Clinical Study Protocol

Open-Label Extension of Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 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-0203
IND No.:	135103
Investigational Medicinal Product (IMP) Name:	Fosgonimeton (ATH-1017)
Development Phase:	Phase 3
Emergency Telephone Number:	(Refer to the study contacts page)
SAE Reporting FAX Number/Email:	[redacted]
Date of Final Protocol:	12 APR 2024
Version:	4

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

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: Open-Label Extension of Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 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)

[redacted]

Athira Pharma, Inc.

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: Open-Label Extension of Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 in Subjects with Mild to Moderate Alzheimer's Disease

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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:	Open-Label Extension of Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 in Subjects with Mild to Moderate Alzheimer's Disease	
Study Number:	ATH-1017-AD-0203	
Development Phase:	Phase 3	
Sponsor:	Athira Pharma, Inc.	
Type of Study	Interventional	
Study Centers:	The study will be conducted at approximately 65 centers across the US	
Study Objectives and Endpoints:	**Primary Objective**	**Primary Endpoints**
	To determine the safety and tolerability of ATH-1017 over an additional 206-week period in subjects with mild to moderate Alzheimer's disease (AD) who completed the 26-week randomized treatment in Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202	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, and Columbia – Suicide Severity Rating Scale (C-SSRS)
	[redacted]	[redacted]
Study Design:	This is a multicenter, OLEX study of ATH-1017 treatment in subjects with a clinical diagnosis of mild to moderate Alzheimer's disease (AD) who completed 26 weeks of treatment in the randomized, placebo-controlled, double-blind studies ATH-1017-AD-0201 and ATH-1017-AD-0202; hereafter referred to as the 'parent studies'. The study will be conducted at approximately 65 centers across the United States (US) for a total of 206 weeks (47.5 months) open-label treatment. Eligible subjects will roll over directly from the parent studies, such that Visit 1 (Day 0) of this study is the Week 26 visit from either of the two parent studies All subjects who complete the Week 26 visit of either of the two parent studies and meet the inclusion/exclusion criteria of Study ATH-1017-AD-0203 will be assigned to open-	

	label active treatment with ATH-1017 at a dose of 40 mg/day, unless the safety results obtained at Visit 7 of the parent studies or new baseline safety labs suggest otherwise, in which case they will not be eligible for this OLEX study.. Subjects who do not tolerate ATH-1017 40 mg/day, and/or who meet the stopping criteria, will be withdrawn from the study. As of v3 of this protocol (01 JUN 23), the dose of 70 mg/day ATH1017 was discontinued- and subjects who were previously assigned to this dose were reassigned to the dose of 40 mg/day ATH-1017. Study drug will be administered by subcutaneous (SC) injection once daily (OD), preferably during the daytime. Subjects will take their last dose of blinded IMP (assigned to them in Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202) on site under supervision of site staff at Visit 8/Day 182 of the parent studies (i.e., Visit 1/ Day 0 of this OLEX study). The first dose of open-label IMP from this study will be administered by subject or caregiver at the clinic the next day (Visit 2/Day 1), followed by a safety observation window of 1 hour (± 15 minutes) post-dose. Subjects must not take more than one dose within 8 hours of the previous dose. The subject should withhold study drug administration on the day of 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, in accordance with all protocol requirements. During the open-label treatment period, clinic visits will take place on Day 0 and thereafter at Day 1, Weeks 2, 6, 12, 18, 22, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, and 206. Telephone call visits are scheduled for Week 1 (Day 7), and Week 4 (Day 28). A safety follow-up visit is scheduled 4 weeks after completion of the open-label period at Week 210 (see Table 1 for Schedule of Assessments). Subjects may live at home, in a senior residential setting, or an institutional setting without the need for continuous nursing care. The end of the study is defined as the date of the safety follow-up visit, Visit 41/Week 210. Subjects who terminate prior to Visit 40 are to complete same assessments as Visit 40/early termination (ET) within 2 weeks of the date of ET. An independent Data Safety Monitoring Board will conduct periodic review and assessments of safety data (AEs, labs, ECG, etc.) throughout the study to ensure the safety of study subjects.

Treatments Administered:	Subjects will not be randomized to treatment in this OLEX study. All subjects who complete the Week 26 visit of either of the two parent studies, and meet the inclusion/exclusion criteria of Study ATH-1017-AD-0203, with no safety concerns from results obtained at Visit 7 of either of the two parent studies, will be assigned to open-label active treatment with ATH-1017 at a dose of 40 mg/day. -
Investigational Medicinal Products:	Open-label Treatment: ATH-1017 will be presented in prefilled 1 mL syringes of 40 mg/mL. Prior to v3 of this protocol (01 JUN 2023), the 70 mg/mL dose was also presented in prefilled 1 mL syringes.
Number of Subjects:	It is estimated that up to approximately 450 subjects will enter this OLEX study; subjects will roll over from Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 (the parent studies).
Duration of Treatment:	The study will consist of 206 weeks open-label treatment and a 4-week safety follow-up.
Study Population:	**Inclusion** 1. Subject has completed the Week 26 visit of either of the two parent studies. 2. Male subjects and their partners must agree to continue 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. 3. Reliable and capable support person/caregiver, who is willing to accept responsibility for supervising the treatment or, if required, administering study drug in accordance with all protocol requirements. The support person/caregiver must see the subject at least once daily for administering or supervising dose administration. 4. Subject capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form 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. 5. 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. 6. 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). 7. 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.

	8. 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** 9. Subject has experienced a serious treatment-related AE during either of the two parent studies, which in the opinion of the investigator could present an increased safety risk to the subject during the OLEX study, in discussion with the Medical Monitor. 10. New diagnosis of severe major depressive disorder even without psychotic features. Any subject with formalized delusions or hallucinations are excluded. 11. Significant suicide risk as defined by suicidal ideation based on the C-SSRS at Visit 1 (i.e., a 'yes' response to Question 4 or 5, or any specific behaviours). 12. Newly diagnosed malignant tumor, 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. 13. 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:** Safety analyses will be based on the Safety Population consisting of all subjects who received at least one dose of the study medication. All safety parameters will be summarized descriptively. [redacted] **Sample Size Considerations:** For this OLEX study, no formal sample size calculation was used.

Table 1 Schedule of Assessments (Subjects Rolling Over Directly)

	Open-label Treatment Period (206-week)										
	Visit:	1 (Week 26/ Visit 8 from 0201 or 0202 study)	2#	3*	4	5*	6	7	8	9‡	10
	Week:	1	1	1	2	4	6	12	18	22	26
Assessment	**Day:**	0	1	7 (±2)	14 (±7)	28 (±7)	42 (±7)	84 (±7)	126 (±7)	154 (±7)	182 (±7)
Inclusion/Exclusion[a]		X									
Informed Consent		X									
Weight		X†									X
C-SSRS[b]		X†			X		X	X	X		X
[redacted]		[redacted]	[redacted]					[redacted]			[redacted]
[redacted]		[redacted]						[redacted]			[redacted]
[redacted]		[redacted]						[redacted]			[redacted]
Drug Dispensing[e]			X		X		X	X	X	X	X
DB Dose of IMP in clinic[f]		X†									
OL Dose of IMP in clinic[g]			X[h]		X		X	X	X		X
Drug Accountability		X†	X	X	X	X	X	X	X	X	X
Physical and Neurological Exam		X†			X		X	X	X		X
12-Lead ECG[i]		X†			X		X	X	X		X
Vital signs[j]		X†			X		X	X	X		X
Safety Labs[k]		X†			X		X	X	X		X
AE[l]		X†	X	X	X	X	X	X	X	X	X
Conmeds[m]		X†	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]						[redacted]			[redacted]
Subject/caregiver experience study[p]											X

	Open-label Treatment Period (206-week) (continued)																	
	Visit:	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
	Week:	32	38	44	50	56	62	68	74	80	86	92	98	104	110	116	122	128
Assessment	**Day:**	224 (±7)	266 (±7)	308 (±7)	350 (±7)	392 (±7)	434 (±7)	476 (±7)	518 (±7)	560 (±7)	602 (±7)	644 (±7)	686 (±7)	728 (±7)	770 (±7)	812 (±7)	854 (±7)	896 (±7)
Weight					X					X				X				
C-SSRS[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
Drug Dispensing[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OL Dose of IMP in clinic[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical and Neurological Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Labs[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conmeds[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		

	Open-label Treatment Period (206-week) (continued)														Safety Follow-up
	Visit:	28	29	30	31	32	33	34	35	36	37	38	39	40/ET[o]	41
	Week:	134	140	146	152	158	164	170	176	182	188	194	200	206	210
Assessment	**Day:**	938 (±7)	980 (±7)	1022 (±7)	1064 (±7)	1106 (±7)	1148 (±7)	1190 (±7)	1232 (±7)	1274 (±7)	1316 (±7)	1358 (±7)	1400 (±7)	1442 (±7)	1470 (±7)
Weight		X				X					X			X	X
C-SSRS[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Drug Dispensing[e]		X	X	X	X	X	X	X	X	X	X	X	X		
OL Dose of IMP in clinic[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical and Neurological Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Labs[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conmeds[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]			[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	

[redacted] AE = Adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; ET = early termination; IMP = investigational medicinal product; [redacted] OL = open-label.

a For inclusion/exclusion criteria that are dependent upon laboratory data results, the Week 20 (Visit 7) laboratory data from Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202 can be used; results from Visit 1 in this study (Visit 8 of the parent studies) will be confirmatory.

b 'C-SSRS Since Last Visit' version will be administered at all visits. C-SSRS will be performed anytime during the visit.

[redacted]

e Dispensing of kits containing study drug will occur during clinic visits at the study site or as needed by direct-to-subject shipment; larger provision of study drug is permitted to accommodate personal need, e.g., vacation; drug returns will be recorded and compliance calculated. IMP administration by the subject or caregiver will be assessed at all clinic visits.

f Subjects should withhold last dose of DB IMP (from Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202) on Day 0 (Visit 1) (Visit 8 of the parent studies); IMP administration will be done on site under supervision of site staff at this visit; investigator discharge from the clinic will be required.

g Subjects should withhold OL IMP dose on the day of clinic visits, whereupon IMP administration will be done on site under supervision of site staff. There is no specified in-clinic observation period for clinic visits (except for Visit 1/Day 0), but investigator discharge from the clinic will be required.

h Subjects will administer first dose of OL IMP (from this study, ATH-1017-AD-0203) at the clinic, followed by a safety observation window of 1 hour (± 15 minutes) post-dose.

i 12-lead ECGs will be performed 30 (± 15) minutes post-dose in triplicate, sequentially.

j Vital signs will be performed pre-dose at 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 (see footnote 'a' also, regarding lab values at Visit 1 being confirmatory).

l AEs will be reported by the subject (or, when appropriate, by a caregiver, support person, or the subject's legally authorized representative). AE reporting will begin after the first dose of open-label IMP at Visit 2 (Day 1) and will continue until the end of the study (Visit 41 – Safety Follow-up).

m Prior or concurrent medications.

[redacted]

o Subjects who terminate prior to Visit 40 are to complete same assessments as Visit 40/ET (early termination) unless they completed the assessment within 4 weeks of the ET visit.

[redacted]

* Visit 3 (Day 7/Week 1) and Visit 5 (Day 28/Week 4) are phone call visits.

‡ Visit 9 (Week 22) is a dispensing visit; caregivers will also provide information on drug accountability, AEs, and concomitant medication at this visit.

† Procedures performed at Visit 8 (Week 26) of Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202 do not need to be repeated at Visit 1/Day 0 in the open-label study.

\# For subjects who completed the Visit 9 (Week 30-safety follow-up) of the parent studies before entering this open-label study, Visit 1 (Day 0) is not applicable. Procedures performed at Visit 8 (Week 26) of Study ATH-1017-AD-0201 and Study ATH-1017-AD-0202 will be repeated in Visit 2 (Day 1) during the first visit of the open-label study; inclusion/exclusion, informed consent, and drug dispensing for the open-label study will be performed at Visit 2 (Day 1) in such cases. If Visit 2 of this open-label study is ≤ 2 weeks from completion of Visit 9 of one of the parent studies, the visit will follow the schedule of assessments as outlined in the table above. If Visit 2 of this open-label study is > 2 weeks from completion of Visit 9 of one of the parent studies, then the inclusion/exclusion criteria, informed consent, [redacted] and safety-related

assessments (C-SSRS, vital signs, safety labs, 12-Lead ECG, physical exam/neurological exam, AEs, and concomitant medications) will be performed at Visit 2 (Day 1) prior to administration of the first dose of open-label study treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	[redacted]
AD	Alzheimer's disease
AE	Adverse event
AKT	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoE	Apolipoprotein E
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CBC	Complete blood count
CPK	Creatine phosphokinase
CNS	Central nervous system
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalogram
ERP	Event-related potential(s)
ET	Early termination
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	Gamma-glutamyl transferase
HGF	Hepatocyte growth factor
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
LAR	Legally authorized representative
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase

MET	MET receptor tyrosine kinase
MMSE	Mini-Mental State Examination
NfL	Neurofilament light chain
NMDA	N-methyl-D-aspartate
OD	Once daily
OLEX	Open-label extension
P	Phosphorylated
PD	Pharmacodynamic(s)
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PKC	Protein kinase C
PLCγ	Phospholipase C-gamma
PM	Plasma membrane
PSP	Post-synaptic potential
[redacted]	[redacted]
PT	Prothrombin time
qEEG	Quantitative electroencephalogram
QTcF	Corrected QT interval using Fridericia's formula
RAC1	Ras-related C3 botulinum toxin substrate 1
RAF	Rapidly accelerated fibrosarcoma (protein)
RAS	Rat sarcoma (protein)
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SOP	Standard operating procedure
STAT3	Signal transducer and activator of transcription 3
ULN	Upper limit of normal
US(A)	United States (of America)
WBC	White blood cells

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 drug 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 drug ATH-1001 acts as a positive modulator at the hepatocyte 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

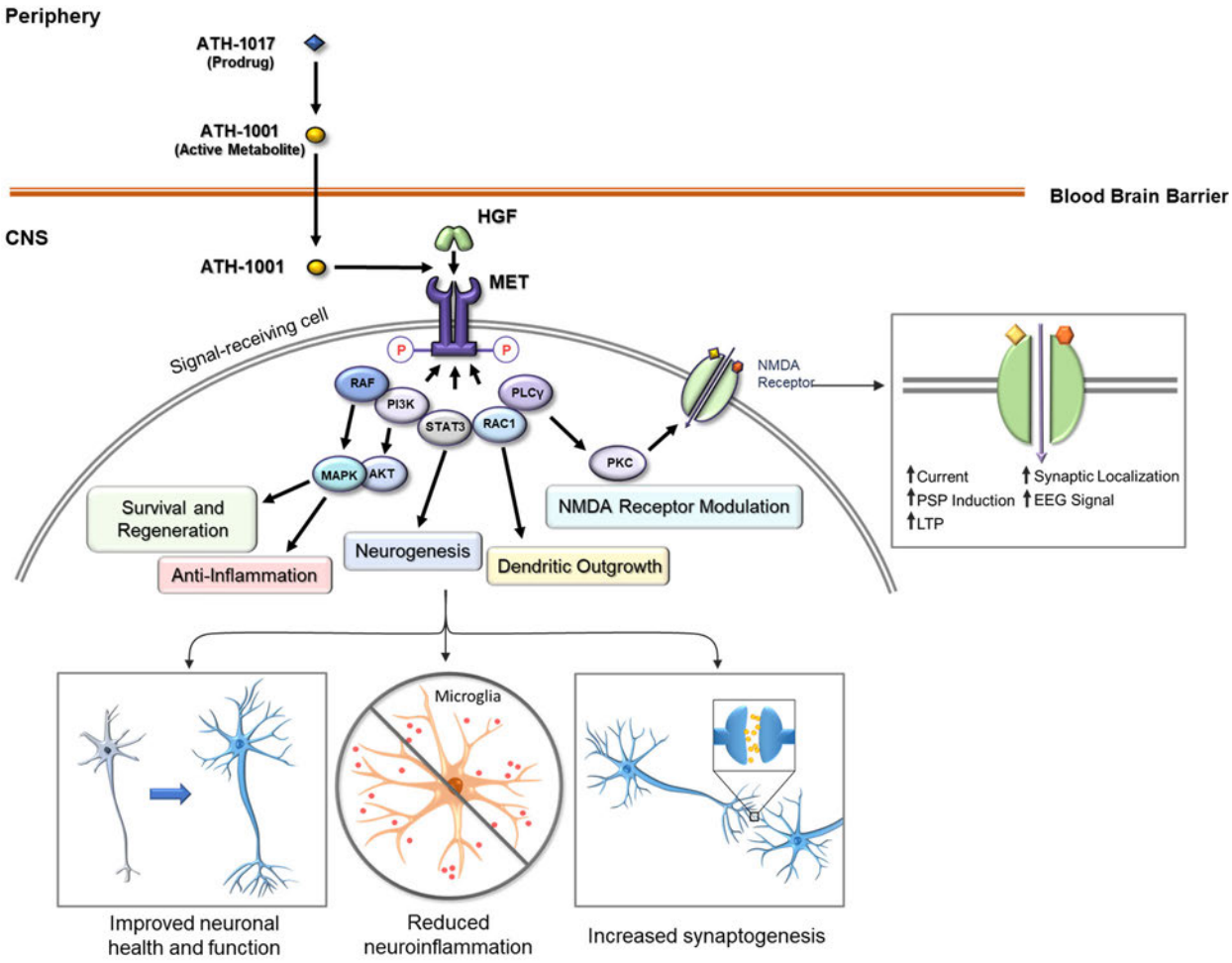
Dementia of the Alzheimer's type (hereafter referred to as AD) is the most common form of dementia and the largest unmet medical need in neurology (Citron, 2010). AD can be further classified based on age of onset and genetic risks. Individuals under age 65 have early-onset AD, and many of whom have 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 electroencephalogram (EEG), including 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/day SC once daily (OD) 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]) 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 and neurodegeneration in subjects taking ATH-1017 without background acetylcholinesterase inhibitor, compared to placebo at 26 weeks (data on file). Subjects who completed the Week 26 visit of study ATH-1017-AD-0202 will be eligible to enroll in this open-label extension (OLEX) study, ATH-1017-AD-0203.

The Phase 3 study, ATH-1017-AD-0201, was subsequently initiated as a double-blind, randomized, placebo-controlled, 26-week, multi-center trial, designed to demonstrate efficacy in mild to moderate AD subjects and establish long-term safety information. Eligible participants, prior to version 7 of ATH-1017-AD-0201 protocol, will receive OD SC injections of ATH-1017 (40 mg or 70 mg) or placebo, over a 26-week double-blind, randomized period, followed by a 4-week safety follow-up. Based on the results of the ATH-1017-AD-0202 ACT-AD study, no

additional subjects on acetylcholinesterase inhibitor therapy will be enrolled and, as of v7 of ATH-1017-AD-0201 protocol, subjects will no longer be randomized to receive 70 mg of ATH-1017, since 40 mg is the dose intended for further development. The 70 mg OD dose was tested in the ATH-1017-AD-0202 study; clinical and biomarker endpoints did not consistently favor 70 mg OD when compared to 40 mg OD. 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, OD or placebo, in a 1:1 ratio. Subjects already randomized to receive the 70 mg dose will complete the study as planned. Subjects who complete the double-blind study will have the option to roll over into a long-term (206-week) OLEX study.

This OLEX study is designed to collect longer term clinical and biomarker measurements on ATH-1017 administration in subjects with mild to moderate AD over an additional 206-week period. All eligible subjects will receive OD SC injections of ATH-1017 (40 mg) over a 206-week period, followed by a 4-week safety follow-up. As of v3 of this protocol (01 JUN 2023), the dose of 70 mg/day ATH-1017 was discontinued and subjects who were previously assigned to this dose were reassigned to the dose of 40 mg/day ATH-1017.

1.3 Risk-Benefit Assessment

While 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) and long-term safety has not been established. Therefore, the benefit to study subjects of participating in this OLEX study is not yet known.

In clinical studies of ATH-1017, single SC administration of 2, 6, 20, 40, 60, and 90 mg in healthy young subjects, and multiple administration of 20, 40, 60, and 80 mg (SC, OD, over 9 consecutive days) in healthy elderly subjects, and 40 mg (SC, OD, over 9 consecutive days) in AD subjects were safe and well tolerated.

Injection site reaction, 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.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is the extended determination of the safety and tolerability of ATH-1017 over an additional 206-week period in subjects with mild to moderate AD who completed the 26-week randomized treatment in Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202.

Safety and tolerability will be assessed by analysis of adverse events (AEs), including injection site AEs; changes from baseline for the following variables: vital signs, 12-lead electrocardiogram (ECG), laboratory tests (chemistry, hematology, urinalysis), concomitant medication assessments, physical and neurological exams, and Columbia-Suicide Severity Rating Scale (C-SSRS).

3 OVERALL DESIGN AND PLAN OF THE STUDY

This is a multicenter, OLEX study of ATH-1017 treatment in subjects with a clinical diagnosis of mild to moderate Alzheimer's disease (AD) who completed 26 weeks of treatment in the randomized, placebo-controlled, double-blind studies, ATH-1017-AD-0201 and ATH-1017-AD-0202; hereafter referred to as the 'parent studies'. The study will be conducted at approximately 65 centers across the United States (US) for a total of 206 weeks' (47.5 months) open-label treatment. Eligible subjects will roll over directly from the parent studies, such that Visit 1 (Day 0) of this study is the Week 26 visit from either of the two parent studies. All subjects who complete the Week 26 visit of either of the two parent studies and meet the inclusion/exclusion criteria of Study ATH-1017-AD-0203 will be assigned to open-label active treatment with ATH-1017 at a dose of 40 mg/day, unless the safety results obtained at Visit 7 of the parent studies or new baseline safety labs suggest otherwise, in which case they will not be eligible for this OLEX study. Subjects who do not tolerate ATH-1017 40 mg/day, and/or who meet the stopping criteria, will be withdrawn from the study.

Study drugs will be administered by SC injection OD, preferably during the daytime. Subjects will take their last dose of blinded IMP (assigned to them in Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202) on site under supervision of site staff at Visit 8/Day 182 of the parent studies (i.e., Visit 1/Day 0 of this OLEX study). The first dose of open-label IMP from this study will be administered by subject or caregiver at the clinic the next day (Visit 2/Day 1), followed by a safety observation window of 1 hour (±15 minutes) post-dose. Subjects must not take more than one dose within 8 hours of the previous dose. The subject should withhold study drug administration on the day of 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, in accordance with all protocol requirements.

During the open-label treatment period, clinic visits will take place on Day 0 and thereafter at Day 1, Weeks 2, 6, 12, 18, 22, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, and 206. Telephone call visits are scheduled for Week 1 (Day 7) and Week 4 (Day 28). A safety follow-up visit is scheduled 4 weeks after completion of the open-label period at Week 210 (see Table 1 for Schedule of Assessments). Subjects may live at home, in a senior residential setting, or an institutional setting without the need for continuous nursing care. The end of the study is defined as the date of the safety follow-up visit, Visit 41/Week 210. Subjects who terminate prior to Visit 40 are to complete same assessments as Visit 40/early termination (ET) within 2 weeks of the date of ET.

[redacted]

An independent Data Safety Monitoring Board will conduct periodic review and assessments of safety data (AEs, labs, ECG, etc) throughout the study to ensure the safety of study subjects (see Section 7.3).

3.1 Justification for Study Design

This OLEX study provides an opportunity for all subjects who consented to participate in placebo-controlled studies ATH-1017-AD-0201 and ATH-1017-AD-0202 to receive active treatment over an additional 206-week period. The study will provide extended exposure information on ATH-1017 administration, primarily at a dose of 40 mg/day, in subjects with mild to moderate AD (based on the National Institute on Aging-Alzheimer's Association diagnostic criteria [McKhann, 2011]) and the inclusion/exclusion criteria of the parent studies, ATH-1017-AD-0201 and ATH-1017-AD-0202). This allows for continued safety data collection at the 40 mg/day dose level. Subjects who do not tolerate ATH-1017 40 mg/day, and/or who meet the stopping criteria, will be withdrawn from the study. As of v3 of this protocol (01 JUN 2023), the dose of 70 mg/day ATH-1017 was discontinued and subjects who were previously assigned to this dose were reassigned to the dose of 40 mg/day ATH-1017.

The safety assessments for the study are generally accepted measures for ensuring safety of subjects during a clinical trial. In addition, subject safety will be closely monitored; stopping criteria will be implemented (see Section 5.8. As for the parent studies, this study will also employ an independent Data Safety Monitoring Board (DSMB) which will conduct periodic review and assessments of safety data (AEs, labs, ECG, etc.) throughout the study.

3.2 Justification for Dose

The dose selection for this clinical study is based on the targeted dose in the ongoing pivotal ATH-1017-AD-0201 study, which is supported by nonclinical and clinical data.

The doses of ATH-1017 selected for the initial studies, ATH-1017-AD-0201 and ATH-1017-AD-0202 (40 mg/day and 70 mg/day), 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- Good Laboratory Practice nonclinical toxicology studies in animals at equivalent doses.

For further details on justification of dose, please refer to Section 3.2 of the ATH-1017-AD-0201 and ATH-1017-AD-0202 Clinical Study Protocols.

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.

Evaluation of safety lab data from Visit 7 of either of the two parent studies is allowed for assessment of subject eligibility. Subjects who are considered by the investigator to have safety or tolerability issues at Visit 7 of either of the two parent studies should be carefully re-considered for transition into this OLEX study at the final study visit of Study ATH-1017-AD-0201 or Study ATH-1017-AD-0202 (i.e., Visit 1 of this study, ATH-1017-AD-0203). Safety lab data from Visit 7 of the parent studies is to be confirmed with safety lab data from Visit 1 of this study. Subjects who are subsequently found to be not eligible based on safety lab data from Visit 1 will be discontinued.

4.1 Number of Subjects

It is estimated that up to approximately 450 subjects from Studies ATH-1017-AD-0201 and ATH-1017-AD-0202 will enter this OLEX study.

4.2 Inclusion Criteria

1. Subject has completed the Week 26 visit of either of the two parent studies.
2. Male subjects and their partners must agree to continue 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.
3. Reliable and capable support person/caregiver, who is willing to accept responsibility for supervising the treatment or, if required, administering study drug in accordance with all protocol requirements. The support person/caregiver must see the subject at least once daily for administering or supervising dose administration.
4. Subject capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (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.
5. 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.

6. 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).
7. 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.
8. 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

9. Subject has experienced a serious treatment-related AE during either of the two parent studies, which in the opinion of the investigator could present an increased safety risk to the subject during the OLEX study, in discussion with the Medical Monitor.
10. New diagnosis of severe major depressive disorder even without psychotic features. Any subject with formalized delusions or hallucinations are excluded.
11. Significant suicide risk as defined by suicidal ideation based on the C-SSRS at Visit 1 (i.e., a 'yes' response to Question 4 or 5, or any specific behaviours).
12. Newly diagnosed malignant tumor 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.
13. 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

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

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

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 2.

Table 2 Identity of Investigational Medicinal Products

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

SC = subcutaneous

a The 70 mg/day ATH-1017 dose was discontinued as of v3 of this protocol (01 JUN 2023).

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, adjusted to pH of approximately 7.6.

Prior to discontinuation of the 70 mg/mL dose, pre-filled syringes of active IMP at 70 mg contained 1.0 mL of 70 mg/mL ATH-1017 in a solution of 10 mM sodium phosphate, adjusted to pH of approximately 7.6.

5.2 Supply, Packaging, Labeling, and Storage

IMP (ATH-1017) will be provided as unblinded 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 ambient conditions up to 4 weeks (between 15°C and 25°C) or refrigerated conditions (between 2°C and 8°C).

5.3 Drug Accountability, Dispensing, and Destruction

Dispensation will be controlled by an interactive response technology (IRT) system and will occur at clinic visits through Week 18 (Day 1, and Weeks 2, 6, 12, and 18), the Week 22 dispensing visit, and every clinic visit starting from Week 26 through Week 200, or as needed by direct-to-subject shipment. Larger provision of study drug will be permitted to accommodate personal need, e.g., vacation. Study subjects will be provided with sharps containers for proper disposal of used IMP.

The caregiver/support person will supervise and 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

In this OLEX study, subjects will retain the subject identification number originally assigned to them on entry to the preceding (parent) studies, ATH-1017-AD-0201 and ATH-1017-AD-0202.

5.5 Administration of Investigational Medicinal Products

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.

Subjects will take their last dose of blinded IMP on site under supervision of site staff at Visit 8/Week 26 of Study ATH-1017-AD-0201 or ATH-1017-AD-0202 (corresponding to Visit 1/Day 0 of this study, ATH-1017-AD-0203). The first dose of open-label IMP will be administered by subject or caregiver at the clinic the next day (Visit 2/Day 1), followed by a safety observation window of 1 hour (±15 minutes) post-dose.

Site staff will be expected to observe dose administration on study visit days to ensure safe and effective use. During study visits, there is no specified in-clinic observation period post-IMP administration (except for Visit 2/Day 1 when a safety observation window of 1 hour ± 15 minutes post-dose is specified); however, the subject is required to be discharged from the study site 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. Drug accountability information is collected at clinic visits (Day 1, Weeks 2, 6, 12, 18, 22, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, and 206 as applicable), and additionally at telephone call visits (Weeks 1 and 4).

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

In this OLEX study, treatment allocation will not be blinded; all subjects will receive open-label ATH-1017 at a dose of 40 mg/day.

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 timeframe 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 serious adverse event (SAE) of related causality

  (Note: causality as determined by the Sponsor)
- Other clinical laboratory criteria (confirmed on repeat):
  - 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 parent study eligibility and OLEX study Baseline 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 are defined in a DSMB Charter and shall include making recommendations regarding subject continuation (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 (i.e., 40 mg/day) 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.

Upon discontinuation of study treatment, subjects 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 Safety Variables

6.1.1 Adverse Events

AE reporting will begin after the first dose of open-label IMP at Visit 2 (Day 1) and will continue until the end of the study (28 days from last dose of IMP, Visit 41 – 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 6.1.1.5).

6.1.1.1 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 Day 1 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.

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

6.1.1.2 Recording of Adverse Events

AEs should be collected and recorded for each subject from after the first dose of open-label IMP at Visit 2 (Day 1) until the end of their participation in the study, i.e., from Visit 2 until the subject has discontinued or completed the study, including the post-treatment Safety Follow-up period (at the end of the 206-week open-label period) at the timepoints specified in the Schedule of Assessments (Table 1). 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.

6.1.1.3 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 3 should be selected based on medical judgment, considering the definitions below and all contributing factors. In this study AEs will be considered related to IMP/study procedure if causality is ascribed as either related, probably related, or possibly related.

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

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that**

the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

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

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

Table 3 Assessment of Relationship of Adverse Events to IMP/Study Procedure

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

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

†Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is 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.

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.

6.1.1.4 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 after the first dose of open-label IMP at Visit 2 (Day 1) until completion of the Safety Follow-up. SAEs occurring after the Safety Follow-up Visit and coming to the attention of the investigator must be reported only if there is (in the opinion of the investigator) reasonable causal relationship with the IMP.

The investigator is responsible for updating the Electronic Data Capture system 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:

Email : [redacted]

Fax : [redacted]

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 study Medical Monitor 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.

6.1.1.5 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.

6.1.2 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.

6.1.3 Clinical Laboratory Assessments

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

Table 4 Clinical Laboratory Assessments

Test	Parameters	
Hematology	CBC HbA1c Hemoglobin Hematocrit Erythrocytes (RBC)	Leukocytes (WBC) Differential WBC Platelets
Biochemistry	Sodium Potassium Calcium Chloride Glucose Creatinine ALP AST ALT	GGT CPK Total bilirubin Total protein Albumin Total Cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides
Coagulation	INR PT	aPTT
Urinalysis	pH glucose ketones specific gravity	nitrite protein bilirubin blood

CBC = complete blood count; CPK = creatine phosphokinase; RBC = red blood cells; WBC = white blood cells; AST = aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; PT = prothrombin time; aPTT = activated partial thromboplastin time.

Safety laboratory assessments will be performed at the timepoints detailed in the Schedule of Assessments (Table 1). Any value outside the normal range will be flagged for clinical interpretation by the investigator or designee at the site. In this study, ALT or AST > 2 times the upper limit of normal, or Child-Pugh class B and C (i.e., including total bilirubin, albumin, and INR values), will be exclusionary. For transaminase liver enzymes, a repeat laboratory assessment may be performed if outside of the normal range. If the transaminases remain elevated the investigator should consider stopping study medication and withdrawing the subject as described in Section 5.8.

A medical alert for potential Hy's 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 (203AD_MM@athira.com), and MMS – Sponsor's designated CRO for Drug Safety and Pharmacovigilance (drugsafety@athira.com) 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 resolution. Any clinically significant abnormalities from Visit 1 (Day 0) 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.

Note: clinical laboratory test results, ECGs, and vital signs evaluated at Visit 1 may be repeated if outside the normal range and not considered clinically significant, as per Section 7.1.1 (Unscheduled Visits).

6.1.4 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 or tympanic)
- Respiratory rate (breaths per minute)

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 stood for up to 3 minutes. A drop in blood pressure of ≥ 20 mmHg, or in diastolic blood pressure of ≥ 10 mmHg will be considered abnormal.

6.1.5 12-Lead Electrocardiogram

Standard safety 12-lead ECGs will be performed 30 (± 15) minutes post-dose- at all study visits 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.

6.1.6 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 — skin, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurological, and mental status examination.

Body weight will be assessed at Visit 1 (Day 0), Visit 10 (Week 26), Visit 14 (Week 50), Visit 19 (Week 80), Visit 23 (Week 104), Visit 28 (Week 134), Visit 32 (Week 158), Visit 37 (Week 188), Visit 40/ET (Week 206), and at Visit 41 (Safety follow-up; Week 210).

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.

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

The C-SSRS will be performed at Visit 1 (Day 0), Visit 4 (Week 2), Visit 6 (Week 6), Visit 7 (Week 12), Visit 8 (Week 18), Visit 10 (Week 26), and all subsequent visits through Visit 41 (Safety follow-up) (Week 210) (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.

[redacted]

017-AD-0201 and does not need to be repeated at Visit 2 (Day 1) in the open-label study.

[redacted]

[redacted]

7 STUDY CONDUCT

- Study procedures and their timing are summarized in the Schedule of Assessments (Table 1).
- Protocol exemptions related to enrollment criteria are only allowed with prior Investigator and Sponsor approval, supported by documented agreement from the IRB/IEC.
- Immediate safety concerns should be discussed with the Medical Monitor 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 Visit 1 evaluations for study eligibility (excluding safety lab data) must be completed and reviewed to confirm that potential subjects meet all eligibility criteria; evaluation of safety lab data from Visit 7 of either of the two parent studies is allowed for assessment of subject eligibility (to be confirmed with safety lab data from Visit 1 of this study).

7.1 Schedule and Order of Assessments

Following informed consent and confirmation of eligibility at Visit 1, the study will consist of 206 weeks of open-label treatment and a 4-week safety follow-up.

All assessments to be performed during the study are detailed by visit/timepoint in Table 1.

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):

- Study visits should be conducted on-site if conditions permit, but flexibility will be allowed upon agreement between sites, CRO, and sponsor. Study 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

In continuation from the two parent studies, ATH-1017-AD-0201 and ATH-1017-AD-0202, an independent DSMB will conduct periodic review and assessments of safety data (AEs, labs, ECG, etc.) throughout the OLEX study (ATH-1017-AD-0203) to ensure the safety of study subjects. Based on 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 5).

Table 5 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. o 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 (PRN up to two times a day) (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; ISR = injection site reaction; SAE = serious adverse event; SOP = standard operating procedure.

7.5 Concomitant Medications and Treatments

7.5.1 Prohibited Treatments During the Study

Concomitant use of the following drugs is excluded during the study:

- Memantine in any form, combination, or dosage
- Addition of acetylcholinesterase inhibitors during the study (subjects on stable doses on entry may remain on them)

All allowed medications should remain stable throughout the study; for medications affecting cognition, the doses should be stable throughout the study, unless otherwise noted.

The following drugs are prohibited during the study:

- Psychoactive medications (including antipsychotics, tricyclic antidepressants, anxiolytics, or sedative hypnotics, including barbiturates) having significant anticholinergic effects and/or believed to affect cognitive function (for exceptions see Section 7.5.2).
- 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 enrollment into the study
- Systemic immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses in the judgment of the investigator (for exceptions see Section 7.5.2)
- Anti-epileptic 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 study visits)
- Sedating H_1 antihistamines; non-sedating H_1 antihistamines are allowed
- Systemic moderate to strong Cytochrome P450 3A4 (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 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

Subjects who roll over into this OLEX study from either Study ATH-1017-AD-0201 or ATH-1017-AD-0202 should continue to take any ongoing medications. The dosage(s) of concomitant medications should remain constant during the course of this study. Dose adjustment or termination of any ongoing medications, including for example donepezil, should first be discussed between the investigator and the Medical Monitor.

Immunosuppressant use for allergy or other inflammation, e.g., asthma, topical otics, opthalmologics, skin creams, and intra-articular injections is allowed.

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

The Sponsor or CRO should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.3 Other Restrictions

7.5.3.1 Food and Food Supplements

The consumption of grapefruit or grapefruit-containing products is prohibited during the study.

Food supplements and nutraceuticals that were being taken during a subject's participation in either of the two parent studies are allowed, and may be continued during this study as long as they remain stable.

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, if not prompted by an AE or lack of efficacy. If the latter, then that should be recorded as the reason for ET.
  - Physician decision
  - Non-compliance with study drug (see Section 5.6)
  - 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 40 (Week 206), unless the cause is screen failure, should return for an early termination visit and complete all the assessments scheduled for the Week 206 visit (Visit 40); see the schedule of activities (Table 1) for data to be collected.
- Unless the reasons of premature discontinuation prevent further meaningful testing, investigators should make every effort to motivate subjects who discontinue early (and caregiver) to return for a Visit 40 (Week 206) for final assessments within 2 weeks of ET.

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

- 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 Safety population

The Safety population will include all 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.

Percentages are based on the number of subjects 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 and overall for the given population.

8.3 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, and frequency rates. The timepoint of each event will also be summarized.

8.3.1 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

8.3.2 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.

8.3.3 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.

8.3.4 Columbia-Suicide Severity Rating Scale

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

8.4 Determination of Sample Size

For this OLEX study, no formal sample size calculation was used. It is estimated that up to approximately 450 subjects will enter this OLEX study from Studies ATH-1017-AD-0201 and ATH-1017-AD-0202.

[redacted]

8.9 Interim Analysis

Given the open label nature of this study, data may be evaluated from time to time to assess ongoing disease activity and safety.

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.

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 standard operating procedures (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 this OLEX 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
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) • Risperidone (Risperdal) • Trimipramine (Surmontil) • Ziprasidone (Geodon, Zeldox)

Category of Prohibited Medications	Examples: General Name (Trade Name)
	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 • Voriconazole (Vfend)

Category of Prohibited Medications	**Examples: General Name (Trade Name)**
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

ATH-1017-AD-0203 Protocol_V4

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