis included approximately the first 100 subjects not on background AChEIs who had completed the trial (either completion of Week 26 assessments or else terminated early). This corresponded to approximately a 45% information fraction, based on a planned final sample size of approximately 175 subjects not on background AChEIs. The futility stopping and SSR rules were based on the CP calculated for the primary efficacy endpoint (GST score), using a pooled analysis of the ATH-1017 cohorts versus the placebo cohort, at a one-sided 0.05 level. Subject enrollment proceeded without interruption while the interim analysis was ongoing.

Detailed definitions of the zones, sample size increase rule within the promising zone and statistical methods used for the interim analysis were pre-specified in a separate iSAP prior to the actual interim analysis. An Independent Data Monitoring Committee (IDMC) reviewed the SSR report and provided an appropriate recommendation for a sample size increase from among several pre-specified options, which were each keyed to various potential CP results. The written recommendation was provided to the Sponsor for implementation of the new recommended sample size as described in the iSAP. The final analysis will apply the combination function

method (Cui-Hung-Wang method; Cui, 1999) to account for the sample size increase resulting from the interim, refer to the study SAP for details.

The specific required sample size post-interim analysis recommended by IDMC was not communicated to staff involved in the day-to-day conduct of this clinical trial.

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 MMSE, CDR, ADAS-Cog$_{11}$, [redacted] will take place for rating quality control purpose. 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 x-rays 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 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.

9.6 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.

9.7 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.

9.8 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

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
Acetylcholinesterase inhibitors	• Donepezil (Aricept) • Galantamine (Rasadyne) • Rivastigmine (Alzest, Exelon, Kerstipon, Nimvastid, Prometax)
Peripherally acting anticholinergics	• 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, anti-depressants (tricyclic), anxiolytics or sedative hypnotics.	Antipsychotics (Please refer to Exclusion 23c 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) • Aripiprazole (Abilify) • 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) Tricyclic antidepressants • 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 • Sedating H_1 antihistamines • Chronic opioids • S-ketamine • Anti-epileptics
Systemic moderate or strong CYP3A4 inhibitors	• Boceprevir (Victrelis) • Cannabidiol • 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) • Troleandomycin • Verapamil

Category of Prohibited Medications	Examples: General Name (Trade Name)
	• Voriconazole (Vfend)
Systemic moderate or strong CYP3A4 inducers	• Avasimibe • Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro, Teril) • Mitotane (Lysodren) • Modafinil *(at doses 400 mg qd 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