A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AL002 IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE

Protocol Number:	AL002-2
Version Number:	7.0
Name of Investigational Product:	AL002
Developmental Phase of Study:	Phase 2
Indication:	Alzheimer's Disease
Sponsor:	Alector Inc. 131 Oyster Point Blvd, Suite 600 South San Francisco, CA 94080 US
Regulatory Agency Identifier Numbers:	IND Number: [redacted] EudraCT Number: 2019-001476-11
Approval Date:	20 June 2023

This study is to be performed in compliance with the protocol, Good Clinical Practices, and applicable regulatory requirements.

PROTOCOL SIGNATURE PAGE

A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of AL002 in Participants with Early Alzheimer's Disease

Study Number: AL002-2

Version: 7.0

Date of Issue: 20 June 2023

Signature of Approval for Protocol (Version 7.0)

Name	Signature	Date
Gary Romano, MD, PhD [redacted] Jingjing Gao, PhD [redacted] Alector, Inc.	Refer to signature manifest at the end of the document	

This study is to be performed in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6(R2) (Guideline for Good Clinical Practice), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations, Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application).

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of AL002 in Participants with Early Alzheimer's Disease".

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol Version 7.0, dated 20 June 2023, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guideline E6(R2): Good Clinical Practice, and all applicable government regulations. I agree to administer study drug only to participants under my personal supervision or the supervision of a Subinvestigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Participant personal identification will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Alector.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

SUMMARY OF CHANGES FROM PREVIOUS VERSIONS

Herein is a summary of the changes made to Version 6.0 of the protocol, dated 21 September 2022, and reflected in the amended Version 7.0 of the protocol, dated 20 June 2023.

Amended Protocol Sections	Summary of Change(s)	Rationale
Throughout	Typographical, formatting corrections, minor administrative changes, and minor text clarifications; updates to the Table of Contents, List of Tables, List of Figures, and List of Abbreviations.	Minor changes made to correct errors, conform to revised style standards, and/or reflect updates to the content.
Synopsis	The synopsis was revised with all relevant updates included in the body of the protocol amendment detailed below.	Revised for consistency with updates to the body of the document.
Section 1.3	Detailed, specific content related to early amyloid-related imaging abnormality (ARIA) cases was removed as this content is now outdated; we have maintained the cross-reference to the Investigator's Brochure (IB) to ensure the most recent data is provided.	Revised to ensure Investigators are directed to the most recent safety content provided in the IB.
Section 2 (Table 1), Section 8.3.2.1	The estimand description for the primary endpoint was updated to include a change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) from Weeks 24, 48, 72, and 96 to Weeks 25, 49, 73, and 97.	Revised to align with appropriate analytical timing of evaluations.
Section 3.1, Section 8.1	The number of participants enrolled was updated from 264 to 328 and sample size calculations were also updated to account for the increase. The number of sites may also increase, so rather than stating "up to 90 sites," it now states, "approximately 90 sites."	The study was expanded to include additional participants.
Section 3.1.4, Section 5.2.1, Previous Section 14.4.9, Section 14.4.10	Content related to potential study drug administration in a home setting was removed.	To maintain scientific rigor, study drug administration in a home setting is no longer an option.
Section 3.1.9, Section 3.3.1, Section 14.1 (Table 8, Table 9), Section 14.4.3	Adjusted language to clarify that extensions to the screening period may be given for reasons other than Coronavirus disease 2019 (COVID-19) and imaging study-related delays. All extensions must be approved by the Sponsor.	To improve patient centricity by reducing unnecessary burden on patients and sites due to avoidable rescreenings.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 4.1	Revisions were made to the following inclusion criteria: • #1: content related to requirements for the Alzheimer's continuum was revised in relation to required historical studies. • #2c: content related to the Delayed Memory Index (DMI) was revised.	Criteria were revised for clarity, safety, and to eliminate redundancies and reduce potential protocol deviations.
Section 4.2	Revisions were made to the following exclusion criteria, including renumbering following additions: • #9: content related to uveitis, chronic conditions of the eye, and cataracts were revised. • #10: content related to treatment with antidepressant medications was simplified and made more general. • #18: content related to an abnormal electrocardiogram (ECG) was revised to include abnormal findings that are considered clinically significant by the Investigator. • #22: content related to hepatitis B was simplified and clarified. • #24: content related to immune disorders and the use of prednisone was clarified. • #32: content was updated to indicate that only one or more of the exceptions need be satisfied in relation to history of cancer. • #39: content related to use of medications known to impair consciousness was expanded for clarity. • #45: content related to atypical antipsychotics was revised for clarity. • #48: The explanatory parenthetical phrase following short term (<1 week) was removed. • #50: in part a., the parenthetical phrase following short term (<1 week) was removed and part b. was added regarding the use of trazadone, mirtazapine, and melatonin for insomnia.	Revised for safety and clarity.
Section 6.2	Rescreening criterion #4 was updated to include a positive PrecivityAD™-Aβ blood test assessment.	Revised to indicate that participants are not required to repeat a positive PrecivityAD™-Aβ blood assessment.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 6.5.7	Content related to ophthalmological examinations was updated to indicate that signs and symptoms indicative of uveitis should be recorded as adverse events (AEs) and followed by ophthalmology until they have resolved or uveitis is ruled out. Unscheduled assessments may be added as needed.	Revised for safety.
Section 7.11.1.2	Content and references for ARIA-related symptoms and signs were added for Investigator awareness.	Revised for safety.
Section 14.1	In Table 8, Footnote x was updated to indicate that participants need a high or intermediate score on the PrecivityAD™-Aβ blood test vs. "amyloid positive." Footnote gg was updated.	Revised for clarity.

Herein is a summary of the changes made to Version 5.0 of the protocol, dated 23 August 2021, and reflected in the amended Version 6.0 of the protocol, dated 21 September 2022.

Amended Protocol Sections	Summary of Change(s)	Rationale
Throughout	Typographical, formatting corrections, minor administrative changes, and minor text clarifications; updates to the Table of Contents, List of Tables, List of Figures, and List of Abbreviations.	Minor changes made to correct errors, conform to revised style standards, and/or reflect updates to the content.
Protocol Signature Page	Updates to signees (removal of Michael Ward, PhD).	Updates to signees for personnel changes.
Synopsis, Section 4.1	Previous Exclusion Criterion #46: 46. Anticoagulation medications within 90 days of screening (for all participants in Part 1 and participants in Part 2 in the optional LP). a. Antiplatelet treatments (eg, aspirin, clopidogrel, dipyridamole) are permitted. Revised Exclusion Criterion #46: 46. Anticoagulant medications other than antiplatelet agents are prohibited within 90 days of screening and throughout the study. Short-term use of anticoagulants to treat an emergent medical need is permitted. a. Treatment with platelet anti-aggregation agents such as aspirin, clopidogrel, or dipyridamole is permitted.	Revised for safety.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 5.6	The following sentence was removed: Participants in Part 2 who are not participating in the optional LPs are permitted to be taking anticoagulation medication. The following sentence was added: Anticoagulant medications other than antiplatelet agents are prohibited within 90 days of screening and throughout the study. Short-term use of anticoagulants to treat an emergent medical need is permitted. Treatment with platelet anti-aggregation agents such as aspirin, clopidogrel, or dipyridamole is permitted.	Revised for safety.
Section 7.11, Table 7	Table 7 was revised to eliminate content indicating participants with amyloid-related imaging abnormality-edema/amyloid-related imaging abnormality-hemosiderin deposits (ARIA-E/ARIA-H) should restart at their current randomized dose and titration schedule following stabilization. The following replacement content was added, "After resolution (ARIA-E) and/or stabilization (ARIA-H), if participant dosing is restarted, they must receive the same dose they received immediately prior to the ARIA-E/ARIA-H findings and continue on that dose for the remainder of the study. After resuming dosing, 5-10 days before their second post-resumption dose, participants must undergo an unscheduled magnetic resonance imaging (MRI) that must be assessed by the Central Reader for ARIA-E/H before the next dose is administered."	Revised for safety.

Herein is a summary of the changes made to Version 4.0 of the protocol, dated 16 August 2021, and reflected in the amended Version 5.0 of the protocol, dated 23 August 2022.

Amended Protocol Sections	Summary of Change(s)	Rationale
Throughout	Typographical, formatting corrections, minor administrative changes, and minor text clarifications; updates to the Table of Contents, List of Tables, List of Figures, and List of Abbreviations.	Minor changes made to correct errors, provide further clarity, conform to revised style standards, and/or reflect updates to the content.
Throughout	Standardization of terminology of "study drug."	Revised for consistency of terminology.

Amended Protocol Sections	Summary of Change(s)	Rationale
Throughout	Revision of Repeatable Battery for the Assessment of Neurophysiological status (RBANS) to include "Update" as in RBANS-Update (note: this change was made throughout the protocol).	Revised for accuracy of naming convention of assessment.
Title Page	Added indication: Alzheimer's Disease (AD).	Revised to conform with Quality Assurance guidelines.
Protocol Signature Page	Updates to signees (from Glenn Morrison, PhD to Gary Romano, MD, PhD, Michael Ward, PhD, and Jingjing Gao, PhD).	Updates to signees for personnel changes.
Synopsis	The synopsis was revised with all relevant updates included in the body of the protocol amendment detailed below.	Revised for consistency with updates to the body of the document.
Section 1.3	Section heading was updated from, "Summary of Potential Risks and Benefits" to, "Summary of Risks and Benefits." Additional content was added related to amyloid-related imaging abnormality (ARIA) risks.	Updated for clarity and safety.
Section 1.3, Section 3.1	Participants randomized after July 2021 to receive 40 or 60 mg/kg will be titrated to their target randomized dose level over the first 2 or 3 doses, respectively, and then continue at their randomly assigned dose for the remainder of study participation. There will be no change to dose for participants randomized to receive 15 mg/kg or placebo.	Revised for safety.
Section 1.3, Section 3.1, Section 4.2, Section 8	Due to emerging ARIA seen in participants with the apolipoprotein E epsilon4/epsilon4 (*APOE e4/e4)* genotype, this study will no longer enroll participants with this genotype.	Revised for safety.
Section 1.3, Section 6.5, Section 7.11, Section 14.1	The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.	Revised for safety.
Section 1.5, Section 3.1, Section 4.1	A score on the RBANS-Update of ≤95 may be considered for eligibility according to the inclusion/exclusion guidelines.	Revised to facilitate recruitment.
Section 1.5, Section 4.1, Section 6.5, Section 14.1	Participants with a high or intermediate Amyloid Probability Score (APS) on the PrecivityAD™-Aβ blood test may proceed to cerebrospinal fluid (CSF) or Amyloid positron emission tomography (PET) confirmation of amyloid pathology. Historical Amyloid PET or CSF assays may be used to satisfy	Revised to facilitate recruitment.

Amended Protocol Sections	Summary of Change(s)	Rationale
	the amyloid positivity requirement. Participants with a positive historical CSF measurement may forego the PrecivityAD™-Aβ blood test and confirmatory Amyloid PET or CSF pTau/Aβ42 measurement, if approved by the Medical Monitor.	
Section 2, Section 8	Content updated to reflect revised estimands and associated analytical methods including revisions to sample size calculations, analysis sets, analyses of the primary efficacy endpoint, secondary efficacy endpoints, and interim analysis.	Revised to enhance precision of statistical analyses.
Section 3.1	Participants may miss doses, have dosing paused, or have dosing discontinued permanently; trial has been designed to follow all participants randomized, irrespective of whether they discontinue study drug, all visits and assessments should be made whenever possible.	Revised for clarity and to encourage participants to remain on study, even if drug has been discontinued.
	Because this trial has been designed to follow all participants randomized, irrespective of whether they discontinue study drug, all visits and assessments should be made whenever possible until the completion of the planned treatment period and through the efficacy follow-up (EFU) and safety follow-up (SFU) visits; specific requirements related to the EFU and SFU are now included.	Revised for clarity and to encourage participants to remain on study, even if drug has been discontinued.
Section 3.1, Section 4.1	Revision of the Mini-Mental State Examination (MMSE) score from ≥22 points to ≥20 points.	Revised to facilitate recruitment.
Section 3.1, Section 3.2, Section 3.3, Section 14.1	To avoid confusion, the Predose Baseline Visit will no longer be characterized as optional.	Revised for clarity.
Section 3.1, Section 3.3, Section 14.1	Participants who have consented to the optional Winterlight Labs Speech Assessments (WLSA) may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1.	Revised to facilitate optional study assessment.
Section 3.1, Section 5.1	Part 2 of the study will now enroll 224 participants vs. 225 participants.	Revised due to updated statistical methods.
	Content revised to remove reference to the dynamic allocation ratio of 1:1:1:1 in Part 2; it will now be 1:1:1:1 throughout Part 2.	Updated based on revised statistical analyses.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 3.1, Section 3.3, Section 6.7, Section 14.1	Additional optional blood samples for PK will now be collected from approximately 64 participants (previously 24) in Part 2 at 4 and 8 and 24 or 48 hours after the end of infusion at one of the following: Week 25 or 37 or 49.	Revised to ensure a sufficient sample size for each dose group.
Section 3.2	Section previously entitled, "Treatment Duration." The heading was updated to, "Study Duration and Planned Treatment Period" and content subsections were added.	Revised for clarity and to accommodate content updates.
Section 3.2, Section 14.1	The treatment period termination date (TPTD) is defined as the single, cross-study date that is the end of the treatment period for all participants in the study.	Revised to define and clarify TPTD.
Section 3.3	Section 3.3 was previously entitled, "Description of Study Procedures." The heading was updated to, "Description of Study Periods and Visits"; subsection heading were also revised.	Revised for clarity and to accommodate content updates.
	Participants who have consented to the optional Tau PET scans may complete the first Tau PET scan after dosing on Day 1, with Sponsor agreement.	Revised to facilitate optional study assessment.
	If eligible participants consent to long-term dosing or open-label extension studies at the end of the planned treatment period, they will not be required to attend the follow-up visits.	Revised for clarity.
Section 3.3, Section 14.1	At the discretion of the Sponsor the screening period may be extended up to an additional 4 weeks to accommodate difficulties scheduling magnetic resonance imaging (MRI) or PET scans.	Revised to accommodate with difficulties with scheduling of radiographic assessments.
Section 4.1	Updates were made to inclusion criterion #1 to provide additional details and refinements related to specific requirements for Alzheimer's disease (AD) eligibility for the study.	Revised for clarity and to facilitate recruitment.
	Updates were made to inclusion criterion #6 to increase the upper limit of body mass index (BMI) from 30 to 34.9.	Revised to facilitate recruitment.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 4.2	Updates were made to the following exclusion criteria: • #3: content refined re: cerebrovascular accidents, transient ischemic attacks, and cortical stroke. • #5: content refined re: intracranial tumor. • #6: content added re: history of infections that resulted in neurologic sequelae. • #16: participants who are able to tolerate MRI with use of an intermittent low-dose benzodiazepine or anxiolytic may be included in the study. • #17: revised requirements related to hypertension. • #18: revised requirements related to abnormal electrocardiograms (ECGs). • #19: revised requirements related to ventricular dysrhythmias. • #23: revised requirements related to tuberculosis (TB). • #28: participant is positive for *APOE e4/e4* genotype. • #29: Plavix removed as example of anticoagulation medication. • #32: cancer that is clinically cured is defined as clear after 5 years from last definitive treatment; prostate cancer does not have significant progression within past 3 years (previously 2 years). • #38: AD medications must not be initiated, modified, or stopped within 60 days prior to screening.	Revised for clarity, safety, and/or to facilitate recruitment.
Section 4.3.3	Section heading was updated from, “Replacements” to, “Addition of Participants to Study if Participants Withdraw from Study.” Participants may be added to the study up to approximately the number of participants who withdrew or prematurely discontinued from the study, at the Sponsor’s discretion.	Revised for clarity of participant replacement.
Section 6.1	Content added to indicate that MRIs will be read by a Central Imaging Reader.	Revised for clarity and safety surveillance.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 6.5	Content updated to indicate that abnormalities observed prior to dosing of study drug (previously "at baseline"), will be recorded in the electronic case report form (eCRF).	Revised for clarity and safety surveillance.
Section 6.5, Section 7.7	Content added to indicate that adverse events (AEs) and special situations related to Neuraceq® must be reported within 24 hours of awareness.	Revised for clarity and safety surveillance.
Section 6.5, Section 7.11, Section 14.1	Surveillance for treatment-emergent amyloid-related imaging abnormalities (ARIA) will be accomplished with post-randomization MRI scans as follows: • In Part 1, on Day 15 and 43, a brain MRI will be performed. Participants with MRI evidence of ARIA will not be eligible to receive further administration of study drug. • In Part 2, surveillance for treatment-emergent ARIA will be accomplished with post-randomization MRI scans as follows: MRIs to be performed 5-10 days before Dose 2 (Day 29), Dose 3 (Day 57), and Dose 4 (Week 13), and 5-10 days before doses at all subsequent visits with MRI (Weeks 25, 49, 73, 97). • If new or worsening ARIA is observed on any of these post-randomization MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA. • Participants with new or worsening radiographic evidence of ARIA on post-baseline MRI scans should be evaluated for neurological signs or symptoms during an unscheduled visit. • In Part 1 and Part 2, all new cases of ARIA will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or ARIA-H has stabilized without new findings. An Amyloid PET scan and LP for CSF may also be requested. • All MRIs will be read within 5 days by a central imaging read with Brain MRI Worksheets (BMWs) provides to the clinical sites and Sponsor.	Revised for clarity and safety surveillance.
Section 6.5, Section 14.1	ECGs will now be obtained approximately 1-3 minutes apart vs. 1 minute apart.	Revised to facilitate obtaining ECGs.
Section 6.9	Section heading was updated from, "Genomic Assessments" to, "Genomic Assessments and	Revised for clarity.

Amended Protocol Sections	Summary of Change(s)	Rationale
	Genetic Disclosure." Content was added to indicate that study sites will follow their local guidelines and regulations regarding disclosure and supportive genetic counseling.	
Section 6.11	Content revised to note that participants are considered to have completed the study if they engage in all procedures and visits as outlined in the Schedules of Assessments. Participants can also be considered completers even if they discontinue study drug but choose to complete all of the remaining visits.	Revised for clarity.
Section 7	Content added to indicate that any adverse event of special interest (AESI) detected after informed consent but prior to the first dose administration of study drug will be considered medical history and recorded as such.	Revised for clarity and safety surveillance.
Section 7.1	Content added to indicate that findings identified during screening examinations, including events of ARIA identified during MRI performed at screening, are not AEs.	Revised for clarity and safety surveillance.
Section 7.2	Content added to note that there are 3 categories of ARIA-hemosiderin deposits (ARIA-H) (as outlined in Section 7.11). Subsection added entitled, "Recording of ARIA-H and ARIA-E as AESI" with details as to capturing ARIA-H and ARIA-edema (ARIA-E) in the eCRF.	Revised for clarity and safety surveillance.
Section 7.6.1	Cross references added to Section 6.5.1 and 7.2.1 for special situations and instructions for recording ARIA-E and ARIA-H.	Revised for clarity and safety surveillance.
Section 7.11, Previous Section 14.4	Section revised to provide a description of radiographic severity, resolution, and stabilization of ARIA findings, MRI surveillance for ARIA, and expectations for Investigator review of BMW reports. Expanded section now includes content previously included in Section 14.4.	Revised for clarity and safety surveillance.
Section 7.12	Content revised to specify that special situations must be reported within 24 hours of becoming aware. Additional content was added for descriptions of off-label use and lack of efficacy/effect.	Revised for clarity of special situations.

PROTOCOL SYNOPSIS

Protocol Title: A Phase 2 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of AL002 in Participants with Early Alzheimer's Disease

Protocol Number: AL002-2

Phase: 2

Objectives and Endpoints:

Objectives	Endpoints
Primary: • To evaluate the efficacy of AL002 in participants with Early AD in delaying disease progression compared to placebo	*Primary Efficacy Endpoint:* • Disease progression as measured by change from baseline in the CDR-SB *Primary Estimand for Primary Efficacy Endpoint: The primary clinical question of interest is what is the potential relative treatment difference between AL002 and placebo, across all post-baseline timepoints in adult patients with Early AD while on study medication, regardless of other interventions.* The estimand is described by the following attributes: • Treatment condition: while on treatment (hypothetical strategy) regardless of other interventions (treatment policy strategy). • Target population: adult patients with Early AD as defined by the protocol inclusion/exclusion criteria. • Primary endpoint: change from baseline in CDR-SB score to Weeks 25, 49, 73, and 97. • Accounting for intercurrent events: a composite strategy will be used to handle intercurrent events as below: – hypothetical strategy for handling premature study drug discontinuation for any reason, – treatment policy strategy for handling all other intercurrent events. • Population-level summary: the percent reduction relative to placebo decline (the proportional treatment effect), comparing each dose level to placebo.

Secondary: • To evaluate the efficacy of AL002 in participants with Early AD on efficacy as measured by the rate of change in COAs	*Secondary Efficacy Endpoints:* • Change from baseline in MMSE • Change from baseline in RBANS-Update • Change from baseline in ADAS-Cog13 • Change from baseline in ADCS-ADL-MCI • Change from baseline in ADCOMS *Secondary Efficacy Estimands:* The main estimand for the secondary efficacy endpoints is defined with similar attributes as for the primary estimand except that it is endpoint specific. The treatment effect is defined as a percentage reduction of the placebo group clinical decline.
Pharmacokinetics: • To estimate the concentration of AL002 in participants with Early AD in serum and CSF (when available)	*Pharmacokinetic Endpoints:* • Serum PK concentrations of AL002 and relevant PK parameters • CSF[a] PK concentrations of AL002 (when available) • Incidence of ADAs
Safety: • To evaluate the safety and tolerability of AL002 in participants with Early AD	*Safety Endpoints:* • Incidences of AEs, including AESI, and SAEs • Changes from baseline in vital signs, physical findings, neurological findings, ophthalmological findings, ECG, and clinical laboratory results • C-SSRS • MRI abnormalities
Exploratory: • To evaluate the effects of AL002 in participants with Early AD on exploratory PD biomarkers	*Exploratory PD Biomarker Endpoints:* • Changes from baseline in levels of sTREM2 in CSF and/or plasma[a] • Changes from baseline in levels of biomarkers related to microglia function in CSF and/or plasma[a] (eg, CSF1R, IL1RN, osteopontin, YKL-40) • Changes from baseline in levels of biomarkers related to AD pathology in CSF and/or plasma[a] (eg, Aβ40, Aβ42, pTau, tTau) • Changes from baseline in levels of neurodegeneration biomarkers in plasma and CSF[a] (eg, NfL) • Changes from baseline in brain volume, assessed by volumetric MRI • Changes from baseline in brain pathological tau burden as assessed by Tau PET[b] (for participants who agree to participate in the optional assessment only) • Changes from baseline in brain amyloid burden as assessed by longitudinal Amyloid PET[b] scanning (for participants who agree to participate in the optional assessment only)

	• Changes from baseline in speech measurements via the WLSA (for participants who agree to participate in the optional assessment only)

Aβ40=amyloid beta (1-40); Aβ42=amyloid beta (1-42); AD=Alzheimer's disease; ADA=anti-drug antibodies; ADAS-Cog13=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS=Alzheimer's Disease Composite Score; ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study- Activities of Daily Living – Mild Cognitive Impairment Scale; AE=adverse event; AESI=adverse event of special interest; CDR-SB=Clinical Dementia Rating – Sum of Boxes; COA=clinical outcome assessments; CSF=cerebrospinal fluid; CSF1R=colony stimulating factor 1 receptor; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IL1RN=interleukin 1 receptor antagonist; LP=lumbar puncture; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; NfL=neurofilament light; PET=positron emission tomography; PD=pharmacodynamic(s); PK=pharmacokinetic(s); pTau=phosphorylated tau; RBANS-Update=Repeatable Battery for the Assessment of Neuropsychological Status-Update; SAE=serious adverse event; sTREM2=soluble triggering receptor expressed on myeloid cells 2; tTau=total tau; WLSA=Winterlight Labs Speech Assessment; YKL-40=chitinase 3-like 1.

[a] CSF collection applies to all participants in Part 1 and those participants in Part 2 who consent to the optional LP.

[b] Longitudinal Amyloid PET and/or Tau PET imaging applies to those participants who consent and participate in the optional exploratory biomarker assessment.

Study Design:

This is a two-part Phase 2, randomized, double-blind, parallel-group, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of AL002 in participants with Early Alzheimer's disease (AD). The study is a multicenter, global trial that will enroll approximately 328 participants at approximately 90 sites in North America, New Zealand, Australia, Europe, and South America.

Participant Population

Participants must be in the Alzheimer's continuum as defined by the 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework (Jack 2018); this requires evidence of cerebral amyloidosis (A+) as detailed in the inclusion criteria. Participants must also demonstrate a clinical severity consistent with Stages 2, 3, or early Stage 4 as defined in the 2018 Research Framework, further constrained by entrance criteria defined for the Clinical Dementia Rating-Global Score (CDR-GS) (0.5 or 1), the Mini-Mental State Examination (MMSE) (≥20 points), and the Repeatable Battery for the Assessment of Neurophysiological Status-Update (RBANS-Update) Delayed Memory Index (DMI) (85 or lower; 95 or lower may be considered for eligibility according to the guidelines set forth in the inclusion and exclusion criteria). These clinical severity criteria are designed to be consistent with a definition of Early AD as described in the Food and Drug Administration (FDA) (FDA 2018) and European Medicines Agency (EMA) (EMA 2018) guidelines. Clinical diagnosis for each participant must be supported by information provided on a Research Diagnostic Verification Form (RDVF). For more details on the RDVF review process, see the description of the screening period in Section 3.1.9.

Due to emerging amyloid-related imaging abnormalities (ARIA) data seen in participants with the apolipoprotein E epsilon4/epsilon4 (*APOE* e4/e4) genotype, this study will no longer enroll participants with this genotype.

Study Objectives

The objectives of this Phase 2 study are the assessment of the efficacy and safety of intravenous (IV) AL002 treatment for up to 96 weeks. Multiple dose levels of AL002 will be studied against placebo at a dosing frequency of every 4 weeks. Participants with the *APOE* e4/e4 genotype who were enrolled

under Versions 1–4 of this protocol will not receive any further study drug treatment, but should continue with the remaining planned visits in the Schedules of Assessments (Section 14.1).

Efficacy will be assessed with clinical outcome assessments (COAs) as well as fluid and imaging biomarker measures. Safety will be assessed through monitoring of adverse events (AEs) (including adverse events of special interest [AESI] and serious adverse events [SAEs]), changes in laboratory and vital sign values, incidence of findings from physical, neurological, electrocardiogram (ECG), magnetic resonance imaging (MRI) and ophthalmological exams, and reports of suicidal ideation or behavior. Pharmacokinetics (PK) in both the serum and cerebrospinal fluid (CSF) will be assessed for investigation of exposure-response and exposure-safety relationships. Blood biomarker and MRI biomarker measures will be assessed for all participants.

In this study, several optional pharmacodynamic (PD) assessments will be performed for those participants who consent to the assessments. These include CSF collection for fluid biomarkers (except for Part 1, where CSF collection is mandatory for all visits), positron emission tomography (PET) imaging with the tau radiotracer fluorine-18 MK-6240 ([^{18}F]MK-6240), longitudinal Amyloid PET imaging, and/or speech assessment with the Winterlight Labs Speech Assessment (WLSA).

Enrollment in Part 1 and 2

In Part 1, each dose level tested will consist of a minimum of 10 participants. Approximately 40 participants will be randomized at a 1:1:1:1 ratio to receive either AL002 15 mg/kg, 40 mg/kg, 60 mg/kg, or placebo, administered via IV infusion every 4 weeks. The remainder of the study will be enrolled as Part 2 which will include approximately 288 participants. The allocation ratio in Part 2 will also be 1:1:1:1. Participants randomized after July 2021 to receive 40 or 60 mg/kg will be titrated to their target randomized dose level over the first 2 or 3 doses, respectively, and then continue at their randomly assigned dose for the remainder of study participation. There will be no change to dose for participants randomized to receive 15 mg/kg or placebo.

After approximately 20 participants have completed their Day 43 visit, the independent Data Monitoring Committee (iDMC) will perform the first safety review of all available safety and tolerability data (including from the MRI and neurological and ophthalmological examinations) from all participants up to that timepoint in an unblinded manner. A second safety review will be made by the iDMC after approximately 40 (minimum of 32 in case higher than expected discontinuation rate) participants have completed the Day 43 visit. The remainder of the study will be enrolled as Part 2. Randomization may be paused to allow the iDMC to review data prior to Part 2 commencing.

Eligibility criteria for study inclusion will be the same for Part 1 and Part 2 with the exception of eligibility criteria related to mandatory tests in Part 1 and participants with the *APOE* e4/e4 genotype, who are no longer eligible for enrollment in Part 2. Participants in Part 1 and participants with the *APOE* e4/e4 genotype, who are no longer eligible for enrollment in Part 2 will have additional assessments as outlined in Table 8, and will continue onto Part 2 as outlined in Table 9. In addition, lumbar punctures (LPs) will be mandatory for participants enrolled in Part 1 as defined in Table 8 and Table 9; LPs are optional for participants enrolled in Part 2.

Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit (if applicable) and/or prior to dosing on Day 1. Participants who have provided consent to participate in the optional clinical and biomarker assessments (LP for CSF collection, Tau PET Imaging, longitudinal Amyloid PET imaging, and/or WLSA assessments) will be randomized prior to or at the Predose Baseline Visit. Participants who will not be participating in the optional assessments will be randomized prior to or at the Day 1 Visit.

Treatment group assignment for Part 1 and Part 2 will be stratified based on *APOE* e4 status (carrier vs noncarrier). The detailed randomization plan will be documented in the randomization specifications.

After randomization, a Predose Baseline Visit will occur for participants undergoing the optional LP for CSF collection (if applicable), optional clinical and biomarker assessments (LP for CSF collection,

Tau PET imaging, longitudinal Amyloid PET imaging, and/or WLSA assessments). Note: participants who have consented to the optional WLSA may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1. Part 1 participants must have an LP during screening. Participants who consent to optional longitudinal Amyloid PET Imaging may have the baseline scan during screening. Participants who will not participate in the aforementioned optional assessments will not have a Predose Baseline Visit. For Part 2 participants who do not receive an LP during the screening period, but agree to participate in the optional CSF sampling, a Predose Baseline Visit will occur for an LP prior to Day -5.

Participants may provide consent to participate in the optional WLSA assessment to include at-home and in-clinic assessments, or in-clinic assessments only. Participants who have provided consent to participate in the optional WLSA assessment will be trained by site staff at the Predose Baseline Visit (or the Day 1 Visit) regarding the use of the device including, but not limited to, the frequency and the assessments to be completed. For all participants who consent to WLSA, assessments will be administered at the clinic during the Predose Baseline Visit (or the Day 1 Visit), every 24 weeks following commencement of dosing, and at the end of study (early termination [ET] visit). For participants who consent to at-home WLSA, additional assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments), within 7 days prior to the treatment administration visit. Participants who do not have the appropriate device to participate in the optional WLSA at-home may still participate in the assessments administered at the clinic. At-home assessments will be supervised by the study partner. Site staff will contact the participant/caregiver to remind them to conduct the appropriate assessment per the Schedules of Assessments (Section 14.1). Refer to the applicable WLSA Manual for additional information. The baseline assessment for the optional WLSA must be completed prior to dosing on Day 1.

Study Drug Treatment Period

Study drug will be administered via IV infusion at the study site on Day 1 after randomization (and after all baseline assessments have been completed) and will be repeated subsequently once every 4 weeks throughout the treatment period. In order to maintain the blind across all dose groups and allow step titration to the higher doses, the dose for each participant will be titrated starting with a dose of 15 mg/kg (or placebo equivalent) for the first dose administration on Day 1. For the second dose administration, the dose will increase to 40 mg/kg for participants randomized to receive 40 mg/kg or 60 mg/kg, while doses in the other 2 groups will remain constant. For the third dose administration, the dose will increase to receive 60 mg/kg for participants randomized to receive 60 mg/kg while doses in the other 3 groups will remain constant. The titration algorithm is provided in Section 5.2.

Randomized participants will be treated for at least 48 weeks (up to a total of 13 doses) and up to 96 weeks (up to a total of 25 doses). Please see Section 3.2 for a determination of the planned treatment period for each participant. Participants may miss doses, have dosing paused, or have dosing discontinued permanently. Because this trial has been designed to follow all participants randomized, irrespective of whether they discontinue study drug, all visits and assessments should be made whenever possible until the completion of the planned treatment period and through the efficacy follow-up (EFU), if applicable, and safety follow-up (SFU) visits. If a participant discontinues the study prior to the end of their planned treatment period, they will need to return for an ET visit. If there are studies that offer an extension of study drug dosing to a participant, the EFU and/or SFU visits might be eliminated.

Efficacy Assessments

A battery of COAs (Appendix 2 [Section 14.2]) will be administered as efficacy assessments over the course of the study, with the primary endpoint being the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Efficacy assessments, including COAs and biomarker assessments, will be made at baseline (screening, Predose Baseline Visit, or on Day 1 prior to dosing), throughout the 48- to

96-week treatment period and, when applicable, at an EFU visit 4 weeks after the last treatment visit. The occurrence of the EFU visit is dependent on the interval of time since the last efficacy assessment during the treatment period; please see sections related to follow-up visits in this protocol and the footnotes to the Schedule of Assessments (Section 14.1) for details. Clinical outcomes and biomarker assessments may or may not occur at an ET visit in the case of early discontinuation; this is also dependent on the interval of time since the last efficacy assessment during the treatment period and is detailed in the footnotes of the Schedules of Assessments (Section 14.1).

Safety Assessments

Safety assessments will be performed during screening (and at the Predose Baseline Visit, if applicable), throughout the 48- to 96-week treatment period, and at an 8-week SFU visit after the last dose of study drug or ET visit. The Schedules of Assessments are provided in Section 14.1.

ARIA Monitoring and Management:

Part 1

On Day 15 and 43 of Part 1, a brain MRI will be performed. Participants with MRI evidence of ARIA will not be eligible to receive further administration of study drug. Additionally, on Day 43, an ophthalmological examination, neurological examination, and an LP will be performed. Participants in Part 1 with ARIA after Day 43 will be managed according to the guidelines in Section 7.11.

All new cases of ARIA-edema (ARIA-E) and/or new cases of ARIA-hemosiderin deposits (ARIA-H) will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or ARIA-H has stabilized without new findings. An Amyloid PET scan may also be requested after the first occurrence of ARIA-E and/or ARIA-H for those participants who have opted-in to have longitudinal Amyloid PET performed. An unscheduled LP for CSF analysis may be requested after any occurrence of ARIA-E and/or ARIA-H.

Part 2

Surveillance for treatment-emergent ARIA will be accomplished with post-randomization MRI scans as follows: MRIs to be performed 5-10 days before Dose 2 (Day 29), Dose 3 (Day 57), and Dose 4 (Week 13), and 5-10 days before doses at all subsequent visits with MRI (Weeks 25, 49, 73, 97) (see Section 14.1). The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

If new or worsening ARIA is observed on any of these post-randomization MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 7).

Participants with new or worsening radiographic evidence of ARIA on post-baseline MRI scans should be evaluated for neurological signs or symptoms during an unscheduled visit.

All new cases of ARIA-E and/or new cases of ARIA-H will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or ARIA-H has stabilized without new findings. An Amyloid PET scan may also be requested after the first occurrence of ARIA-E and/or ARIA-H for those participants who have opted-in to have longitudinal Amyloid PET performed. An unscheduled LP for CSF analysis may be requested after any occurrence of ARIA-E and/or ARIA-H.

PK, PD, and Anti-Drug Antibody (ADA) Assessments

The PK and PD measurements will be made from blood samples (all participants) and from CSF samples in a subset of participants (required for Part 1 and optional for Part 2 participants). Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at one of the following timepoints: Week 25 or 37 or 49. Blood samples for assessment of ADA will be taken throughout the study. Imaging PD biomarkers will also be assessed with MRI (all participants) and

with optional PET scans using an amyloid tracer and the tau-tracer [^{18}F]MK-6240 (in a subset of participants). Tau PET and longitudinal Amyloid PET imaging should be conducted in accordance with local/country regulations for participants that opt to participate in the assessment. Phonemic/Linguistic assessment of speech using the WLSA will be made as an optional assessment in a subset of participants who are proficient in English, French, German, or Spanish.

Description of Study Procedures:

Screening Period

Participants who consent will be screened within 8 weeks prior to the Predose Baseline Visit or to Day 1 to determine eligibility. (Note: At the discretion of the Sponsor the screening period may be extended to accommodate delays for reasons including but not limited to coronavirus disease 2019 (COVID-19), laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.) Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit and/or Day 1 Visit. Participants who have provided consent to participate in the optional Tau PET imaging, optional longitudinal Amyloid PET imaging (if applicable), optional LP for CSF collection (if applicable), and/or optional WLSA will be randomized prior to or at the Predose Baseline Visit. Note: participants who have consented to the optional WLSA may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1. Participants who have consented to the optional Tau PET scans may complete the first Tau PET scan after dosing on Day 1, with Sponsor agreement (see the Schedule of Assessments [Section 14.1] for details). Participants who will not be participating in the optional assessments will be randomized prior to or at the Day 1 Visit.

Predose Baseline Visit (Part 1 or Part 2 Participants, if Applicable)

A Predose Baseline Visit from Day -22 to Day -1 will occur for participants in the following situations:

- For participants participating in any of the optional Tau PET imaging procedures, a Predose Baseline Visit will be performed to schedule and include PET imaging prior to Day 1. In some cases, with Sponsor agreement, participants may receive their first (ie, baseline) Tau PET scan after dosing has commenced. Participation in the optional Tau PET procedures may not be permitted in some regions.
- Participants enrolled in Part 1 must have LP performed at screening. For Part 2 participants who do not receive an LP during the screening period, but agree to participate in the optional CSF sampling, a Predose Baseline Visit will occur to schedule and perform an LP prior to Day -5.
- Participants who are undergoing the optional longitudinal Amyloid PET imaging procedures may also use the Predose Baseline Visit to schedule and perform Amyloid PET imaging prior to Day 1 if a new Amyloid PET scan was not obtained at screening.
- For all participants participating in the optional WLSA, a baseline assessment can be done at the Predose Baseline Visit or at any time prior to dosing on Day 1.
- Participants who have provided consent to participate in the optional at-home WLSA assessment will be trained by site staff at the Predose Baseline Visit regarding the use of the device including, but not limited to, the frequency and the assessment to be completed. For all participants who consent to WLSA, assessments will be administered at the clinic during the Predose Baseline Visit, every 24 weeks following commencement of dosing, and at the end of study. For participants who consent to at-home WLSA, additional assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments),

within 7 days prior to a treatment administration visit. Participants who do not have the appropriate device to participate in the optional WLSA at home may still participate in the assessments administered at the clinic. At-home assessments will be supervised by the study partner. Site staff will contact the participant/caregiver to remind them to conduct the appropriate assessment per the Schedules of Assessments (Section 14.1). Refer to the applicable WLSA Manual for additional information. The baseline assessment for the optional WLSA must be completed prior to dosing on the Day 1 Visit.

Treatment Period

The planned study drug period will be a minimum of 48 weeks and a maximum of 96 weeks. After July 2021, all participants randomized to AL002 will start with 15 mg/kg on Day 1; participants randomized to 40 mg/kg or 60 mg/kg will be titrated to their target dose over the next 2 or 3 doses, respectively. Study drug will be administered via IV infusion at the site on Day 1 and every 4 weeks thereafter. Safety assessments will be performed at screening (and at the Predose Baseline Visit, if applicable) and throughout the treatment period. COAs, PK assessments, and PD assessments (fluid collection and imaging) will be performed at prior to dosing (screening, Predose Baseline Visit, or on Day 1) and at specific timepoints during the treatment period and in the follow-up period after the end of treatment. Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at Week 25 or 37 or 49. The full Schedules of Assessments are provided in Section 14.1.

Participants may participate in an optional exploratory assessment to evaluate changes in the brain as measured by imaging with Tau PET or longitudinal Amyloid PET. Details for the optional imaging assessments including objectives, eligibility criteria, sample collection, and imaging specifications are provided in the PET Imaging Procedures Manual. Participants enrolled in Part 2 may also participate in an optional PK assessment with additional blood at one of the following: Week 25 or 37 or 49. Consent for the optional assessments will be documented. Participation in the optional PET imaging procedures will be allowed according to local country regulations.

In this protocol, the term "study drug" refers to AL002 (or placebo). The term "radiotracer" refers to any PET radiotracer used for any PET imaging assessment in the study.

All reasonable efforts should be made to keep every randomized participant active in the study and complete all required assessments as outlined in the Schedules of Assessments (Section 14.1), even if they prematurely discontinue study drug at any time during the course of their participation. Participants should complete all visits per their planned treatment period, (see Section 3.2), regardless of whether or not study drug has been paused or discontinued.

If eligible participants consent to long-term dosing or open-label extension studies at the end of the planned treatment period, they will not be required to attend the follow-up visits.

Follow-up Visits

When a randomized participant completes all study visits and procedures up to and including the final visit of their planned treatment period, an SFU visit will follow 8 weeks after this last treatment period visit, unless the participant enrolls in the AL002-LTE study. The end of a given participant's planned treatment period is defined by the treatment period termination date (TPTD) as noted above. For participants who had paused dosing or who had prematurely discontinued dosing, the TPTD as noted above, will still define the end of their planned treatment period. The SFU visit will follow 8 weeks after the end of the planned treatment period for each participant, unless the participant enrolls in the AL002-LTE study. If a participant enrolls in the AL002-LTE study, an SFU visit is not required.

An EFU visit may or may not be required for a given participant, who has completed the planned treatment period and does not enroll in the AL002-LTE study. If a participant enrolls in the AL002-LTE study, an EFU visit is not required. For participants who do not enroll in the AL002-LTE study,

an EFU visit is required 4 weeks prior to the SFU visit if the final COA and biomarker assessments were not completed within the defined time intervals as follows:

- An EFU visit is required if the last COA visit was done more than 12 weeks since the date the EFU visit would occur.
- An EFU visit is required if the last LP was done more than 12 weeks since the date the EFU visit would occur.
- An EFU is required if the last Amyloid or Tau PET was done more than 24 weeks since the date the EFU visit would occur.

If the COA, LP, or PET biomarker assessments were not collected in the specified time period noted above, the participant will need to complete an EFU visit 4 weeks prior to the SFU visit.

An ET visit is performed only in cases where participation is permanently discontinued. If the participant withdraws or is discontinued from the study for any reason, the ET is completed 8 weeks after the last administered dose. Participants who complete an ET visit will not require a SFU visit, if the safety assessments were collected at a regularly scheduled study visit 8 weeks after the final dosing visit. Similarly, to the EFU visits for those who have completed the planned treatment period, the following efficacy and biomarkers are required as part of the ET visit if the following conditions are met:

- COA visit was done more than 12 weeks since the date the ET visit would occur.
- LP was done more than 12 weeks before the date the ET visit would occur.
- Amyloid or Tau PET was done more than 24 weeks since the date the ET visit would occur.

Please see the Schedules of Assessments (Section 14.1) for additional information.

Study Sites:

Approximately 328 participants will be enrolled at approximately 90 sites in North America, New Zealand, Australia, Europe, and South America.

Treatment Duration:

The total duration of study participation for each participant will be up to approximately 115 weeks. This includes the screening period of up to 8 weeks prior to the Predose Baseline Visit or to Day 1, a Predose Baseline Visit of up to 21 days prior to Day 1, a treatment period of a minimum of 48 weeks and a maximum of 96 weeks, a possible final efficacy assessment visit 4 weeks after the last dose administration, and a mandatory SFU visit approximately 8 weeks after the last planned dose administration.

Planned Number of Participants:

Part 1 consists of the first approximately 40 participants. Part 2 consists of approximately 288 participants. In total, approximately 328 participants are expected to be enrolled.

Criteria for Inclusion and Exclusion:

Each participant must meet all of the following criteria to be enrolled in this study:

Key clinical inclusion criteria for the study:

1. Participants must be in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework (Jack 2018); this requires evidence of cerebral amyloidosis (A+). This evidence requirement can be satisfied by any one of the following 3 pathways:
    a. Historical Amyloid PET may be allowed to fulfill this criterion if it meets all of the following:
        i. Must utilize either [^{18}F]florbetaben, [^{18}F]florbetapir, or [^{18}F]flutametamol.
        ii. Must have adequate scan parameters and image quality as determined by the central imaging reader.
        iii. Must have the raw data available to send to the core PET laboratory.
        iv. Must have been read positive (elevated amyloid) by the core PET laboratory.
    b. Historical CSF measurements may be allowed to fulfill this criterion after review by the Medical Monitor. At a minimum, documentation of historical CSF testing must contain the following details:
        i. Identification of which laboratory did the testing.
        ii. Identity of the type of assay used (eg, Roche Elecsys, Fujirebio Lumipulse, Athena ADMark).
        iii. Reference ranges for values reported.
    c. If historical testing is not available, the participant must undergo a 2-step verification of amyloid positivity:
        i. As an initial screen for cerebral amyloidosis, the participant must have a high or intermediate APS as measured by Precivity AD™ Aβ blood test. Participants with a low APS are not eligible for study participation. (Note: Historical studies that do not meet the full criteria in a. or b. may still be considered sufficient, after consultation with the Medical Monitor, to allow a participant to forego Precivity AD™ screening and thus allow the participant to proceed to steps outline in 1.c.ii – amyloid confirmation.
        ii. Participants need confirmation of amyloid positivity with either:
            - New positive Amyloid PET scan (see footnote a below).
            - New positive CSF phosphorylated Tau (p/Tau)/Aβ42 (see footnote b below).
            - Participants who do not have a confirmation of amyloid pathology based on an initial Amyloid PET scan may opt to have a second assessment with CSF. Participants who do not have a confirmation of amyloid pathology on an initial CSF pTau/amyloid beta/Aβ42 measurement may opt to have a second assessment with an Amyloid PET scan as outlined in the table below:

Initial Confirmatory Test	Second Assessment, if Initial Test is Negative	Third Assessment, if Second Assessment is Negative
Historical positive Amyloid PET prior to screening start	NA	NA
Historical CSF positive amyloid	NA	NA
PrecivityAD™ positive, followed by new Amyloid PET[a]	New CSF pTau/Aβ42[b]	Not allowed; participant not eligible
PrecivityAD™ positive, followed by new CSF pTau/Aβ42[c]	New Amyloid PET[a]	Not allowed; participant not eligible

Aβ42=amyloid beta (1-42); CSF=cerebrospinal fluid; NA=not applicable; PET=positron emission tomography; pTau=phosphorylated Tau.

[a] Alector may decline performing a new Amyloid PET if participant has a negative historical Amyloid PET that was performed ≤12 months prior to the start of screening.

[b] The CSF pTau/Aβ42 ratio will be measured by the Roche Elecsys assay and will be considered positive with a ratio of >0.024.

2. Participants must demonstrate a clinical severity consistent with Stages 2, 3, or early Stage 4 as defined in the 2018 NIA-AA Research Framework, also described as mild cognitive impairment and mild dementia in the 2018 NIA-AA Research Framework. Further, participants must meet the following inclusion criteria to define clinical severity:
    a. Participant has mild symptomatology as defined by a screening MMSE score of ≥20 points.
    b. Participant has a CDR-GS of 0.5 to 1.0.
    c. Participant has evidence of episodic memory impairment as demonstrated by the RBANS-Update DMI score:
        i. If the DMI score ≤85, the participant meets this requirement without additional evidence needed.
        ii. If the DMI is >85 and ≤95, the participant may still be considered for participation if they have a history of cognitive and functional decline consistent with diagnosis of Early AD. Agreement between the Investigator and the Medical Monitor that the participant meets criteria for clinical severity consistent with mild cognitive impairment or mild dementia due to Early AD must be documented prior to randomization.
3. If the participant is receiving symptomatic AD medications (for memory and/or behavioral symptoms), the dosing regimen must have been stable for 60 days prior to screening and not expected to change during study participation.

General inclusion criteria for the study:

4. Participant is willing and able to give informed consent. Where not permitted by local regulations, participants deemed not able to provide informed consent by the Investigator will not be enrolled. Where local regulations permit inclusion of participants deemed not able to provide informed consent, a legally authorized representative must provide informed consent on his or her behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
5. Participant can be male or female, and is 50 to 85 years of age, inclusive.

6. Participant weighs ≤120 kg; body mass index (BMI) is between 18.5 and 34.9, inclusive.
7. At screening, female participants must be nonpregnant and nonlactating, and 1 of the following conditions must apply:
    a. Participant is not a woman of childbearing potential (WOCBP) (either surgically sterilized, or physiologically incapable of becoming pregnant, or at least 1-year postmenopausal [amenorrhea duration of 12 consecutive months with no identified cause other than menopause]).
    b. Participant is a WOCBP and agrees to use an acceptable contraceptive method from screening until 12 weeks after the last dose of study drug. Acceptable contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom, or the sole sexual partner to a vasectomized male. Vasectomized males must have received medical assessment of surgical success. In addition, total abstinence, in accordance with the lifestyle of the participant, is acceptable.
    c. A WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedules of Assessments (Section 14.1).
8. Male participants must agree to use acceptable contraception and not donate sperm from screening until 12 weeks after the last dose of study drug. Acceptable contraception for the male participant when having sexual intercourse with a WOCBP who is not currently pregnant is defined as using a condom. In addition, WOCBP partners must use hormonal contraceptives or an intrauterine device. Vasectomized male participants should have received medical assessment of surgical success.
9. Participant has availability of a person (“study partner”) who, in the Investigator's opinion, has frequent and sufficient contact with the participant (eg, approximately 10 hours per week of in person contact), is able to provide accurate information regarding the participant’s cognitive and functional abilities, agrees to provide information at clinic visits (which require partner input for scale completion), and signs the necessary consent form.
    a. The study partner must have sufficient cognitive capacity, in the Investigator’s opinion, to accurately report upon the participant’s behavior, cognitive, and functional abilities. The study partner should be in sufficiently good general health, in the Investigator’s opinion, to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the study duration.
    b. Every effort should be made to have the same study partner participate throughout the duration of the study.
10. Participant and study partner are fluent in the language of the tests used at the study site as assessed by site personnel.
11. Participant is willing and able to complete all aspects of the study (including MRI, LP, genotyping, and PET imaging, as applicable). The participant should be capable of completing assessments either alone or with the help of the study partner.
12. Participant has adequate visual and auditory acuity, in the Investigator’s opinion, sufficient to perform the neuropsychological testing (corrective lenses and hearing aids are permitted).
13. Participant agrees not to donate blood or blood products for transfusion for the duration of the study and for 1 year after the final dose of study drug.

Inclusion criteria for participants participating in the optional Tau PET imaging assessment with [^{18}F]MK-6240 only:

14. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
15. [^{18}F]MK-6240 is available to the PET imaging center based on manufacturing distribution network and local regulations.

Inclusion criteria for participants participating in the optional longitudinal Amyloid PET imaging assessment only:

16. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
17. An approved amyloid radiotracer is available to the PET imaging center based on manufacturing distribution network and local regulations.

Inclusion criteria for participants participating in the optional at-home and/or in-clinic WLSA only:

18. For at-home participation:
    a. Participant has an available and willing study partner to administer the WLSA.
    b. Participant has WiFi access in their residence or WiFi access in a nonpublic area where the testing can take place.
    c. Participant has access to an iPad or iPhone.
19. For at-home and in-clinic participation, participant is proficient in and from an English-, French-, German-, or Spanish-speaking country.

Participants meeting any of the following criteria will be excluded from the study:

Central Nervous System (CNS) disorders-related exclusion criteria:

1. Participant has any evidence of a condition other than AD that may affect cognition, including but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington disease, normal pressure hydrocephalus, hypoxic injury, seizure disorder, static encephalopathy, closed brain injury, or developmental disability.
2. Participant has history or presence of vascular disease that has the potential to affect cognitive function (eg, clinically significant carotid, vertebral stenosis, or plaque; aortic aneurysm; intracranial aneurysm; macro-hemorrhage; arteriovenous malformation).
3. Participant has a history or presence of cerebrovascular accident within the past 2 years, or recent transient ischemic attack within 180 days before screening, or has radiologic evidence of any cortical stroke regardless of age.
4. Participant has history of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (eg, cerebral contusion).
5. Participant has history or presence of intracranial tumor (eg, glioma, except for benign brain tumors that, in the opinion of the Investigator, are not likely to impair cognition).
6. Participant has ongoing infections that may affect brain function (eg, human immunodeficiency virus [HIV], syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis), or history of infections that resulted in neurologic sequelae.
7. Participant currently has or has had an acute illness that requires or required IV antibiotics within 30 days prior to first study drug administration.

8. Participant has history or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (eg, multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease).
9. Participant has any of the following eye conditions: a history of uveitis, a serious chronic inflammatory condition of the eye, a current eye infection, or any ongoing eye disorder requiring anticipated invasive eye procedures or injectable medical therapy (eg, ranibizumab or aflibercept for macular degeneration or diabetic eye disease) during the study period.
10. Participant has any history of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder.
    a. A history of major depression is acceptable if no episode has been reported within the previous 2 years. Treatment with antidepressant medications is allowed.
11. Participant is at risk of suicide in the Investigator's opinion.
12. Participant has history of alcohol and/or moderate to severe substance use disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) within the past 2 years.
    a. Nicotine use is allowed.

Imaging-related exclusion criteria:

13. Participant has MRI evidence of
    a. >2 lacunar infarcts.
    b. Any territorial infarct >1 cm^3.
    c. White matter hyperintense lesions on the fluid-attenuated inversion recovery (FLAIR) sequence that correspond to an overall Fazekas score of 3.
14. Participant has presence on MRI of >5 microbleeds and/or >1 area of leptomeningeal hemosiderosis based on central read.
15. Participant has presence of significant cerebral vascular pathology as assessed by the MRI Central Reader.
16. Participant is unable to tolerate MRI procedures (eg, due to anxiety or claustrophobia) or has a contraindication to MRI, including but not limited to, the presence of pacemakers that are not MRI compatible, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that would pose a potential hazard in combination with MRI. Those who are able to tolerate MRI with intermittent use of low-dose benzodiazepine or anxiolytic are permitted and may be included in the study.

Cardiovascular disorders-related exclusion criteria:

17. Uncontrolled hypertension defined as average of 3 systolic blood pressure (SBP)/diastolic blood pressure (DBP) readings >165 mmHg and/or >100 mmHg at screening (blood pressure [BP] measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the participant to be eligible for the study), or persistent SBP/DBP reading >180 mmHg and/or >100 mmHg 3 months prior to randomization that, in the opinion of the Investigator, are indicative of chronic, uncontrolled hypertension.
18. Participant has an abnormal ECG that is considered clinically significant by the Investigator.
19. Participant has unstable ventricular dysrhythmias.

Hepatic/renal disorders:

20. Participant has significant kidney disease as indicated by either of the following:
    a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation. Note: MDRD equation is as follows:

    eGFR (mL/min/1.73 m^2) = 175 × (standardized serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if black), or

    b. Creatinine ≥2 mg/dL.
21. Participant has impaired hepatic function as indicated by screening aspartate aminotransferase or alanine aminotransferase ≥2.5×the upper limit of normal (ULN), or total bilirubin ≥2.0×ULN. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor.

Infections and immune disorders:

22. Participant is positive for hepatitis B surface antigen, HIV-1 or -2 antibodies or antigen, or history of spirochetal infection of the CNS (eg, syphilis, borreliosis, or Lyme disease). Participants with a positive hepatitis C virus antibody will be allowed if hepatitis C ribonucleic acid (RNA) is negative.

    Note: Prospective participants positive for total hepatitis B core antibody should be excluded unless both:
    a. Hepatitis B surface antibody is positive and
    b. Hepatitis B surface antigen is negative.
23. Participants with active or latent tuberculosis (TB) disease should not be enrolled in the trial.
24. Any chronic active immune disorder requiring systemic immunosuppressive therapy within 1 year prior to study enrollment and/or causing bone marrow dysfunction (based upon hemoglobin <10 g/dL, absolute neutrophil count <1,000/mm^3, or platelet count <150,000/mm^3.)
    a. Continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed if treated with a stable regimen for at least 90 days prior to study drug.
    b. Intermittent short-term use of prednisone or an equivalent corticosteroid is allowed to treat an acute condition.

Metabolic/endocrine disorders:

25. Participant has abnormal screening thyroid-stimulating hormone (TSH) or tests that remain abnormal on retest or require a new treatment or an adjustment of current treatment.
    a. A participant may be rescreened if there is no improvement in cognition in the Investigator's opinion after 90 days of adequate treatment for thyroid function.
26. Participant has screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency may be contributing to cognitive impairment.
    a. A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for vitamin deficiency.
27. Participant has screening hemoglobin A1c >8% or poorly controlled diabetes (including hypoglycemic episodes).
    a. A participant may be rescreened after 90 days to allow optimization of diabetic control.

General exclusions:

28. Participant is positive for *APOE* e4/e4 genotype.
29. Participant has contraindication for LP including deformity of the lumbosacral region of the spine that in the Investigator's opinion would contraindicate LP for all participants in Part 1 and for participants in Part 2 who can only be CSF eligible due to regional lack of availability of PET ligands or consent to the optional LP assessments. Participants undergoing the LP must not be currently taking anticoagulation medications, such as warfarin, that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatory medications are allowed. Participants requiring fluoroscopy-guided LP are not eligible for participation.
30. Participant has clinically significantly abnormal screening blood or urine results that remain clinically significantly abnormal at retest.
31. Participant has impaired coagulation (screening prothrombin time >1.2×ULN that remains impaired on retest).
32. Participant has history of cancer except if one or more of the following exceptions are satisfied:
    a. Is considered clinically cured as defined by being clear of recurrence after 5 years from last definitive treatment.
    b. Is not being actively treated with anticancer therapy or radiotherapy and will not require treatment in the ensuing 3 years except for adjuvant hormonal therapy for localized breast cancer.
    c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible).
    d. For prostate cancer, has not had clinically significant progression within the past 3 years.
33. Participant has known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
34. Participant has had any surgery (major or emergent) or hospitalization within 30 days prior to first study drug administration.
35. Participant has any other severe or unstable medical condition that could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care.
36. Participant resides in a skilled nursing facility, convalescent home, or long-term care facility. Participants who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement.
37. Any other issue which, in the opinion of the Investigator, would compromise participant safety or the integrity of the study data.

Medication-related exclusion criteria:

The following medications are prohibited for a prespecified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study drug):

38. AD medications must not be initiated, modified, or stopped within 60 days prior to screening.
39. Use of medications known to impair consciousness or cognition in doses which in the opinion of the Investigator may interfere with diagnosis of dementia or interfere with study assessments

(use of these medications during the study may be allowed, if necessary, for the treatment of a medical condition with the approval of the Medical Monitor).

40. Any investigational active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline. Routinely recommended vaccinations are allowed, as well as any vaccine against COVID-19 (either approved or administered under an Emergency Use Authorization).
41. Any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline within 1 year of screening.
42. Any other investigational treatment within 5 half-lives or 90 days of screening, whichever is longer.
43. Any previous treatment with medications used to treat Parkinsonian symptoms or any other neurodegenerative disorder (with the exception of medications to treat AD; see Inclusion Criteria 3) within 1 year of screening.
    a. Certain medications are acceptable, pending Medical Monitor approval, if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (eg, pramipexole).
44. Typical antipsychotic or neuroleptic medication within 180 days of screening except as brief treatment for a nonpsychiatric indication (eg, emesis).
45. Atypical antipsychotics unless on a stable regimen for at least 90 days prior to study drug administration; intermittent short-term use of atypical antipsychotics may be allowed to treat an acute condition after consultation with the Medical Monitor.
46. Anticoagulant medications other than antiplatelet agents are prohibited within 90 days of screening and throughout the study. Short-term use of anticoagulants to treat an emergent medical need is permitted.
    a. Treatment with platelet anti-aggregation agents such as aspirin, clopidogrel, or dipyridamole is permitted.
47. Systemic immunosuppressive therapy use or anticipated systemic immunosuppressive therapy use during the study.
    a. Continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed if treated with a stable regimen for at least 90 days prior to study drug administration; intermittent short-term use of prednisone or an equivalent corticosteroid is allowed to treat an acute condition.
48. Chronic use of opiates or opioids (including long-acting opioid medication) within 90 days of screening.
    a. Intermittent short-term use of short acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
49. Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 30 days of screening and throughout the study.
50. Chronic use of benzodiazepines, barbiturates, or hypnotics from 90 days before screening.
    a. Intermittent short-term use of benzodiazepines, buspirone or short acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
    b. Trazodone, mirtazapine, and melatonin are allowed for insomnia if on a stable regimen for 90 days before screening.

Clinical Outcome Assessments – Neurocognitive and Functional Tests:

The following neurocognitive and functional tests (described in Section 14.2) will be performed. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (eg, blood collections, LPs, imaging).

- Clinical Dementia Rating (CDR)
- MMSE
- RBANS-Update
- Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13)
- Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment Scale (ADCS-ADL-MCI)
- WLSA (optional)

If a participant is taking intermittent or short-term regimens of medications known to impair consciousness or cognition, such medication must be stopped 2 days or 5 half-lives (whichever is longer) prior to any cognitive or behavioral assessment. Use of cannabinoids (other than cannabidiol [CBD]) is prohibited within 72 hours prior to any cognitive or behavioral assessment.

Safety Assessments:

Safety assessments will consist of physical, ophthalmological, and neurological examinations and monitoring of AEs, vital signs, ECGs, clinical laboratory analytes, suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS), and brain MRI.

Pharmacodynamic Biomarker Assessments:

The exploratory PD biomarker endpoints for this study are presented in Section 2.

The PD biomarker assessments will consist of, but are not limited to, blood-based biomarkers, CSF-based biomarkers (when available), and imaging biomarkers, as follows:

Blood-based biomarkers:

- Soluble triggering receptor expressed in myeloid cells 2 (sTREM2) in plasma
- Plasma biomarkers relevant to AD (eg, Aβ42, amyloid beta (1-40) [Aβ40], total tau [tTau], pTau, neurofilament light [NfL])
- Other exploratory PD biomarkers which may include transcriptional analysis of whole blood following PAX gene extraction of cellular RNA to assess triggering receptor expressed in myeloid cells 2 (TREM2) expression as well as other genes of interest

CSF-based biomarkers (CSF collections apply to participants in Part 1 and those participants in Part 2 who consent to the optional LPs only):

- sTREM2 in CSF
- CSF biomarkers relevant to AD (eg, Aβ42, Aβ40, tTau, pTau, NfL) and to microglia function (eg, chitinase 3-like 1 [YKL-40], osteopontin)
- Other exploratory PD biomarkers

Imaging biomarkers:

- MRI imaging measures
- Optional longitudinal Amyloid PET imaging measures
- Optional Tau PET imaging measures

Timing and frequency of all PD biomarker assessments are presented in the Schedules of Assessments (see Section 14.1).

Pharmacokinetic Assessments:

PK blood, CSF (mandatory for Part 1 participants for all visits through study completion; optional for Part 2 participants), and ADA collections will be performed, and AL002 concentrations will be measured. Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at 4 and 8 and 24 or 48 hours after the end of infusion at one of the following: Week 25 or 37 or 49.

Genomic Assessments and Genetic Disclosure:

A blood sample will be collected at screening for DNA extraction to genotype *APOE* variants. Participants will be stratified during randomization based on *APOE* e4 status (carrier vs noncarrier).

Blood samples will be collected at baseline (or the next available visit) for DNA extraction to enable analysis of targeted genomic variants and whole genome sequencing (WGS) analysis to identify common and rare genetic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with safety findings, or can increase the knowledge and understanding of disease biology. WGS samples will be collected where acceptable by local regulations.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of larger datasets will assist in identification of important pathways, guiding the development of new targeted agents.

Targeted genomic assessments will include, but not limited to, the following:

- *APOE* e4 allele; and
- TREM2 variants, sialic acid-binding immunoglobulin-like lectin 3 (CD33) variants, Transmembrane Protein 106B (TMEM106b) variants, and CLUSTERIN variants.

Study sites will follow their local guidelines and regulations regarding disclosure and supportive genetic counseling.

Study Drug, Dose, and Mode of Administration:

AL002 is a recombinant humanized agonistic TREM2 monoclonal antibody. AL002 will be administered as an IV infusion over approximately 60 minutes. The IV dose will be calculated based on the participant's screening weight (reference weight) unless the participant's current weight changes (increases or decreases) ≥10% from the screening weight. If this occurs, the current weight will become the reference weight for subsequent dosing. If the participant's weight again changes ≥10% from the reference weight, the IV dose will again be recalculated.

AL002 placebo is provided in an identical presentation to the active drug and shares the same concentrations of excipients in solution.

Reference Product, Dose, and Mode of Administration:

Not applicable

Statistical Hypothesis:

The primary objective of the study is to evaluate the efficacy of AL002 in participants with Early AD in delaying disease progression compared to placebo. The treatment effect is defined as a percentage reduction of the placebo group clinical decline (eg, increase in CDR-SB).

The following hypothesis will be tested using a 1-sided 5% significance level:

- H_0 (null): $\theta <= 0$, indicating that treatment does not slow disease progression relative to placebo control

- H_1 (alternative): $\theta>0$, indicating that treatment slows disease progression relative to placebo control

Each dose of AL002 will be compared to placebo. To adjust for multiplicity among the multiple doses for the primary endpoint, a fixed testing order will be used with the highest dose compared first, followed by the next lower dose, and then the next lower dose after that.

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LIST OF ABBREVIATIONS

Abbreviation	Term or Definition
[^{18}F]MK-6240	fluorine-18 MK-6240
Aβ	amyloid beta
Aβ40	amyloid beta (1-40)
Aβ42	amyloid beta (1-42)
AD	Alzheimer's disease
ADAs	anti-drug antibodies
ADAS-Cog13	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment Scale
AE	adverse event
AESI	adverse event of special interest
APOE	apolipoprotein E
APOE e4	apolipoprotein E epsilon4
APS	Amyloid Probability Score
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemosiderin deposits
BMI	body mass index
BMW	Brain MRI Worksheet
BP	blood pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CBD	cannabidiol
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CFR	Code of Federal Regulations
CNS	central nervous system
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	clinical research organization

Abbreviation	Term or Definition
CSF	cerebrospinal fluid
CSF1R	colony stimulating factor 1 receptor
CSR	clinical study report
CT	computerized tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DLAE	dose-limiting AE
DMI	Delayed Memory Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFU	efficacy follow-up
eGFR	estimated glomerular filtration rate
ET	Early Termination
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient-recalled echo
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	independent Data Monitoring Committee
IEC	independent ethics committee
Ig	immunoglobulin
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
IV	intravenous(ly)
LP	lumbar puncture

Abbreviation	Term or Definition
LS-mean	least squares mean
MAR	missing at random
mCi	millicurie
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MMSE	Mini-Mental Status Examination
MRI	magnetic resonance imaging
mSv	Millisievert
NfL	neurofilament light
NIA-AA	National Institute on Aging/Alzheimer's Association
NOAEL	no-observed-adverse-effect level
OCT	optical coherence tomography
PD	pharmacodynamic(s)
PE	physical examination
PET	positron emission tomography
PK	pharmacokinetic(s)
pMMRM	proportional mixed effect model with repeated measurement
PPS	Per-Protocol Analysis Set
pTau	phosphorylated tau
QTcF	QT interval by Fredericia
RBANS-Update	Repeatable Battery for the Assessment of Neuropsychological Status-Update
RDVF	Research Diagnostic Verification Form
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SFU	safety follow-up
SOP	standard operating procedures
sTREM2	soluble triggering receptor expressed on myeloid cells 2

Abbreviation	Term or Definition
TB	tuberculosis
TMEM106b	transmembrane protein 106b
TPTD	treatment period termination date
TREM2	triggering receptor expressed on myeloid cells 2
tTau	total tau
ULN	upper limit of normal
WGS	whole genome sequencing
WHO DD	World Health Organization Drug Dictionary
WLSA	Winterlight Labs Speech Assessment
WOCBP	woman of childbearing potential
YKL-40	chitinase 3-like 1

1. INTRODUCTION

1.1. Background

Worldwide, more than 46.8 million people had dementia in 2015, with the largest incidence rates in Asia and Europe (Prince 2015). The worldwide prevalence of dementia is expected to exceed 130 million by 2050. Alzheimer's disease (AD) is a degenerative brain disease and is the most common cause of dementia in the US, affecting approximately 5.8 million Americans as of 2019 (Alzheimer's Association Report 2019). Of the top 10 causes of death in the US, Alzheimer's disease is the only major cause of morbidity and mortality without suitable treatments for preventing, slowing, or curing (Alzheimer's Association Report 2019).

Current therapies for AD such as acetylcholinesterase inhibitors (eg, donepezil) and N-methyl-D-aspartate receptor antagonists (eg, memantine) show only modest and transient benefits to cognition and behavior parameters in AD patients but do not slow or halt the progression of the disease (Cummings 2004). Recently (June 2021), Aduhelm® (aducanumab) and (January 2023) Leqembi® (lecanemab) received US FDA Accelerated Approval for the treatment of AD based on the reduction of amyloid and the reasonable possibility for cognitive benefit associated with a lower amyloid burden. Given the large number of patients with AD and the expected increases in this patient population due to an extended life expectancy and a major worldwide growth in the population of older adults, an effective treatment for AD remains an urgent unmet medical need.

Human genetic studies have identified inherited mutations that underlie familial forms of AD, but these mutations are rare, occurring in less than 5% of all cases. More recently, large human genetic association studies have revealed genetic loci that modify the risk of common sporadic forms of AD (Tanzi 2012). Many of these loci encode for proteins expressed primarily on innate immune cells, including microglia, macrophages, and dendritic cells. Microglia are resident macrophages of the central nervous system (CNS) and serve protective housekeeping functions such as facilitating clearance of cellular debris through phagocytosis, maintaining synapses, and secreting growth factors. Thus, in the course of neurodegenerative diseases such as AD, these cells may serve an important protective role when activated appropriately.

The most prominent microglial gene that modifies the risk of common sporadic forms of AD encodes for a type I transmembrane protein that is a member of the immunoglobulin (Ig) receptor superfamily, a triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 is an Ig-like receptor that is expressed primarily on myeloid lineage cells, such as macrophages, dendritic cells, and microglia (Colonna 2016). TREM2 is thought to play a key role in modulating the innate immune response, such as in response to bacteria in the context of infection or to dying neurons and other debris in neurodegenerative disorders including AD (Colonna 2016).

Heterozygous mutations in the TREM2 gene increase the risk of AD by up to 3-fold (Guerreiro 2013; Jonsson 2013) and increase the rate at which brain volume shrinks (Rajagopalan 2013).

Recent mouse genetic model studies strongly support a key role for TREM2 in AD, with the AD-associated R47H mutation in TREM2 being associated with increased pathology (Cheng-Hathaway 2018). Similarly, Wang et al (Wang 2015) showed that in the 5xFAD

transgenic mouse model of AD, deficiency in TREM2 function exacerbated AD pathology. Subsequent studies detailed the pathological changes seen in 5xFAD mice lacking one or both copies of TREM2, showing a consistent defect in the ability of TREM2 mutant microglia to effectively surround and engulf amyloid plaques (Wang 2016; Yuan 2016; Jay 2017a). In these TREM2-defective microglia, a reduction in microglia per plaque was associated with more diffuse plaques and more axonal damage and more tau aggregation in the vicinity of plaques (Yuan 2016; Leyns 2019).

Furthermore, TREM2 activation enhances microglial cell survival, proliferation, and differentiation, and regulates microglial chemotaxis and phagocytosis. In the context of AD pathology, TREM2 expression impacts tau hyperphosphorylation and aggregation and affects synaptic and neuronal loss (Jay 2017b). Conversely, AD pathology is reduced in mice overexpressing TREM2 (Lee 2018).

In summary, the loss of TREM2 function is detrimental as demonstrated in human and mouse genetic studies, while conversely, activating TREM2 on microglial cells is protective against damage in the process of neurodegeneration. This suggests that application of TREM2 agonistic antibodies may potentially improve cognitive function under pathological conditions.

Alector's approach is to utilize a TREM2 agonistic antibody to ameliorate AD pathology through activation of the innate immune system, thereby improving the clearance and sequestration of the molecular factors causing pathology. Alector has generated a TREM2 selective agonistic antibody that synergizes with endogenous ligands to treat AD. Alector has developed a humanized therapeutic TREM2 antibody, AL002, with optimized agonistic activity. As demonstrated in the data from Alector preclinical studies, activating TREM2 with a variant of AL002 can effectively suppress AD pathology in vivo.

AL002-1 is a first-in-human, Phase 1 study that evaluated the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles in blood and cerebrospinal fluid (CSF) in normal healthy volunteers and participants with AD following intravenous (IV) administration with AL002 has been completed (AL002-1). In this Phase 2 study (AL002-2), Alector proposes to evaluate the efficacy and safety of IV administered AL002 in participants with Early AD (Refer to Section 1.5 for definition of Early AD).

1.2. Summary of Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

The pharmacology, PK, and toxicology of AL002 has been comprehensively assessed in nonclinical studies.

Pharmacology studies conducted to date include: (i) in vitro cell-based assays to describe the proposed mechanism of action of AL002, (ii) in vivo pharmacology studies evaluating brain target engagement of AL002 in different species, and (iii) correlation of these changes to reversal of behavior deficits in mouse models of AD.

In vitro, AL002 activates human TREM2 expressed in cell lines or primary myeloid cells and causes membrane TREM2 down regulation and activation of downstream signal transduction to enhance survival of multiple myeloid cell populations. AL002 can also synergize with endogenous ligands such as phosphatidylserine and apolipoprotein E (APOE). In vivo, in a

bacterial artificial chromosome transgenic mouse model with over expressed human TREM2, a single-dose of AL002 increased microglia numbers and microglial genes, such as colony stimulating factor 1 receptor (CSF1R), in the brain, indicating that peripherally administered AL002 is able to activate brain TREM2 signalling. In the cynomolgus monkey, dose-dependent reductions in soluble triggering receptor on myeloid cells 2 (sTREM2) and brain TREM2 were observed after either a single IV dose or repeat weekly doses of AL002 indicating effective brain target engagement. Moreover, there was a significant increase in CSF1R levels in the monkey brain. A second downstream microglial activation marker, osteopontin, was also found to be elevated in cynomolgus monkey CSF. In vivo, a variant of AL002 reduced disease pathology in a mouse model of AD.

The cynomolgus monkey was selected as the nonclinical species for toxicokinetic and toxicology evaluations because AL002 binds with similar and high affinities to both human and cynomolgus monkey TREM2, does not bind to rodent TREM2, and lacks pharmacologic activity in rodents.

Nonclinical PK of AL002 were evaluated in single IV dose and preliminary non-GLP repeat-dose toxicology studies, as well as part of the 4-week and 26-week repeat-dose GLP toxicology studies to guide human clinical dose and regimen selection, and to estimate clinical safety factors for the initial Phase 1 first-in-human and Phase 2 multi-dose clinical studies. After once weekly IV administration of AL002 to cynomolgus monkeys in the 4-week and 26-week GLP studies, systemic exposure (as assessed by C_{max} and AUC from time 0 to 168 hours) increased slightly less than dose proportionally with increasing dose. Some accumulation of AL002 after multiple doses in monkeys was observed after weekly dosing. Animals were confirmed to have been exposed throughout the duration of the intended exposure period, although anti-drug antibodies (ADAs) were identified in some animals in all AL002 dosing groups in both the 4-week and 26-week GLP studies.

A preliminary dose range finding study, a GLP repeat-dose (4-week) IV toxicology study, a GLP repeat-dose (26-week) IV toxicology study, a GLP tissue cross reactivity study, and a GLP local tolerance study have been conducted to characterize the toxicology of AL002. In addition, the potential for AL002 to induce cytokine release was studied in vitro. The toxicology program was designed to support the proposed clinical trial and to comply with existing regulatory guidance, including International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline S6(R1). AL002 was administered by IV slow bolus in the toxicology studies to mimic the route of clinical administration in Study AL002-1 (IV infusion).

There were no AL002-related adverse findings in the toxicology assessments in the 4-week GLP study. IV administration of AL002 at doses up to 250 mg/kg weekly for 4 weeks was well tolerated in this study, and the no-observed-adverse-effect level (NOAEL) was 250 mg/kg.

In the 26-week GLP study, AL002 administered at doses up to 250 mg/kg weekly was well tolerated. AL002-related findings were limited to microscopic observations in the eye and consisted of unilateral or bilateral minimal to marked granulomatous inflammation in the ciliary body and/or choroid of animals administered 80 or 250 mg/kg, with no corresponding ophthalmic findings or associated clinical observations. The NOAEL was 20 mg/kg.

Local tolerability of AL002 by IV dosing was evaluated in the 4-week and 26-week GLP toxicology studies with no findings at the injection site. In addition, a local tolerance study in

rabbits following a single-dose subcutaneous injection was conducted with no AL002-related adverse findings. When incubated with human peripheral blood mononuclear cells in vitro, AL002 did not induce cytokine release when compared to isotype control human IgG antibody. An in vitro tissue cross reactivity study indicated the distribution of the staining observed was very similar between human and monkey.

Overall, the nonclinical package for AL002 supports the design of Study AL002-2 and the overall safety of study participants.

Nonclinical studies conducted for AL002 are described in further detail in the AL002 Investigator's Brochure (IB).

1.2.2. Clinical Studies

Study AL002-1 assessed the safety, tolerability, PK, and PD of IV administration of AL002 administered as a single-dose to healthy volunteers as well as multiple doses to participants with mild to moderate AD. Study AL002-1 was closed to enrollment by Alector on 14 May 2020 given the available data already obtained and limitations on enrollment due to the coronavirus disease 2019 (COVID-19) pandemic.

A total of 64 healthy volunteers enrolled in the first portion of the AL002-1 study, which evaluated single-dose IV infusion administration of AL002 with doses ranging from 0.003 to 60 mg/kg. All participants in these single ascending dose cohorts reached the end of their dose-limiting adverse event (DLAE) assessment windows. Fifty-three participants were exposed to AL002 and 11 participants were on placebo. All participants have completed the study, with the exception of 1 participant (60 mg/kg) who withdrew consent after receiving one dose of AL002.

The second portion of the study evaluated AL002 administered in multiple doses in participants with AD. Due to the closing of enrollment, only 5 of the planned 32 participants with AD were enrolled in the MD part of Study AL002-1. Three participants (2 on AL002 and 1 on placebo) were enrolled on a schedule that evaluated AL002 15 mg/kg weekly for 4 doses. Following a protocol amendment, an additional 2 participants (1 on AL002 and 1 on placebo) were enrolled on a schedule that evaluated AL002 60 mg/kg every 4 weeks for 2 doses.

Across the healthy volunteer and patient parts of the study, there were no deaths, no DLAEs, no treatment-related serious adverse events (SAEs), and no adverse events of special interest (AESI). One participant in the pooled placebo group had a Grade 3 injury (attributed to trauma) that was serious and was considered unrelated to study drug. Two participants in the single ascending dose part of the study experienced AEs considered probably related to AL002 that led to withdrawal of study drug. Overall, AL002 was considered generally safe and well tolerated in this trial.

For additional information regarding these cohorts, please refer to Section 5 of the IB.

1.3. Summary of Risks and Benefits

Based on preclinical observations and evidence reported in the literature, the proposed mechanism of action of AL002 (ie, agonism of TREM2) has the potential to alter the course of AD progression. Due to a paucity of therapeutic options for prevention, slowing, or cure for AD, a safe and effective therapy that targets TREM2 without blocking the ability of natural ligands to

induce an additive or synergistic effect may provide a favorable risk/benefit profile to participants with this condition.

Preclinical toxicology studies evaluating AL002 with long-term, dose-intensive regimens has identified ocular toxicity as a potential risk for AL002. Cynomolgus monkeys treated with 80 mg/kg or 250 mg/kg weekly for 27 doses had postmortem microscopic findings of inflammation in the ciliary body and choroid of the eye with no corresponding ophthalmic findings or associated clinical observations (for additional information, please see Section 4.3 of the IB). Because of these findings, uveitis has been added as a potential risk to treatment with AL002, and all treated participants will be monitored by an eye specialist (see Section 6.5.3 of the IB and Section 6.5.7 in this protocol). In the Phase 1 study (Study AL002-1), eye-related AEs have been limited to mild and transient events.

Amyloid-related imaging abnormalities-edema (ARIA-E) and amyloid-related imaging abnormalities-hemosiderin deposits (ARIA-H) have been observed in Study AL002-2. These data are described in the IB, including any issued addenda. Additional magnetic resonance imaging (MRI) monitoring has been added to this protocol and the Dosing Guidelines for ARIA have been updated (Section 7.11 and Schedules of Assessments [Section 14.1]). Because serious and severe symptomatic cases occurred in participants with an *APOE* e4/e4 genotype, participants with this genotype may no longer be enrolled into this trial. All currently enrolled participants with an *APOE* e4/e4 genotype will no longer receive study drug, but should continue with all study visits and assessments.

For this Phase 2 study, AL002 is to be administered for up to 96 weeks via IV infusion and is expected to be generally safe and well tolerated. To further mitigate potential risks associated with dosing, enrolled participants randomized to 40 or 60 mg/kg will be titrated to their assigned dose over 2 or 3 doses, respectively.

Potential risks associated with AL002 administration include uveitis, infusion-related reactions, immunogenicity (see Section 6.5 of the IB). Identified risks include MRI findings of ARIA-E and ARIA-H (Section 7.11, also see Section 6.4.1 of the IB). To minimize risks to study participants, careful monitoring of each participant will be conducted at timepoints delineated throughout the study to detect any AEs or safety signals through physical, neurological and ophthalmological examination, and assessment of electrocardiogram (ECG) findings, brain MRI scans, suicidality findings, vital signs, hematology and coagulation, chemistry, and urinalysis parameters. AE reporting and review of concomitant medication use, and other specific safety assessments will occur as delineated in the Schedules of Assessments (Section 14.1). Based on the monitoring of AEs, the Sponsor may request additional unscheduled MRIs to ensure early identification of ARIA. If additional MRIs are requested for a participant, an assessment of signs and symptoms should also occur. Samples to assess the development of ADAs will be collected prior to and throughout the treatment period of the study. For more details on potential and identified risks, see the IB.

AL002 will be administered to study participants and all procedures related to the study will be performed by scientifically and medically qualified persons at investigational sites suitable for conducting human studies of this nature. In some circumstances, study drug administration and relevant safety assessments may be conducted in a home setting by qualified medical personnel. In addition, some clinical outcome assessments may be conducted remotely. See Section 14.4 for details regarding at-home and remote assessments.

Suicidality will be assessed in AL002-2 with regular participant interviews using the Columbia-Suicide Severity Rating Scale (C-SSRS). Brain MRI (including but not limited to 3DT1, fluid-attenuated inversion recovery [FLAIR] and T2*-weighted gradient-recalled echo [GRE] sequences) will be undertaken to detect the occurrence of brain abnormalities. Please see Section 7.11 and the Schedules of Assessments (Section 14.1) for a description of ARIA risk mitigation steps and management guidelines.

1.4. AL002 Dosage Determination

In this Phase 2 study, eligible participants with Early AD (Refer to Section 1.5 for definition of Early AD) will each receive 1 of the following 4 treatments: placebo, 15 mg/kg AL002, 40 mg/kg AL002, or 60 mg/kg AL002.

The doses selected for this Phase 2 study are based on the clinical experience during the dose-escalation Phase 1 study conducted in healthy volunteers (Study AL002-1). Population pharmacokinetic and pharmacodynamic modeling has been performed on the preliminary data from Study AL002-1. Dose-response outputs from the model support dosing with 15 mg/kg, 40 mg/kg, and 60 mg/kg in the Phase 2 study.

Based on simulations of serum concentrations of AL002, the 75th percentile for 15 mg/kg is lower than the 25th percentile for 40 mg/kg. The 40 mg/kg and 60 mg/kg simulations are closer together with the 75th percentile from 40 mg/kg being close to the median for 60 mg/kg. Simulations of concentrations of AL002 in the CSF produced similar results.

Based on simulations of the target engagement marker sTREM2 in CSF, the 75th percentile for 15 mg/kg is slightly higher than the 25th percentile for 40 mg/kg. The simulations for 40 mg/kg and 60 mg/kg suggest that a similar effect on sTREM2 may be seen for these 2 doses. Based on these simulations sTREM2, the predication is that downstream biological activity will be similar for the 40 mg/kg and 60 mg/kg dose levels, with a somewhat higher likelihood of activity for the highest dose level at 60 mg/kg.

A 15 mg/kg dose is considered a low dose, but one that has an effect on sTREM2 in the brain and that could still provide benefit. The 40 mg/kg dose is currently predicted to provide a similar effect on sTREM2 compared to the 60 mg/kg dose, but with lower exposure. The 60 mg/kg dose will provide a higher exposure and PK/PD data in participants should 40 mg/kg not provide sufficient clinical benefit. Testing these doses in the current Phase 2 study is expected to provide adequate information for selecting the dose for subsequent Phase 3 studies.

PK in serum of the healthy volunteers of Study AL002-1 is characterized by a terminal half-life of 9.0 days at an IV dose of 15 mg/kg and 9.1 days at an IV dose of 60 mg/kg. C_{max} and total AUC (AUC_{inf}) were generally dose proportional. For additional information regarding PK data in these cohorts, please refer to Section 5 of the IB.

1.5. Participant Population

This Phase 2 study will be conducted in participants in the AD continuum as defined in the 2018 National Institute on Aging/Alzheimer's Association (NIA-AA) Research Framework (Jack 2018) with a clinical severity consistent with Early AD (FDA 2018; EMA 2018), and who meet all inclusion criteria and none of the exclusion criteria. The expected population will be in

Stages 2 and 3 and early Stage 4 as defined in the 2018 NIA-AA Research Framework (Jack 2018).

All participants must demonstrate amnestic deficits as measured at screening by the Delayed Memory Index (DMI) of the Repeatable Battery for the Assessment of Neuropsychological Status-Update (RBANS-Update) (see Section 14.2). An inclusion criterion of ≤85 (95 or lower may be considered for eligibility according to the guidelines set forth in the inclusion and exclusion criteria) has been selected for the DMI, corresponding to 1 standard deviation below population-based normative data. For confirmation of participant eligibility, documentation of evidence of prior decline through observations made by clinician or caregiver on the Research Diagnostic Verification Form (RDVF) is required (Refer to Section 3.1.9 for additional details regarding the RDVF). The Medical Monitor will review the RDVF to assure that participants are enrolled on the basis of objectively ascertained and well-documented evidence of a progressive course and a clinical severity expected in Early AD. The Medical Monitor may review pseudonymized source documents and may solicit advice from other qualified Sponsor staff or external, independent experts during this review. The scope and detailed procedures for the diagnostic verification process will be described in the study documents and documented for review on the RDVF.

This study will utilize the PrecivityAD™-Aβ blood assessment (previously known as APTUS™) prior to assessment via positron emission tomography (PET) or CSF. Studies have demonstrated that amyloid beta (Aβ) ratios in the blood can predict Amyloid PET status (Doecke 2020; Schindler 2019, Nakamura 2018, Risacher 2019, Ovod 2017). The PrecivityAD™-Aβ blood test combines the blood concentration of Aβ isoforms amyloid beta (1-42) (Aβ42), amyloid beta (1-40) (Aβ40) and APOE isoforms, as measured by mass spectrometry along with age (Schindler 2019).

Participants must be amyloid positive (ie, have a high or an intermediate Amyloid Probability Score [APS]) by the PrecivityAD™-Aβ blood test prior to proceeding with either the Amyloid PET or CSF studies for confirmation of Aβ pathology (refer to Section 4.1). Confirmation of amyloid pathology by Amyloid PET or CSF phosphorylated tau (pTau)/ amyloid beta (1-42)(Aβ42) ratio is required as described in Inclusion Criterion I (see Section 4.1). Historical Amyloid PET or CSF assays may be used to satisfy the amyloid positivity requirement, also as described in Inclusion Criterion 1 (see Section 4.1).

Efficacy, safety, PK, and PD parameters will be assessed for all participants.

1.6. Background on [^{18}F]MK-6240 and Rationale for Optional Tau PET Imaging

Tau protein has been identified as one of the key pathological features of AD (Grundke 1986; Kosik 1986; Wood 1986). Tau is the primary protein composing neurofibrillary tangles and postmortem studies have shown that neurofibrillary tangle density correlates with neurodegeneration and cognitive impairment (Duyckaerts 1987; Delaére 1989; Duyckaerts 1990; Arriagada 1992; McLean 1999). A PET imaging agent that binds to aggregated tau has the potential to serve as a biomarker for disease severity or neurodegeneration and may be useful for monitoring disease progression in therapeutic trials. Use of Tau PET imaging in this trial will

allow the monitoring of the spatial progression of tau pathology in the brain, and the correlation of tau pathology with cognitive and functional outcome measures.

Fluorine-18 MK-6240 ([^{18}F]MK-6240) has been developed as a positron emitting radioligand for in vivo imaging of tau protein aggregates. Available safety data from the completed and ongoing clinical studies with [^{18}F]MK-6240 show that exposure to [^{18}F]MK-6240 and imaging procedures are generally well tolerated. There have been no deaths and no commonly recurring AEs following administration of [^{18}F]MK-6240. Each [^{18}F]MK-6240 scan involves a 5 millicurie (mCi) (370 megabecquerel) dose. The anticipated effective dose of each scan will be 6.4 millisievert (mSv), including radiation from the associated attenuation computerized tomography scan. Refer to the [^{18}F]MK-6240 IB for more details on these studies, including a full nonclinical evaluation of the tracer as well as the clinical experience to date and radiation precautions.

2. OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary: • To evaluate the efficacy of AL002 in participants with Early AD in delaying disease progression compared to placebo	*Primary Efficacy Endpoint:* • Disease progression as measured by change from baseline in the CDR-SB *Primary Estimand for Primary Efficacy Endpoint: The primary clinical question of interest is what is the potential relative treatment difference between AL002 and placebo, across all post-baseline timepoints in adult patients with Early AD while on study medication, regardless of other interventions.* The estimand is described by the following attributes: • Treatment condition: while on treatment (hypothetical strategy) regardless of other interventions (treatment policy strategy). • Target population: adult patients with Early AD as defined by the protocol inclusion/exclusion criteria. • Primary endpoint: change from baseline in CDR-SB score to Weeks 25, 49, 73, and 97. • Accounting for intercurrent events: a composite strategy will be used to handle intercurrent events as below: – hypothetical strategy for handling premature study drug discontinuation for any reason, – treatment policy strategy for handling all other intercurrent events. • Population-level summary: the percent reduction relative to placebo decline (the proportional treatment effect), comparing each dose level to placebo.

Objectives	Endpoints
Secondary: • To evaluate the efficacy of AL002 in participants with Early AD on efficacy as measured by the rate of change in COAs	*Secondary Efficacy Endpoints:* • Change from baseline in MMSE • Change from baseline in RBANS-Update • Change from baseline in ADAS-Cog13 • Change from baseline in ADCS-ADL-MCI • Change from baseline in ADCOMS *Secondary Efficacy Estimands:* The main estimand for the secondary efficacy endpoints is defined with similar attributes as for the primary estimand except that it is endpoint specific. The treatment effect is defined as a percentage reduction of the placebo group clinical decline.
Pharmacokinetics: To estimate the concentration of AL002 in participants with Early AD in serum and CSF (when available)	*Pharmacokinetic Endpoints:* • Serum PK concentrations of AL002 and relevant PK parameters • CSF[a] PK concentrations of AL002 (when available) • Incidence of ADAs
Safety: To evaluate the safety and tolerability of AL002 in participants with Early AD	*Safety Endpoints:* • Incidences of AEs, including AESI, and SAEs • Changes from baseline in vital signs, physical findings, neurological findings, ophthalmological findings, ECG, and clinical laboratory results • C-SSRS • MRI abnormalities

Objectives	Endpoints
Exploratory: • To evaluate the effects of AL002 in participants with Early AD on exploratory PD biomarkers	*Exploratory PD Biomarker Endpoints:* • Changes from baseline in levels of sTREM2 in CSF and/or plasma[a] • Changes from baseline in levels of biomarkers related to microglia function in CSF and/or plasma[a] (eg, CSF1R, IL1RN, osteopontin, YKL-40) • Changes from baseline in levels of biomarkers related to AD pathology in CSF and/or plasma[a] (eg, Aβ40, Aβ42, pTau, tTau) • Changes from baseline in levels of neurodegeneration biomarkers in plasma and CSFa (eg, NfL) • Changes from baseline in brain volume, assessed by volumetric MRI • Changes from baseline in brain pathological tau burden as assessed by Tau PET[b] (for participants who agree to participate in the optional assessment only) • Changes from baseline in brain amyloid burden as assessed by longitudinal Amyloid PET[b] scanning (for participants who agree to participate in the optional assessment only) • Changes from baseline in speech measurements via the WLSA (for participants who agree to participate in the optional assessment only)

Aβ40=amyloid beta (1-40); Aβ42=amyloid beta (1-42); AD=Alzheimer's disease; ADA=anti-drug antibodies; ADAS-Cog13=Alzheime''s Disease Assessment Scale-Cognitive Subscale; ADCOMS=Alzheimer's Disease Composite Score; ADCS-ADL-MCI=Alzheime''s Disease Cooperative Study- Activities of Daily Living – Mild Cognitive Impairment Scale; AE=adverse event; AESI=adverse event of special interest; CDR-SB=Clinical Dementia Rating – Sum of Boxes; COA=clinical outcome assessment; CSF=cerebrospinal fluid; CSF1R=colony stimulating factor 1 receptor; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IL1RN=interleukin 1 receptor antagonist; LP=lumbar puncture; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; NfL=neurofilament light; PD=pharmacodynamic(s); PET=positron emission tomography; PK=pharmacokinetic(s); pTau=phosphorylated tau; RBANS-Update=Repeatable Battery for the Assessment of Neuropsychological Status-Update; SAE=serious adverse event; sTREM2=soluble triggering receptor expressed on myeloid cells 2; tTau=total tau; WLSA=Winterlight Labs Speech Assessment; YKL-40=chitinase 3-like 1.

[a] CSF collection applies to all participants in Part 1 and those participants in Part 2 who consent to the optional LP.

[b] Longitudinal Amyloid PET and/or Tau PET imaging applies to those participants who provide consent and participate in the optional exploratory biomarker assessment.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a two-part Phase 2, randomized, double-blind, parallel-group, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of AL002 in participants with Early AD. The study is a multicenter, global trial that will enroll approximately 328 participants at approximately 90 sites in North America, Australia, New Zealand, Europe, and South America.

3.1.1. Patient Population

Participants must be in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework (Jack 2018); this requires evidence of cerebral amyloidosis (A+) as detailed in the inclusion criteria. Participants must also demonstrate a clinical severity consistent with Stages 2, 3 or early Stage 4 as defined in the 2018 Research Framework, further constrained by entrance criteria defined for the Clinical Dementia Rating-Global Score (CDR-GS) (0.5 or 1), the Mini-Mental Status Examination (MMSE) (≥20 points), and the RBANS-Update DMI (85 or lower; 95 or lower may be considered for eligibility according to the guidelines set forth in the inclusion and exclusion criteria). These clinical severity criteria are designed to be consistent with a definition of Early AD as described in the Food and Drug Administration (FDA) (FDA 2018) and European Medicines Agency (EMA) (EMA 2018) guidelines. Clinical diagnosis for each participant must be supported by information provided on an RDVF. For more details on the RDVF review process, see the description of the screening period in Section 3.1.9.

Due to emerging ARIA data seen in participants with the *APOE* e4/e4 genotype, this study will no longer enroll participants with this genotype.

3.1.2. Study Objectives

The objectives of this Phase 2 study are the assessment of the efficacy and safety of IV AL002 treatment for up to 96 weeks. Multiple dose levels of AL002 will be studied against placebo at a dosing frequency of every 4 weeks. Participants with the *APOE* e4/e4 genotype who were enrolled under Versions 1–4 of this protocol will not receive any further study drug treatment, but should continue with the remaining planned visits in the Schedules of Assessments (Section 14.1).

Efficacy will be assessed with clinical outcome assessments (COAs) as well as fluid and imaging biomarker measures. Safety will be assessed through monitoring of AEs (including AESI and SAEs), changes in laboratory and vital sign values, incidence of findings from physical, neurological, ECG, MRI and ophthalmological exams, and reports of suicidal ideation or behavior. PK in both the serum and CSF will be assessed for investigation of exposure-response and exposure-safety relationships. Blood biomarker and MRI biomarker measures will be assessed for all participants.

In this study, several optional PD assessments will be performed for those participants who consent to the assessments. These include CSF collection for fluid biomarkers (except for Part 1, where CSF collection is mandatory for all visits), PET imaging with the tau radiotracer [^{18}F]MK-6240, longitudinal Amyloid PET imaging, and/or speech assessment with the Winterlight Labs Speech Assessment (WLSA).

3.1.3. Enrollment in Part 1 and Part 2

In Part 1, each dose level tested will consist of a minimum of 10 participants. Approximately 40 participants will be randomized at a 1:1:1:1 ratio to receive either AL002 15 mg/kg, 40 mg/kg, 60 mg/kg, or placebo, administered via IV infusion every 4 weeks. The remainder of the study will be enrolled as Part 2 which will include approximately 288 participants. The allocation ratio in Part 2 will also be 1:1:1:1. Participants randomized after July 2021 to receive 40 or 60 mg/kg will be titrated to their target randomized dose level over the first 2 or 3 doses, respectively, and then continue at their randomly assigned dose for the remainder of study participation. There will be no change to dose for participants randomized to receive 15 mg/kg or placebo.

After approximately 20 participants have completed their Day 43 visit, the independent Data Monitoring Committee (iDMC) will perform the first safety review of all available safety and tolerability data (including from the MRI and neurological and ophthalmological examinations) from all participants up to that timepoint in an unblinded manner. A second safety review will be made by the iDMC after approximately 40 (minimum of 32 in case higher than expected discontinuation rate) participants have completed the Day 43 visit. The remainder of the study will be enrolled as Part 2. Randomization may be paused to allow the iDMC to review data prior to Part 2 commencing. Participants randomized after July 2021 to receive 40 or 60 mg/kg will be titrated to their target randomized dose level over the first 2 or 3 doses, respectively, and then continue at their randomly assigned dose for the remainder of study participation. There will be no change to dose for participants randomized to receive 15 mg/kg or placebo.

Eligibility criteria for study inclusion will be the same for Part 1 and Part 2, with the exceptions of eligibility criteria related to mandatory tests in Part 1 and participants with the *APOE* e4/e4 genotype, who are no longer eligible in Part 2. Participants in Part 1 and participants with the *APOE* e4/e4 genotype, who are no longer eligible for enrollment in Part 2 will have additional assessments as outlined in Table 8, and will continue onto Part 2 as outlined in Table 9. In addition, lumbar punctures (LPs) will be mandatory for participants enrolled in Part 1 as defined in Table 8 and Table 9; LPs are optional for participants enrolled in Part 2.

Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit (if applicable) and/or prior to dosing on Day 1. Participants who have provided consent to participate in the optional clinical and biomarker assessments (LP for CSF collection, Tau PET imaging, longitudinal Amyloid PET imaging, and/or WLSA assessments) will be randomized prior to or at the Predose Baseline Visit. Participants that will not be participating in the optional assessments will be randomized prior to or at the Day 1 Visit. Note: participants who have consented to the optional WLSA may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1.

Treatment group assignment for Part 1 and Part 2 will be stratified based on *APOE* e4 status (carrier vs noncarrier). The detailed randomization plan will be documented in the randomization specifications.

After randomization, a Predose Baseline Visit will occur for participants undergoing the optional clinical and biomarker assessments (LP for CSF collection, Tau PET imaging, longitudinal Amyloid PET imaging, and/or WLSA assessments). Part 1 participants must have an LP during screening. Participants who consent to optional longitudinal Amyloid PET imaging may have the

baseline scan during screening. Participants who will not participate in the aforementioned optional assessments will not have a Predose Baseline Visit. For Part 2 participants who do not receive an LP during the screening period, but agree to participate in the optional CSF sampling, a Predose Baseline Visit will occur for an LP prior to Day -5.

Participants may provide consent to participate in the optional WLSA assessment to include at-home and in-clinic assessments, or in-clinic assessments only. Participants who have provided consent to participate in the optional at-home WLSA assessment will be trained by site staff at the Predose Baseline Visit (or the Day 1 Visit) regarding the use of the device including, but not limited to, the frequency and the assessments to be completed. For all participants who consent to WLSA, assessments will be administered at the clinic during the Predose Baseline Visit (or the Day 1 Visit), every 24 weeks following commencement of dosing, and at the end of study. For participants who consent to at-home WLSA, additional assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments), within 7 days prior to a treatment administration visit. Participants who do not have the appropriate device to participate in the optional WLSA at-home may still participate in the assessments administered at the clinic. At home assessments will be supervised by the study partner. Site staff will contact the participant/caregiver to remind them to conduct the appropriate assessment per the Schedules of Assessments (Section 14.1). Refer to the applicable WLSA Manual for additional information. The baseline assessment for the optional WLSA must be completed prior to dosing on Day 1.

3.1.4. Study Drug Treatment Period

Study drug will be administered via IV infusion at the study site on Day 1 after randomization (and after all baseline assessments have been completed) and will be repeated subsequently once every 4 weeks throughout the treatment period. In order to maintain the blind across all dose groups and allow step titration to the higher doses, the dose for each participant will be titrated starting with a dose of 15 mg/kg (or placebo equivalent) for the first dose administration on Day 1. For the second dose administration, the dose will increase to 40 mg/kg for participants randomized to receive 40 mg/kg or 60 mg/kg, while doses in the other 2 groups will remain constant. For the third dose administration, the dose will increase to receive 60 mg/kg for participants randomized to receive 60 mg/kg while doses in the other 3 groups will remain constant. The titration algorithm is provided in Section 5.2.

Randomized participants will be treated for at least 48 weeks (up to a total of 13 doses) and up to 96 weeks (up to a total of 25 doses). Please see Section 3.2 for a determination of the planned treatment period for each participant. Participants may miss doses, have dosing paused, or have dosing discontinued permanently. Because this trial has been designed to follow all participants randomized, irrespective of whether they discontinue study drug, all visits and assessments should be made whenever possible until the completion of the planned treatment period and through the efficacy follow-up (EFU), if applicable, and safety follow-up (SFU) visits, if applicable. If a participant discontinues the study prior to the end of their planned treatment period, they will need to return for an early termination (ET) visit. All participants who are consent and meet the eligibility criteria for the AL002 long-term extension (AL002-LTE) study of this study will have the opportunity to be enrolled in the AL002-LTE study at their final visit of the treatment period (refer to the study protocol of the AL002-LTE study for more details). If participants enroll in the AL002-LTE study, the EFU and/or SFU visits are not required.

3.1.5. Efficacy Assessments

A battery of COAs (Appendix 2 [Section 14.2]) will be administered as efficacy assessments over the course of the study, with the primary endpoint being the Clinical Dementia Rating – Sum of Boxes (CDR-SB). Efficacy assessments, including COAs and biomarker assessments, will be made at baseline (screening, Predose Baseline Visit, or on Day 1 prior to dosing), throughout the 48- to 96-week treatment period and, when applicable, at an EFU visit 4 weeks after the last treatment visit. The occurrence of the EFU visit is dependent on the interval of time since the last efficacy assessment during the treatment period; please see sections related to follow-up visits in this protocol and the footnotes to the Schedules of Assessments (Section 14.1) for details. Clinical outcomes and biomarker assessments may or may not occur at an ET visit in the case of early discontinuation; this is also dependent on the interval of time since the last efficacy assessment during the treatment period and is detailed in the footnotes of the Schedules of Assessments (Table 8, Table 9).

3.1.6. Safety Assessments

Safety assessments will be performed during screening (and at the Predose Baseline Visit, if applicable), throughout the 48- to 96-week treatment period, and during an 8-week SFU visit after the last dose of study drug or ET visit. For detailed information regarding safety assessments, see Section 6.5. In addition, the Schedules of Assessments are provided in Section 14.1.

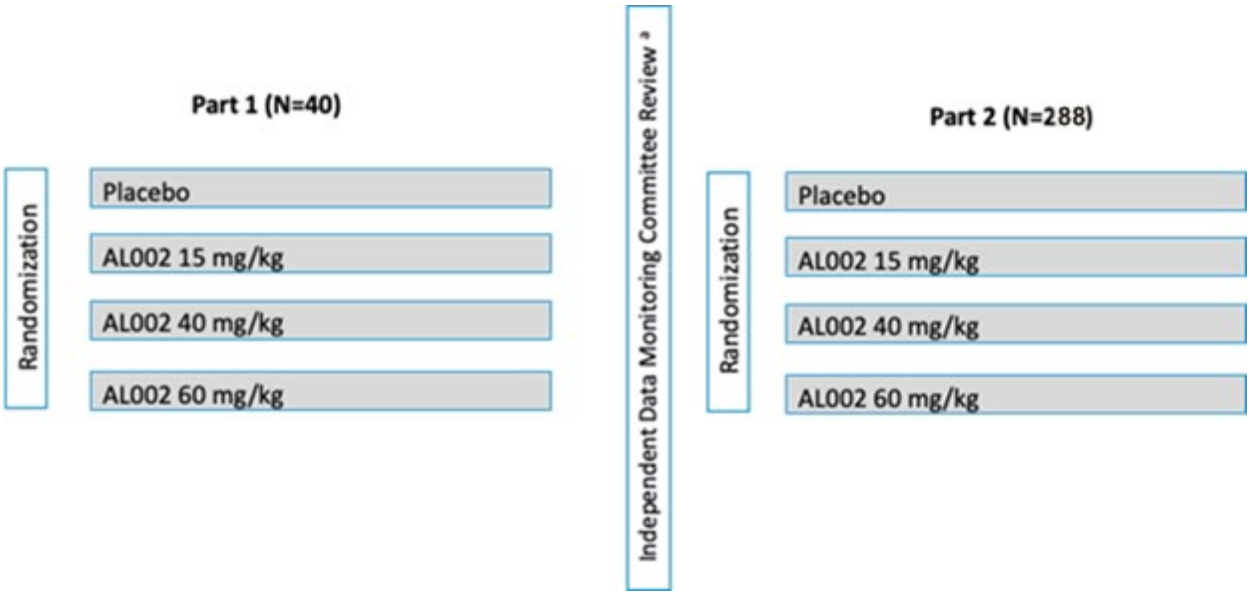
3.1.7. PK, PD, and ADA Assessments

The PK and PD measurements will be made from blood samples (all participants) and from CSF samples in a subset of participants (required for Part 1 and optional for Part 2 participants). Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at one of the following timepoints: Week 25 or 37 or 49. Blood samples for assessment of ADA will be taken throughout the study. Imaging PD biomarkers will also be assessed with MRI (all participants) and with optional PET scans using an amyloid tracer and the tau-tracer [^{18}F]MK-6240 (in a subset of participants). Tau PET and longitudinal Amyloid PET imaging should be conducted in accordance with local/country regulations for participants that opt to participate in the assessment. Phonemic/Linguistic assessment of speech using the WLSA will be made as an optional assessment in a subset of participants who are proficient in English, French, German, or Spanish.

3.1.8. Study Schematic

An outline of the study design is presented in Figure 1 and details on the study assessments and timing can be found in the Schedules of Assessments (Section 14.1).

Figure 1: Study Design



[a] After at least 40 participants (see Section 3.1.10) in Part 1 have completed the Day 43 visit, safety, tolerability and PK data from Part 1 will be reviewed by the iDMC. Randomization may be paused to allow the iDMC to review data prior to Part 2 commencing. Participants randomized to 40 or 60 mg/kg will be titrated to their assigned dose over 2 or 3 doses, respectively (see Section 5.2).

3.1.9. Screening and Diagnostic Verification

After signing the informed consent form (ICF), participants enter a screening period of up to 8 weeks prior to the Predose Baseline Visit or to Day 1 to determine eligibility. (Note: At the discretion of the Sponsor the screening period may be extended to accommodate delays for reasons including but not limited to COVID-19, laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.)

An RDVF must be completed by the Investigator and submitted to the Sponsor or Sponsor delegate. The RDVF will be reviewed by the Medical Monitor during eligibility review as applicable. The RDVF must contain results from the MMSE, RBANS-Update, and Clinical Dementia Rating (CDR), along with information supportive of an Early AD diagnosis. Confirmation that results for the MMSE, RBANS-Update, and CDR meet the entry criteria must be received prior to performing MRI, Amyloid PET scans, or LP. Participants who are determined to be not eligible for the study based on the results of the screening procedures, may be rescreened at a later date at the discretion of the Sponsor, if changes occur to the participant's condition or situation that might render the participant eligible to participate. Refer to Section 6.2 for more information on rescreening of participants.

3.1.10. Part 1 Description

Part 1 consists of the first approximately 40 participants who will receive study drug (AL002 or placebo) on Day 1 and Day 29. In Part 1, the administration of the first infusion (Day 1) between any 2 participants at any site will be separated by at least 24 hours. After the Day 43 visit, participants in Part 1 will be treated and followed according to the same dosing and assessment

schedule outlined for Part 2 for the remainder of their study participation (starting at the Week 9 visit). The iDMC will review all safety data from Part 1 when approximately the 20th participant and approximately the 40th participant (minimum of 32nd) completes their Day 43 visit (see Section 12.1.1). The Part 1 sample size may be increased if there are higher than expected early dropouts (not attributed to safety) to ensure at least 32 participants complete their Day 43 visit.

Part 1 participants will have available safety, tolerability, and PK data at the Day 43 visit, including data from the brain MRI and neurological and ophthalmological examinations reviewed by the iDMC. All participants in Part 1 will receive 2 infusions of study drug (1 infusion on Day 1 and a second infusion on Day 29), and safety and tolerability assessments on Day 8 (±2 days), Day 15 (±2 days), Day 29 (±2 days), and Day 43 (±2 days). On Day 15 and 43, a brain MRI will be performed; participants with MRI evidence of ARIA will not be eligible to receive further administration of study drug. Additionally, on Day 43, an ophthalmological examination, neurological examination, and an LP will be performed.

3.1.11. Definition of a DLAE and the DLAE Assessment Window in Part 1

For Part 1 participants, a DLAE is defined as an AE occurring in the first 43 days that meets any of the following criteria:

- Any SAE that has no other clearly attributable cause beyond study drug, as determined by the Investigator or the Sponsor.
- Any AESI that has no other clearly attributable cause beyond study drug, as determined by the Investigator or the Sponsor.
- Any AE of Grade 3 or higher that has no other clearly attributable cause beyond investigational drug, as determined either by the Investigator or the Sponsor.

If any of the Part 1 participants experiences a DLAE during the DLAE Assessment Window (Day 1 to 43), that participant will discontinue study drug and will be followed for safety until resolution or stabilization of the event.

If, at any time during the DLAE Assessment Window in Part 1, 1 or more participants within a dose level who received active drug experiences a serious DLAE, or more than 2 participants within a dose level experience a nonserious DLAE, evaluation of all available safety data by the iDMC will be performed prior to administering of additional doses to any participant in this dose level.

If, at any time during the DLAE Assessment Window in Part 1, 2 or more participants among all dose levels who received active drug experiences a serious DLAE, or more than 3 participants among all dose levels experience a nonserious DLAE, evaluation of all available safety data by the iDMC will be performed prior to administering of additional doses to any participant in Part 1.

3.1.12. Part 2 Description

Part 2 consists of approximately 288 participants. Each participant in Part 2 will receive up to 96 weeks of treatment. Efficacy, safety, and tolerability assessments will be performed as detailed in Table 9. Brain MRI will be performed prior to dosing at Weeks 5, 9, 13, and 25, and then every 24 weeks. Additional brain MRI may be requested by the Sponsor based on review of

AEs (see Section 7.11). The iDMC will review cumulative safety data approximately every 6 months. The iDMC may convene on an ad-hoc basis, as required, to review cumulative safety data. See Section 8.3.7 for further details.

3.2. Study Duration and Planned Treatment Period

The total duration of study participation for each participant will be up to approximately 115 weeks. This includes the screening period of up to 8 weeks prior to the Predose Baseline Visit or to Day 1, Predose Baseline Visit of up to 21 days prior to Day 1, a treatment period of a minimum of 48 weeks and a maximum of 96 weeks, a possible final efficacy assessment visit 4 weeks after the last planned dose administration, and a mandatory SFU visit approximately 8 weeks after the last planned dose administration. A final efficacy assessment visit will be required for a given participant only if a minimum number of weeks have elapsed since the previous efficacy assessments (COAs, fluid and imaging biomarkers) for that participant. Please see the section regarding follow-up in this protocol and the Schedules of Assessments (Section 14.1) for details on when a final efficacy assessment visit is required.

3.2.1. Planned Treatment Period

The planned treatment period for each participant in this study will be a minimum of 48 weeks and a maximum of 96 weeks, with treatment duration varying for each participant. The earliest randomized participants will have a treatment period of 96 weeks and the last randomized participants will have a treatment period of approximately 48 weeks. When participants pause or discontinue study drug, the expectation is that the participant will return for all visits and undergo all assessments throughout their planned treatment period (ie, regardless of whether they were being “treated” with study drug).

3.2.2. Treatment Period Termination Date

A treatment period termination date (TPTD) is defined as the single, cross-study date that is the end of the treatment period for all participants in the study. For participants who did not pause or discontinue dosing, the TPTD will determine the last date they may receive a dose of study drug; an EFU visit (if applicable) and an SFU visit (if applicable) will follow any final dosing visit that occurs for that participant. For participants who had paused dosing or who had discontinued dosing, the TPTD still defines the end of their planned treatment period, and an EFU visit (if applicable) and an SFU visit (if applicable) will follow the end of the planned treatment period for that participant.

The TPTD for all participants in the study will be based on the date when the last randomized participant receives the first dose of study drug on their Day 1 Visit, and the TPTD will occur 48 weeks from that date (ie, the TPTD is the projected Week 49 Visit for the last participant randomized). All study sites will be informed of the TPTD when the last randomized participant receives their first dose of study drug, as that will determine when all participants in the study will receive their last dose of study drug.

All participants must have their final visit of their treatment period (whether dosed with study drug or not) on or before the TPTD, and all visits after the TPTD will be follow-up. In the event that the visit window (+5 days) for a given participant falls after the TPTD, it will be modified

for this participant such that the visit window will instead end on the TPTD. This will ensure the final visit of the treatment period, for all participants, will be on or before the TPTD.

All participants who are consent and meet the eligibility criteria for the AL002-LTE study will have the opportunity to be enrolled in the AL002-LTE study at their final visit of the treatment period (refer to the study protocol of the AL002-LTE study for more details). For participants who completed 96 weeks of treatment, enrolling in the AL002-LTE study would occur at their Week 97 Visit. For participants who did not complete 96 weeks of treatment but were still on treatment at their final visit of the treatment period on or before the TPTD, they will have the opportunity to be enrolled in the AL002-LTE study at their final visit of the treatment period on or before the TPTD.

3.3. Description of Study Periods and Visits

3.3.1. Screening Period

Participants will be consented and screened within 8 weeks prior to the Predose Baseline Visit or to Day 1 to determine eligibility. (Note: At the discretion of the Sponsor the screening period may be extended to accommodate delays for reasons including but not limited to COVID-19, laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.) Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit and/or Day 1 Visit. Participants who have provided consent to participate in the optional Tau PET imaging, optional longitudinal Amyloid PET imaging (if applicable), optional LP for CSF collection (if applicable), and/or optional WLSA will be randomized prior to or at the Predose Baseline Visit. Note: participants who have consented to the optional WLSA may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1. Participants who have consented to the optional Tau PET scans may complete the first Tau PET scan after dosing on Day 1, with Sponsor agreement (see the Schedules of Assessments [Section 14.1] for details). Participants who will not be participating in the optional assessments will be randomized prior to or at the Day 1 Visit.

3.3.2. Predose Baseline Visit (Part 1 or Part 2 Participants, if Applicable)

A Predose Baseline Visit from Day -22 to Day -1 will occur for participants in the following situations:

- For participants participating in the optional Tau PET imaging procedures, a Predose Baseline Visit will be performed to schedule and include PET imaging prior to Day 1. In some cases, with Sponsor agreement, participants may receive their first (ie, baseline) Tau PET scan after dosing has commenced. Participation in the optional Tau PET procedures may not be permitted in some regions.
- Participants enrolled in Part 1 must have an LP performed at screening. For Part 2 participants who do not receive an LP during the screening period, but agree to participate in the optional CSF sampling, a Predose Baseline Visit will occur to schedule and perform an LP prior to Day -5.

- Participants who are undergoing the optional longitudinal Amyloid PET imaging procedures may also use the Predose Baseline Visit to schedule and perform Amyloid PET imaging prior to Day 1 if a new Amyloid PET scan was not obtained at screening.
- For all participants participating in the optional WLSA, a baseline assessment can be done at the Predose Baseline Visit or at any time prior to dosing on Day 1.
- Participants who have provided consent to participate in the optional at-home WLSA assessment will be trained by site staff at the Predose Baseline Visit regarding the use of the device including, but not limited to, the frequency and the assessment to be completed. For all participants who consent to WLSA, assessments will be administered at the clinic during the Predose Baseline Visit, every 24 weeks following commencement of dosing, and at the end of study. For participants who consent to at-home WLSA, additional assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments), within 7 days prior to a treatment administration visit. Participants who do not have the appropriate device to participate in the optional WLSA at home may still participate in the assessments administered at the clinic. At home assessments will be supervised by the study partner. Site staff will contact the participant/caregiver to remind them to conduct the appropriate assessment per the Schedules of Assessments (Section 14.1). Refer to the applicable WLSA Manual for additional information. The baseline assessment for the optional WLSA must be completed prior to dosing on the Day 1 Visit.

3.3.3. Treatment Period

The planned study drug period will be a minimum of 48 weeks and a maximum of 96 weeks. Study drug will be administered via IV infusion at the site on Day 1 and every 4 weeks thereafter. After July 2021, all participants randomized to AL002 will start with 15 mg/kg on Day 1; participants randomized to 40 mg/kg or 60 mg/kg will be titrated to their target dose over the next 2 or 3 doses, respectively.

Safety assessments will be performed at screening (and at the Predose Baseline Visit, if applicable) and throughout the treatment period. COAs, PK assessments, and PD assessments (fluid collection and imaging) will be performed prior to dosing (screening, Predose Baseline Visit, or on Day 1) and at specific timepoints during the treatment period and in the follow-up period after the end of treatment. Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at Week 25 or 37 or 49. The full Schedules of Assessments are provided in Section 14.1.

Participants may participate in an optional exploratory assessment to evaluate changes in the brain as measured by imaging with Tau PET or longitudinal Amyloid PET. Details for the optional PET imaging assessments including objectives, eligibility criteria, sample collection, and imaging specifications are provided in the PET Imaging Procedures Manual. Participants enrolled in Part 2 may also participate in an optional PK assessment with additional blood at one of the following: Week 25 or 37 or 49. Consent for the optional assessments will be documented. Participation in the optional PET imaging procedures will be allowed according to local country regulations.

In this protocol, the term "study drug" refers to AL002 or placebo. The term "radiotracer" refers to any PET radiotracer used for any PET imaging assessment in the study.

All reasonable efforts should be made to keep every randomized participant active in the study and complete all required assessments as outlined in the Schedules of Assessments (Section 14.1), even if they prematurely discontinue study drug at any time during the course of their participation. Participants should complete all visits per their planned treatment period (see Section 3.2), regardless of whether or not study drug has been paused or discontinued.

If eligible participants consent to long-term dosing or open-label extension studies at the end of the planned treatment period, they will not be required to attend the follow-up visits as outlined in Section 3.3.4. Follow-up Visits below.

3.3.4. Follow-Up Visits

When a randomized participant completes all study visits and procedures up to and including the final visit of their planned treatment period, an SFU visit will follow 8 weeks after this last treatment period visit, unless the participant enrolls in the AL002-LTE study. The end of a given participant's planned treatment period is defined by the TPTD as noted above. For participants who had paused dosing or who had prematurely discontinued dosing, the TPTD as noted above, will still define the end of their planned treatment period. The SFU visit will follow 8 weeks after the end of the planned treatment period for each participant, unless the participant enrolls in the AL002-LTE study. If a participant enrolls in the AL002-LTE study, an SFU visit is not required.

An EFU visit may or may not be required for a given participant, who has completed the planned treatment period and does not enroll in the AL002-LTE study. If a participant enrolls in the AL002-LTE study, an EFU visit is not required. For participants who do not enroll in the AL002-LTE study, an EFU visit is required 4 weeks prior to the SFU visit if the final COA and biomarker assessments were not completed within the defined time intervals as follows:

- An EFU is required if the last COA visit was done more than 12 weeks since the date the EFU visit would occur.
- An EFU visit is required if the last LP was done more than 12 weeks since the date the EFU visit would occur.
- An EFU is required if the last Amyloid PET or Tau PET was done more than 24 since the date the EFU visit would occur.

If the COA, LP, or PET biomarker assessments were not collected in the specified time period noted above, the participant will need to complete an EFU visit 4 weeks prior to the SFU visit.

An ET visit is performed only in cases where participation is permanently discontinued. If the participant withdraws or is discontinued from the study for any reason, the ET is completed 8 weeks after the last administered dose. Participants who complete an ET visit will not require a SFU visit, if the safety assessments were collected at a regularly scheduled study visit 8 weeks after the final dosing visit. Similarly, to the EFU visits for those who have completed the planned treatment period, the following efficacy and biomarkers are required as part of the ET visit if the following conditions are met:

- COA visit was done more than 12 weeks since the date the ET visit would occur.

- LP was done more than 12 weeks before the date the ET visit would occur.
- Amyloid or Tau PET was done more than 24 weeks since the date the ET visit would occur.

Please see the Schedules of Assessments (Section 14.1) for additional information.

4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

Participants will be assigned to study drug only if they meet all the inclusion criteria and none of the exclusion criteria. Central eligibility review of diagnosis will be performed as described in Section 3.1.9.

Participation in the optional PET imaging procedures will be allowed according to local country regulations.

4.1. Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

Key clinical inclusion criteria for the study:

1. Participant must be in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework (Jack 2018); this requires evidence of cerebral amyloidosis (A+). This evidence requirement can be satisfied by any one of the following 3 pathways:
    a. Historical Amyloid PET may be allowed to fulfill this criterion if it meets all of the following:
        i. Must utilize either [^{18}F]florbetaben, [^{18}F]florbetapir, or [^{18}F]flutametamol.
        ii. Must have adequate scan parameters and image quality as determined by the central imaging reader.
        iii. Must have the raw data available to send to the core PET laboratory.
        iv. Must have been read as positive (elevated amyloid) by the core PET laboratory.
    b. Historical CSF measurements may be allowed to fulfill this criterion after review by the Medical Monitor. At a minimum, documentation of historical CSF testing must contain the following details:
        i. Identification of which laboratory did the testing.
        ii. Identity of the type of assay used (eg, Roche Elecsys, Fujirebio Lumipulse, Athena ADMark).
        iii. Reference ranges for the values reported.
    c. If historical testing is not available, the participant must undergo a 2-step verification of amyloid positivity:
        i. As an initial screen for cerebral amyloidosis, the participant must have a high or intermediate APS as measured by the PrecivityAD™ Aβ blood test. Participants with a low APS are not eligible for study participation. (Note: Historical studies that do not meet the full criteria in a. or b. may still be considered sufficient, after consultation with the Medical Monitor, to allow a participant to forego PrecivityAD™ screening and thus allow the participant to proceed to steps outlined in 1.c.ii – amyloid confirmation.).
        ii. Participants need confirmation of amyloid positivity with either:
            - New positive Amyloid PET scan (see Table 2, footnote a).

- New positive CSF pTau/Aβ42 (see Table 2, footnote b).
- Participants who do not have confirmation of amyloid pathology based on an initial Amyloid PET scan may opt to have a second assessment with CSF. Participants who do not have confirmation of amyloid pathology on an initial CSF pTau/Aβ42 measurement may opt to have a second assessment with an Amyloid PET scan (Table 2).

Table 2: Amyloid Positivity for Study Eligibility

Initial Confirmatory Test	Second Assessment, if Initial Test is Negative	Third Assessment, if Second Assessment is Negative
Historical positive Amyloid PET ≤24 months prior to screening start	NA	NA
Historical CSF positive amyloid	NA	NA
PrecivityAD™ positive, followed by new Amyloid PET[a]	New CSF pTau/Aβ42[b]	Not allowed; participant not eligible
PrecivityAD™ positive, followed by new CSF pTau/Aβ42[c]	New Amyloid PET[a]	Not allowed; participant not eligible

Aβ42=amyloid beta (1-42); CSF=cerebrospinal fluid; NA=not applicable; PET=positron emission tomography; pTau=phosphorylated Tau.

[a] Alector may decline performing a new Amyloid PET if participant has a negative historical Amyloid PET that was performed ≤12 months prior to the start of screening.

[b] The CSF pTau/Aβ42 ratio will be measured by the Roche Elecsys assay and will be considered positive with a ratio of >0.024.

2. Participants must demonstrate a clinical severity consistent with Stages 2, 3, or early Stage 4 as defined in the 2018 NIA-AA Research Framework, also described as mild cognitive impairment and mild dementia in the 2018 NIA-AA Research Framework. Further, participants must meet the following inclusion criteria to define clinical severity:
   a. Participant has mild symptomatology as defined by a screening MMSE score of ≥20 points.
   b. Participant has a CDR-GS of 0.5 to 1.0.
   c. Participant has evidence of episodic memory impairment as demonstrated by the RBANS-Update DMI score:
      i. If the DMI score is ≤85, the participant meets this requirement without additional evidence needed.
      ii. If the DMI >85 and ≤95, the participant may still be considered for participation if they have a history of cognitive and functional decline consistent with diagnosis of Early AD. Agreement between the Investigator and the Medical Monitor that the participant meets criteria for clinical severity consistent with mild cognitive impairment or mild dementia due to Early AD must be documented prior to randomization.
3. If the participant is receiving symptomatic AD medications (for memory and/or behavioral symptoms), the dosing regimen must have been stable for 60 days prior to screening and not expected to change during study participation.

General inclusion criteria for the study:

4. Participant is willing and able to give informed consent. Where not permitted by local regulations, participants deemed not able to provide informed consent by the Investigator will not be enrolled. Where local regulations permit inclusion of participants deemed not able to provide informed consent, a legally authorized representative must provide informed consent on his or her behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
5. Participant can be male or female, and is 50 to 85 years of age, inclusive.
6. Participant weighs ≤120 kg; body mass index (BMI) is between 18.5 and 34.9 inclusive.
7. At screening, female participants must be nonpregnant and nonlactating, and 1 of the following conditions must apply:
    a. Participant is not a woman of childbearing potential (WOCBP) (either surgically sterilized, or physiologically incapable of becoming pregnant, or at least 1-year postmenopausal [amenorrhea duration of 12 consecutive months with no identified cause other than menopause]).
    b. Participant is a WOCBP and agrees to use an acceptable contraceptive method from screening until 12 weeks after the last dose of study drug. Acceptable contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom, or the sole sexual partner to a vasectomized male. Vasectomized males must have received medical assessment of surgical success. In addition, total abstinence, in accordance with the lifestyle of the participant, is acceptable.
    c. A WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedules of Assessments (Section 14.1).
8. Male participants must agree to use acceptable contraception and not donate sperm from screening until 12 weeks after the last dose of study drug. Acceptable contraception for the male participant when having sexual intercourse with a WOCBP who is not currently pregnant is defined as using a condom. In addition, WOCBP partners must use hormonal contraceptives or an intrauterine device. Vasectomized male participants should have received medical assessment of surgical success.
9. Participant has availability of a person ("study partner") who, in the Investigator's opinion, has frequent and sufficient contact with the participant (eg, approximately 10 hours per week of in person contact), is able to provide accurate information regarding the participant's cognitive and functional abilities, agrees to provide information at clinic visits (which require partner input for scale completion), and signs the necessary consent form.
    a. The study partner must have sufficient cognitive capacity, in the Investigator's opinion, to accurately report upon the participant's behavior, cognitive, and functional abilities. The study partner should be in sufficiently good general health, in the Investigator's opinion, to have a high likelihood of maintaining the same level of

interaction with the participant and participation in study procedures throughout the study duration.
   b. Every effort should be made to have the same study partner participate throughout the duration of the study.

10. Participant and study partner are fluent in the language of the tests used at the study site as assessed by site personnel.
11. Participant is willing and able to complete all aspects of the study (including MRI, LP, genotyping, and PET imaging, as applicable). The participant should be capable of completing assessments either alone or with the help of the study partner.
12. Participant has adequate visual and auditory acuity, in the Investigator's opinion, sufficient to perform the neuropsychological testing (corrective lenses and hearing aids are permitted).
13. Participant agrees not to donate blood or blood products for transfusion for the duration of the study and for 1 year after the final dose of study drug.

Inclusion criteria for participants participating in the optional Tau PET imaging assessment with [18F]MK-6240 only:

14. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
15. [^{18}F]MK-6240 is available to the PET imaging center based on manufacturing distribution network and local regulations.

Inclusion criteria for participants participating in the optional longitudinal Amyloid PET imaging assessment only:

16. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
17. An approved amyloid radiotracer is available to the PET imaging center based on manufacturing distribution network and local regulations.

Inclusion criteria for participants participating in the optional at-home and/or in-clinic WLSA only:

18. For at-home participation
    a. Participant has an available and willing study partner to administer the WLSA.
    b. Participant has WiFi access in their residence or WiFi access in a nonpublic area where the at-home testing can take place.
    c. Participant has access to an iPad or iPhone.
19. For at-home and in-clinic participation, participant is proficient in and from an English-, French-, German-, or Spanish-speaking country.

4.2. Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

Central nervous system (CNS) disorders-related exclusion criteria:

1. Participant has any evidence of a condition other than AD that may affect cognition, including but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington disease, normal pressure hydrocephalus, hypoxic injury, seizure disorder, static encephalopathy, closed brain injury, or developmental disability.
2. Participant has history or presence of vascular disease that has the potential to affect cognitive function (eg, clinically significant carotid, vertebral stenosis, or plaque; aortic aneurysm; intracranial aneurysm; macro-hemorrhage; arteriovenous malformation).
3. Participant has a history or presence of cerebrovascular accident within the past 2 years, or recent transient ischemic attack within 180 days before screening, or has radiologic evidence of any cortical stroke regardless of age.
4. Participant has history of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (eg, cerebral contusion).
5. Participant has history or presence of intracranial tumor (eg, glioma, except for benign brain tumors that, in the opinion of the Investigator, are not likely to impair cognition).
6. Participant has ongoing infections that may affect brain function (eg, human immunodeficiency virus [HIV], syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis), or history of infections that resulted in neurologic sequelae.
7. Participant currently has or has had an acute illness that requires or required IV antibiotics within 30 days prior to first study drug administration.
8. Participant has history or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (eg, multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease).
9. Participant has any of the following eye conditions: a history or presence of uveitis, a serious chronic inflammatory condition of the eye, a current eye infection, or any ongoing eye disorder requiring anticipated invasive eye procedures or injectable medical therapy (eg, ranibizumab or aflibercept for macular degeneration or diabetic eye disease) during the study period.
10. Participant has any history of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder.
    a. A history of major depression is acceptable if no episode has been reported within the previous 2 years. Treatment with antidepressant medications is allowed.
11. Participant is at risk of suicide in the Investigator's opinion.

12. Participant has history of alcohol and/or moderate to severe substance use disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) within the past 2 years.
    a. Nicotine use is allowed.

Imaging-related exclusion criteria:

13. Participant has MRI evidence of
    a. >2 lacunar infarcts.
    b. Any territorial infarct >1 cm^3.
    c. White matter hyperintense lesions on the FLAIR sequence that correspond to an overall Fazekas score of 3.
14. Participant has presence on MRI of >5 microbleeds and/or >1 area of leptomeningeal hemosiderosis based on central read.
15. Participant has presence of significant cerebral vascular pathology as assessed by the MRI Central Reader.
16. Participant is unable to tolerate MRI procedures (eg, due to anxiety or claustrophobia) or has contraindication to MRI, including but not limited to, the presence of pacemakers that are not MRI compatible, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that would pose a potential hazard in combination with MRI. Those who are able to tolerate MRI with intermittent use of a low-dose benzodiazepine or anxiolytic are permitted and may be included in the study.

Cardiovascular disorders-related exclusion criteria:

17. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165 mmHg and/or >100 mmHg at screening (blood pressure [BP] measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the participant to be eligible for the study), or persistent SBP/DBP readings >180 mmHg and/or >100 mmHg 3 months prior to randomization that, in the opinion of the Investigator, are indicative of chronic, uncontrolled hypertension.
18. Participant has an abnormal ECG that is considered clinically significant by the Investigator.
19. Participant has unstable ventricular dysrhythmias.

Hepatic/renal disorders:

20. Participant has significant kidney disease as indicated by either of the following:
    a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation. Note: MDRD equation is as follows:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}), \text{ or}$$

b. Creatinine ≥2 mg/dL.

21. Participant has impaired hepatic function as indicated by screening aspartate aminotransferase or alanine aminotransferase ≥2.5×the upper limit of normal (ULN), or total bilirubin ≥2.0×ULN. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor.

Infections and immune disorders:

22. Participant is positive for hepatitis B surface antigen, total hepatitis B core antibody, HIV-1 or -2 antibodies or antigen, or history of spirochetal infection of the CNS (eg, syphilis, borreliosis, or Lyme disease). Participants with a positive hepatitis C virus antibody will be allowed if hepatitis C RNA is negative.

    Note: prospective participants positive for total hepatitis B core antibody should be excluded unless both

    a. Hepatitis B surface antibody is positive and

    b. Hepatitis B surface antigen is negative.

23. Participants with active or latent tuberculosis (TB) disease should not be enrolled in the trial.

24. Any chronic active immune disorder requiring systemic immunosuppressive therapy within 1 year prior to study enrollment and/or causing bone marrow dysfunction (based upon hemoglobin <10 g/dL, absolute neutrophil count <1000/mm^3, or platelet count <150,000/mm^3.)

    a. Continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed if treated with a stable regimen for at least 90 days prior to study drug.
    b. Intermittent short-term use of prednisone or an equivalent corticosteroid is allowed to treat an acute condition.

Metabolic/endocrine disorders:

25. Participant has abnormal screening thyroid-stimulating hormone (TSH) that remains abnormal on retest or require a new treatment or an adjustment of current treatment.

    a. A participant may be rescreened if there is no improvement in cognition in the Investigator's opinion after 90 days of adequate treatment for thyroid function.

26. Participant has screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency may be contributing to cognitive impairment.

    a. A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for vitamin deficiency.

27. Participant has screening hemoglobin A1c >8% or poorly controlled diabetes (including hypoglycemic episodes).

    a. A participant may be rescreened after 90 days to allow optimization of diabetic control.

General exclusions:

28. Participant is positive for presence of *APOE* e4/e4 genotype.
29. Participant has contraindication for LP including deformity of the lumbosacral region of the spine that in the Investigator's opinion would contraindicate LP for all participants in Part 1 and for participants in Part 2 who can only be CSF eligible due to regional lack of availability of PET ligands or consent to the optional LP assessments. Participants undergoing the LP must not be currently taking anticoagulation medications, such as warfarin, that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatory medications are allowed. Participants requiring fluoroscopy-guided LP are not eligible for participation.
30. Participant has clinically significantly abnormal screening blood or urine results that remain clinically significantly abnormal at retest.
31. Participant has impaired coagulation (screening prothrombin time >1.2×ULN that remains impaired on retest).
32. Participant has history of cancer except if one or more of the following exceptions are satisfied:
    a. Is considered clinically cured as defined by being clear of recurrence after 5 years from last definitive treatment.
    b. Is not being actively treated with anticancer therapy or radiotherapy and will not require treatment in the ensuing 3 years, except for adjuvant hormonal therapy for localized breast cancer.
    c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible).
    d. For prostate cancer, has not had clinically significant progression within the past 3 years.
33. Participant has known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
34. Participant has had any surgery (major or emergent) or hospitalization within 30 days prior to first study drug administration.
35. Participant has any other severe or unstable medical condition that could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care.
36. Participant resides in a skilled nursing facility, convalescent home, or long-term care facility. Participants who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement.
37. Any other issue which, in the opinion of the Investigator, would compromise participant safety or the integrity of the study data.

Medication-related exclusion criteria:

The following medications are prohibited for a prespecified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study drug):

38. AD medications must not be initiated, modified, or stopped within 60 days prior to screening.
39. Use of medications known to impair consciousness or cognition in doses which in the opinion of the Investigator may interfere with diagnosis of dementia or interfere with study assessments (use of these medications during the study may be allowed, if necessary, for the treatment of a medical condition with the approval of the Medical Monitor).
40. Any investigational active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline. Routinely recommended vaccinations are allowed, as well as any vaccine against COVID-19 (either approved or administered under an Emergency Use Authorization).
41. Any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline within 1 year of screening.
42. Any other investigational treatment within 5 half-lives or 90 days of screening, whichever is longer.
43. Any previous treatment with medications used to treat Parkinsonian symptoms or any other neurodegenerative disorder (with the exception of medications to treat AD; see Inclusion Criteria 3) within 1 year of screening.
    a. Certain medications are acceptable, pending Medical Monitor approval, if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (eg, pramipexole).
44. Typical antipsychotic or neuroleptic medication within 180 days of screening except as brief treatment for a nonpsychiatric indication (eg, emesis).
45. Atypical antipsychotics unless on a stable regimen for at least 90 days prior to study drug administration; intermittent short-term use of atypical antipsychotics may be allowed to treat an acute condition after consultation with the Medical Monitor.
46. Anticoagulant medications other than antiplatelet agents are prohibited within 90 days of screening and throughout the study. Short-term use of anticoagulants to treat an emergent medical need is permitted.
    a. Treatment with platelet anti-aggregation agents such as aspirin, clopidogrel, or dipyridamole is permitted.
47. Systemic immunosuppressive therapy use or anticipated systemic immunosuppressive therapy use during the study.
    a. Continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed if treated with a stable regimen for at least 90 days prior to study drug administration;

intermittent short-term use of prednisone or an equivalent corticosteroid is allowed to treat an acute condition.

48. Chronic use of opiates or opioids (including long-acting opioid medication) within 90 days of screening.
    a. Intermittent short-term use of short acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
49. Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 30 days of screening and throughout the study.
50. Chronic use of benzodiazepines, barbiturates, or hypnotics from 90 days before screening.
    a. Intermittent short-term use of benzodiazepines, buspirone or short acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
    b. Trazodone, mirtazapine and melatonin are allowed for insomnia if on a stable regimen for 90 days before screening.

4.3. Withdrawal of Participants from Study Drug and/or Study

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

4.3.1. Withdrawal from Study Drug

A participant may be discontinued from study drug at any time if the participant, the Investigator, or Alector feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study drug discontinuation:

1. Participant is noncompliant with the protocol
2. Participant is lost to follow-up
3. Participant withdraws consent
4. Participant has a serious or intolerable AE that, in the Investigator's opinion, requires withdrawal from the study drug
5. Participant has a finding of ARIA that requires permanently discontinuing study drug (see Section 7.11)
6. Occurrence of an intercurrent illness that, in the Investigator's opinion, will affect assessments of clinical status or safety to a significant degree.
7. Clinically significant progression of Alzheimer's disease during study participation, judged by Investigator or participant/caregiver such that treatment outside of the protocol (ie, initiation of or changes to AD medications) and other than with AL002 is assumed to be in the participant's best interest (however, see Section 5.7, Rescue Medications).
8. Use of a nonpermitted concomitant medication per the Medication-Related Exclusion Criteria in Section 4.2 (as appropriate).

9. Pregnancy
10. Discretion of the Investigator

If a participant is withdrawn from study drug due to an AE, the participant will be followed and treated by the Investigator until the AE has resolved or stabilized (if applicable). Upon occurrence of a serious or intolerable AE, the Investigator may confer with Alector prior to discontinuing the participant from treatment. Any participant may withdraw his or her consent at any time.

Premature discontinuation from study drug, does not mean discontinuation from the study, and remaining study procedures (including all safety, PK, and efficacy assessments) should be completed as indicated by the study protocol. All reasonable efforts should be made to keep participants who prematurely discontinue study drug, to remain active and complete all assessments as outlined in the Schedules of Assessments (Section 14.1). The reason for the participant's early discontinuation of study drug will be specified in the participant's source documents and on the electronic case report form (eCRF).

4.3.2. Withdrawal from Study

A participant may be withdrawn from the study (including follow-up period) at any time if the participant, the Investigator, or Alector feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study discontinuation:

1. Participant withdrawal of consent
2. Lost to follow-up
3. Discretion of the Investigator
4. Death
5. Early termination of the study by Alector for any reason

All participants who discontinue the study at the discretion of the Investigator or due to early termination of the study by Alector should come in for the follow-up visit according to the schedule defined elsewhere in this protocol.

Reasonable attempts will be made by the Investigator to contact the participant prior to deeming the study participant as lost to follow-up (2 documented phone calls on different days, followed by 1 registered letter). The reason for the participant's withdrawal from the study will be specified in the participant's source documents and on the eCRF.

4.3.3. Addition of Participants to Study if Participants Withdraw from Study

The study will be conducted in 2 parts. Part 1 will include approximately 40 (minimum of 32 in case higher than expected discontinuation rate) participants who have completed the Day 43 visit. The remainder of the study will be enrolled as Part 2. Participants may be added to the study up to approximately the number of participants who withdrew or prematurely discontinued from the study, at the Sponsor's discretion.

5. STUDY DRUG

5.1. Method of Assigning Participants to Treatment Groups

Participants in Part 1 (approximately 40 participants total) will be randomly assigned on or prior to the Predose Baseline Visit (if applicable) or on or prior to the Day 1 Visit (if there is no Predose Baseline Visit) by stratification on *APOE* e4 status (carrier vs noncarrier) to receive 15 mg/kg AL002, 40 mg/kg AL002, 60 mg/kg AL002, or placebo in an overall 1:1:1:1 allocation ratio. Participants in Part 2 (approximately 288 participants total) will also be randomly assigned on or prior to the Predose Baseline Visit (if applicable) or on or prior to the Day 1 (if there is no Predose Baseline Visit) by stratification on *APOE* e4 status (carrier vs noncarrier) to receive 15 mg/kg AL002, 40 mg/kg AL002, 60 mg/kg AL002, or placebo. The allocation ratio in Part 2 will be 1:1:1:1. An interactive web response system will be used to administer the randomization schedule.

5.2. Treatments Administered

All participants in Part 1 and Part 2 will receive study drug (placebo, 15 mg/kg AL002, 40 mg/kg AL002, or 60 mg/kg AL002). Study drug administration will begin on Study Day 1 and then will occur once every 4 weeks for the duration of the treatment period according to the Schedules of Assessments (Section 14.1).

In order to maintain the blind across all dose groups and allow step titration to the higher doses, the starting dose for each participant randomized to receive AL002 will be 15 mg/kg (or placebo equivalent) for the first dose administration on Day 1. For the second dose administration, the dose will increase to 40 mg/kg for participants randomized to receive 40 mg/kg or 60 mg/kg, while doses in the other 2 groups will remain constant. For the third dose administration, the dose will increase to 60 mg/kg for participants randomized to receive 60 mg/kg while doses in the other 3 groups will remain constant. The titration algorithm is provided in Table 3.

Table 3: Titration Algorithm

Randomized Group	Titration Step 1 Study Day 1	Titration Step 2 Study Day 29 (Week 5)	Titration Step 3 Study Day 57 (Week 9)
AL002 60 mg/kg	AL002 15 mg/kg	AL002 40 mg/kg	AL002 60 mg/kg
AL002 40 mg/kg	AL002 15 mg/kg	AL002 40 mg/kg	AL002 40 mg/kg
AL002 15 mg/kg[a]	AL002 15 mg/kg	AL002 15 mg/kg	AL002 15 mg/kg
Placebo[a]	Placebo (60 mg/kg equivalent)	Placebo (60 mg/kg equivalent)	Placebo (60 mg/kg equivalent)

[a] Participants randomized to receive 15 mg/kg or placebo will not undergo titration.

5.2.1. Administration Instructions

Dosing solution preparation instructions will be provided separately in the Pharmacy Manual. The IV dose must be prepared by an unblinded pharmacist following the titration algorithm in Table 3, All participants will be administered a total volume of 150 mL containing saline and the calculated volume of AL002.

The IV dose will be calculated based on the participant's screening weight (reference weight) unless the participant's current weight changes (increases or decreases) ≥10% from the screening weight. If this occurs, the current weight will become the new reference weight for dosing. If the participant's weight again changes ≥10% from the reference weight, the IV dose will again be recalculated. Please refer to the Pharmacy Manual for further information.

A volume of 150 mL of study drug will be administered via IV over approximately 60 minutes at the study site by study -trained clinic staff who are blinded to the identity of the study drug, under the supervision of the Investigator or their designee.

The calendar date and 24-hour (local) clock times when the infusion is initiated and concluded, including any interruptions, will be recorded in the source documentation and documented in the eCRF. The end of infusion is the end of the line flush (please see the Pharmacy Manual).

The Investigator is responsible for the education of study staff in the correct administration of the study drug.

Participants will arrive at the treatment unit on the day of study drug administration and will be followed up for at least 60 minutes after the end of infusion and completion of all activities scheduled for that visit day.

5.3. Identity of Study Drug and PET Radiotracers

5.3.1. Study Drug

AL002 is a recombinant humanized agonistic TREM2 monoclonal antibody.

AL002 for infusion will be provided as a liquid solution in a single-use 20R Type I clear glass vial, with coated rubber stopper and flip-off type aluminum seal with red cap. Each single-use vial will contain at least 20 mL of a 50 mg/mL solution of AL002 in 20 mM L-histidine/histidine HCl, 7.5% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at a target solution pH of 6.0. Each vial will contain at least 20 mL of AL002 for IV use only.

AL002 placebo is provided in an identical vial presentation to the active drug product and shares the same concentrations of excipients in solution.

5.3.1.1. Study Packaging and Labeling

The Sponsor will be responsible for the preparation and labeling of bulk study drug and placebo and for providing details of batch numbers, safety, and stability data. This process is described in detail in the Pharmacy Manual.

The study drug (AL002 or placebo) will be manufactured for Alector under contractual and quality agreements at a qualified current Good Manufacturing Practice contract manufacturing organization. The Sponsor will ensure that the products are labeled in accordance with all local regulatory requirements.

5.3.2. [^{18}F]MK-6240 Tau PET Radiotracer

[^{18}F]MK-6240 will be provided under contract with a PET imaging vendor in accordance with approved national and/or local standards; Tau PET will not be conducted in those regions where the Tau PET radiotracer is unavailable and/or where it is not part of the approved Clinical Trial

Application (CTA). [^{18}F]MK-6240 will be supplied as a sterile nonpyrogenic solution in sterile borosilicate glass vials with butyl septa and aluminum ring seals. The vial is contained within an outer lead or tungsten shield ("pig") to protect from gamma radiation. The final product bears a label with the following items: total activity (mCi), volume (mL), strength (mCi/mL), calibration date and time, batch number, study identification, and shelf life. The investigational agent will be stored at ambient temperature in its original container. For information on the formulation and handling of [^{18}F]MK-6240, see the [^{18}F]MK-6240 IB and the PET Imaging Procedures Manual.

The anticipated effective dose of each scan will be 6.4 mSv, including radiation from the associated attenuation computerized tomography (CT) scan.

5.3.3. Amyloid PET Radiotracers

Appropriate Amyloid PET radiotracers will be provided under contract with a PET imaging vendor in accordance with approved national and/or local standards. [^{18}F]florbetaben (Neuraceq®) is the primary radiotracer; where Neuraceq® is not approved or not available, [^{18}F]florbetapir (Amyvid) or [^{18}F]flutametamol (Vizamyl) will be the radiotracer. Refer to the local labeling information and PET Imaging Procedures Manual for details on effective dose, packaging, formulation, and handling of the Amyloid PET radiotracers. Depending on locality, additional information may also be found in the local labeling information or the IB for the particular Amyloid PET radiotracer being used.

The anticipated effective dose of each scan including radiation from the associated attenuation CT scan will be 6.8 mSv with Neuraceq®, 8.0 mSv with Amyvid, and 6.9 mSv with Vizamyl.

5.4. Management of Clinical Supplies

Specific instructions about the storage, preparation, and administration of study drug are provided in the Pharmacy Manual. Additional information about the study drug is provided in the IB and on the Certificate of Analysis.

5.4.1. Study Drug Supply

The Sponsor will supply all study drug to the investigational site, as detailed in the Pharmacy Manual. Investigational drug supplies provided for this study will be manufactured under current Good Manufacturing Process and will be suitable for human use.

5.4.2. Study Drug Storage

Study drug will be shipped at a temperature of 2°C to 8°C.

Upon receipt at the study site, the study drug shall be stored in a secure and temperature-monitored (2°C to 8°C) location. The Investigator will be fully responsible for the security, accessibility, and storage of the study drug while it is at the investigational facility.

Study drug dosing solution must be administered within 24 hours after preparation. Additional details on study drug storage and preparation are provided in the Pharmacy Manual.

5.4.3. Study Drug Accountability

The study site will maintain accurate records of receipt of all study drug, including dates and conditions of receipt. In addition, accurate records will be kept regarding when and how much

study drug is dispensed and used by each participant in the study. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable local regulations. Please see the Pharmacy Manual for additional instructions.

5.4.4. Study Drug Return or Disposal

Study product supplies, including partially used or empty vials, should be disposed of at the site per local standard operating procedures (SOPs). If study product supplies cannot be destroyed on site, they may be shipped back to the return depot. Please see the Pharmacy Manual for additional instructions.

5.5. Blinding

This is a Phase 2, double-blinded randomized study. Treatment group assignment will be stratified based on *APOE* e4 status (carrier vs noncarrier). Participants will be randomly assigned on or before Day 1 prior to study drug administration.

The site Investigator, other site staff, and study participants will remain blinded throughout the study, except in circumstances where unblinding is determined by the site Investigator, the iDMC, or by the Sponsor to be important for the safety of a participant (details of the iDMC are provided in Section 12.1.1). In addition, the clinical site monitor, the clinical research organization (CRO), and Alector (except in rare instances as noted above) will be blinded to the assigned treatment throughout the study.

In addition to iDMC and the independent statistical group supporting the iDMC, the following personnel will be unblinded for the duration of the study:

- Unblinded monitor and clinical trial manager (CRO)
- The study pharmacist and personnel involved in preparation of the study drug dosing solutions for IV infusion
- Unblinded biostatistician/biostatistics team
- Unblinded data manager (CRO)
- Unblinded pharmacovigilance team for safety reporting
- Contract Manufacturing Organization
- Personnel at the bioanalytical laboratory involved in the determination of serum concentrations of AL002

As noted above, the Sponsor may be unblinded to a participant's treatment assignment, if necessary, for safety.

5.5.1. Breaking the Blind

A participant's treatment assignment will not be unblinded by the site until the end of the study unless medical treatment of the participant depends on knowing the study drug the participant received. In the rare event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual participant's treatment allocation through the interactive

web response system. Reasons for treatment unblinding must be clearly explained in the participants study file. The date on which the code was unblinded, together with the identity of the person responsible, must also be documented.

5.6. Prior and Concomitant Therapy

All concomitant medications used by a participant 14 days prior to screening through study completion/ET visit will be recorded in the participant's eCRF and coded using the World Health Organization Drug Dictionary (WHO DD), March 2019 or later. The minimum requirement is that drug name, total daily dose, route, frequency of dosing, indicated use, and the dates of administration are to be recorded. This will include all prescription drugs, herbal or homeopathic products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the participant's eCRF.

During the course of the study, participants are anticipated to continue the use of accepted prescribed medications identified during the screening procedures, in accordance with study inclusion and exclusion criteria. Participants should be advised against taking any new medication, both prescribed and over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use. Use of any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline is prohibited within 1 year of screening and during study participation.

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Any restricted medication must have been stopped as required by the study inclusion and exclusion criterion (Section 4.1 and Section 4.2, respectively); participants who start these medications during the study may be withdrawn from study drug at the discretion of the Sponsor's Medical Monitor.

Use of nonsedating antihistamine medications are permitted as required. Participants who meet all the study inclusion and exclusion criteria defined for hypertension may be taking antihypertensive medication if on a stable dose at screening and for the duration of the study. Participants who meet all the study inclusion and exclusion criteria defined for major depressive disorder may be taking antidepressant medication if on a stable dose for 3 months prior to screening and for the duration of the study. Paracetamol/acetaminophen up to 2000 mg/day may be used for minor ailments during the course of the study without prior consultation with Sponsor's Medical Monitor. Anticoagulant medications other than antiplatelet agents are prohibited within 90 days of screening and throughout the study. Short-term use of anticoagulants to treat an emergent medical need is permitted. Treatment with platelet anti-aggregation agents such as aspirin, clopidogrel, or dipyridamole is permitted.

5.7. Rescue Medication

Participants who experience significant rapid and consistent objective cognitive decline may be able to initiate treatment with approved symptomatic AD drugs, after review and approval by the Medical Monitor.

The assessment of significant rapid and consistent objective cognitive decline will be at the discretion of the Investigator, but can be defined, for example, as a change from baseline of 4 points or greater on the CDR-SB or change from baseline of 6 points or greater on the MMSE.

Participants for which approval is granted would remain on study drug. Initiation would be based on the prescribing information for the approved medication and would be administered concomitantly with study drug. Participants must obtain the approved medication via prescription at their own cost; Alector will not provide the approved medication.

6. STUDY ASSESSMENTS AND PROCEDURES

All potential participants will sign an ICF at screening before performing any study procedures. If the study participant is not competent or becomes incompetent during the study, a legally authorized representative must provide informed consent on their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB/IEC. Where not permitted by local regulations, participants deemed not competent to provide consent by the Investigator will not be enrolled.

Participants will have the opportunity to have any questions answered before signing the ICF. The Investigator or designee must address all questions raised by the participants. The Investigator or designee will also sign the ICF. Further details of informed consent are provided in Section 10.3.

Study visits and timing of assessments and procedures are provided in the Schedules of Assessments (Section 14.1). Study visits may be conducted on two consecutive days. Other adaptations to visits and procedures under the exceptional circumstance of the COVID-19 pandemic are detailed in Section 14.4.

6.1. Timing of Study Drug Administration

Predose study procedures and assessments:

- Perform COAs prior to any potentially stressful procedure (eg, blood collections, LPs, imaging).
- Physical examination (PE) or limited, symptom driven examination
- Neurological examination
- Ophthalmological examination
- Height, weight, and vital signs, including body temperature, respiratory rate, pulse rate, and systolic and diastolic BP
- Triplicate 12-lead ECG
- Obtain blood and urine samples for chemistry, hematology, coagulation, viral serology, pregnancy testing, and urinalysis
- Obtain blood samples for ADAs, PK, and PD
- Obtain blood sample for whole genome sequencing (WGS) – where acceptable by local regulations
- Collect CSF samples via LP for PK and PD (mandatory for Part 1; optional for Part 2)
- Perform MRI and have MRI read by the Central Imaging Reader
- Perform C-SSRS
- Review of concomitant medication(s) (completed before performing COAs to rule out use of medications prohibited within specific time windows)
- Record any AEs, AESI, and SAEs

- Perform optional Tau PET imaging
- Perform optional longitudinal Amyloid PET imaging
- Perform optional WLSA (done at home)
  - Assessments will be administered at the clinic during the Predose Baseline Visit or prior to dosing on Day 1, every 24 weeks following commencement of dosing, and at the end of study (ET visit). All other assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments), within 7 days prior to a treatment administration visit. Assessments will be supervised by the study partner.

Dosing procedures:

- Study drug will be administered to participants per institutional practice and the Pharmacy Manual (Section 5.2).

Post-dose procedures (Day 1 – end of treatment period):

- Obtain blood samples for PK and PD
- Triplicate 12-lead ECG
- Vital signs, including body temperature, respiratory rate, pulse, and systolic and diastolic BP
- Review of concomitant medication(s)
- Record any AEs and SAEs

6.2. Rescreening Criteria

Participants who are not enrolled within the screening period will be screen failed. Rescreening may be allowed following approval by the Medical Monitor and at the discretion of the Sponsor. Participants who are rescreened after the screening period must be reconsented with a new screening number, and the screening assessments must be repeated, with the following exceptions:

1. The participant may not be required to repeat screening laboratory assessments if performed within 6 weeks prior to the start of rescreening.
2. The participant may not be required to repeat MRI, or optional CSF assessment, if performed within 90 days, or PET imaging if performed within 12 months prior to study drug administration, with approval from the Medical Monitor.
3. COAs performed within 8 weeks prior to study drug administration may not be required to be repeated, with approval from the Medical Monitor.
4. None of the participants are required to repeat pharmacogenomic sampling or a positive PrecivityAD™-Aβ blood assessment, and there is no time restriction for repeating.

6.3. Sample Collections

Specific information on clinical safety and bioanalytical laboratory sample collection, processing, storage, and shipment will be provided in a Laboratory Manual.

Unused portions of PK, PD, WGS, and/or ADA samples remaining after all applicable protocol-defined tests have been performed may be retained and maintained for up to 10 years where permitted by local regulations, if the participant agrees and provides consent separately for this as described in Section 10.3. These blood or CSF samples may be used for future testing not described in this protocol. WGS samples will be collected where acceptable by local regulations.

For participants who have provided consent, the samples may be used for testing including the following: further evaluation of PD biomarkers (eg, associated with efficacy, AEs, or disease progression), further clarification or characterization of the disease, further evaluation of the study drug's effects, and/or development of assays (eg, PD biomarker or diagnostic assays).

Timing and frequency of all sample collections are presented in the Schedules of Assessments (Section 14.1).

6.4. Cerebrospinal Fluid Sampling

For participants who will be tested for evidence of the AD amyloid pathology using the CSF pTau/Aβ42 ratio, CSF should be collected via LP at least 5 days prior to randomization. For participants who will be tested for evidence of the AD amyloid pathology using Amyloid PET, and who will also participate in the optional CSF assessments, baseline CSF samples will be collected via LP during the Predose Baseline Visit at least 5 days prior to randomization. LPs should be completed only after the COAs have been administered (eg, CDR). As outlined in Section 6.6.1, COAs should be performed prior to LPs performed on the same day.

For all visits, if an LP and an MRI are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements. Also, for all visits, if an LP and a PET scan (Amyloid PET or Tau PET) are performed in the same visit, either (a) the LP should be performed first or (b) the LP should be performed at least 12 hours after the PET scan.

Post-baseline CSF samples will be collected as specified in the Schedules of Assessments (Section 14.1) to evaluate PK, PD, and exploratory PD biomarker measures. CSF collection to evaluate PK and PD measures is mandatory for Part 1 participants for all visits through study completion, and optional for Part 2 participants.

Participants will be required to stay in the clinic or hospital for a minimum of 30 minutes after the LP for SFU. Any treated participant who discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation. Please refer to Section 6.3 for information regarding sample collection.

6.5. Safety Assessments

One of the objectives of this study is to evaluate the safety of AL002 in participants with Early AD. Safety endpoints for this study are presented in Section 2.

Safety assessments will consist of monitoring incidence of AEs, changes in vital signs, physical, neurological, and ophthalmological findings, ECGs, clinical laboratory analytes, suicidality via the C-SSRS, and MRI abnormalities.

Timing and frequency of all safety assessments are presented in the Schedules of Assessments (Section 14.1).

6.5.1. Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

All AEs, AESI, and SAEs must be recorded and reported, regardless of cause or relationship, after the participant signs the informed consent until the end of study participation.

The following AEs and special situations must also be reported to Alector Drug Safety within 24 hours of awareness:

- AEs assessed as *related* to the radiopharmaceutical Neuraceq® ([^{18}F]florbetaben injection). ***Please note:*** *if the site's imaging facility is located outside of the institutional facility, please ensure the imaging lab is aware of this requirement.*
- Special situations (overdose, off-label use, abuse, misuse, occupational exposure, medication error) associated with Neuraceq® **or** the Alector study drug *regardless of whether the special situation is associated with an AE and regardless of the Investigator's causality assessment of the event with respect to the radiopharmaceutical or the Alector product.*

Any unresolved AEs, AESI, and SAEs will be followed up through resolution or return to baseline. Additionally, SAEs considered related to study drug or radiotracer, which occur at any time during the study will be followed until resolution, participant withdrawal of consent, loss to follow-up, or death. Additional details of AE collection are provided in Section 7.

6.5.2. Concomitant Medications

All concomitant medications used by a participant 14 days prior to screening through study completion/ET visit will be collected and recorded in the participant's eCRF.

6.5.3. Demographics

Year of birth, age (calculated), sex, ethnicity, educational attainment, handedness, and race will be recorded at screening unless disallowed by local regulatory agencies.

6.5.4. Medical History, Social History and Baseline Conditions

Participants will provide a detailed medical, surgical, current disease, and social history during screening.

Any event or change in the participant's condition or health status prior to the initial dosing on Day 1 (or prior to the Predose Baseline visit for participants who receive a PET scan at that time) will be reported in the relevant medical history/current medical conditions section of the participant's eCRF.

Social history includes the following information, past and current, regarding the participant: marital status, employment status, tobacco use (eg, smoking, vaping, chewing, etc.), alcohol consumption, cannabinoid use and recreational drug use history.

6.5.5. Physical Examinations

Complete and limited, symptom-directed PEs will be performed by a physician, a physician's assistant, or a nurse practitioner qualified to perform the assessments. Complete PEs include evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, rectal, and genitourinary exams should be performed as clinically indicated. Complete PEs are performed on all participants at screening.

Limited PEs should include cardiovascular, respiratory, and gastrointestinal systems; further symptom-directed examination may also include any other pertinent system as required. A limited PE will be performed at all other specified timepoints, prior to study drug administration (as specified in the Schedules of Assessments [Section 14.1] or as clinically indicated).

Abnormalities observed prior to dosing of study drug, as well as new or worsened clinically significant abnormalities at all other visits, will be recorded on the eCRF. New abnormal PE findings will be followed up at the next scheduled visit. New or worsened abnormalities should be recorded as AEs on the AE eCRF if considered clinically significant in the Investigator's opinion.

Body height (cm) and body weight (kg) will be measured at the timepoints delineated in the Schedules of Assessments (Section 14.1).

6.5.6. Neurological Examinations

A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Changes from baseline abnormalities should be recorded at each subsequent neurologic examination. New or worsened abnormalities should be recorded as AEs on the AE eCRF if considered clinically significant in the Investigator's opinion.

6.5.7. Ophthalmological Examinations

Ophthalmologic exams include the following:

1. a visual acuity exam (eg, using a Snellen chart)
2. slit-lamp examination before and after dilation
3. dilated exam of the fundus by indirect ophthalmoscopy
4. optical coherence tomography (OCT) exam, including Enhanced Depth Imaging OCT for examination of the choroid

Ophthalmological assessments will be conducted at the timepoints delineated in the Schedules of Assessments (Section 14.1). Changes from baseline abnormalities should be recorded at each subsequent ophthalmological examination. New or worsened abnormalities should be recorded as AEs on the AE eCRF, if considered clinically significant. Signs and symptoms indicative of uveitis should be recorded as AEs and followed by ophthalmology until they have resolved or uveitis is ruled out. Unscheduled assessments may be added as needed. Refer to the Ophthalmological Assessment Manual for further details.

6.5.8. Vital Signs

Vital sign measurements include temperature, respiratory rate, pulse rate, and systolic and diastolic BP while the participant is at rest in a supine position for at least 3 minutes. Heart rate and BP measurements should be obtained with a validated digital monitoring device where available and an appropriately sized cuff. The same arm should be used for all BP measurements if possible. Heart rate and BP should not be measured unless 15 minutes have passed since the last blood draw.

Abnormalities observed prior to dosing of study drug on the general medical history and baseline conditions will be recorded on the eCRF. At subsequent visits, new or worsened clinically significant abnormalities will be recorded on the eCRF. New or worsened abnormalities should be recorded as AEs on the AE eCRF if considered clinically significant in the Investigator's opinion.

6.5.9. Electrocardiograms

Triplicate 12-lead ECGs will be obtained approximately 1-3 minutes apart at screening. Triplicate 12-lead ECGs will also be obtained before blood draws (predose) and 60 to 90 minutes after the end of infusion on Day 1, and Weeks 5, 13, 25 and 49. Each ECG must be performed after the participant has been resting (supine) for at least 10 minutes.

All ECG tracings will be reviewed locally for safety by the Investigator or a qualified designee. Heart rate, QRS, corrected QT interval by Fredericia (QTcF), RR, and result interpretation will be captured in the eCRF. In addition, triplicate ECG tracings from Day 1 and Week 25 or Week 49 for approximately 100 consecutive participants will be read by a core ECG laboratory (*Note*: Central ECG reads may not occur in real time; thus, these results will not be used for safety assessments during study conduct.). Results from centrally read ECGs will not be captured in the eCRF.

6.5.10. Clinical Laboratory Assessments

Blood and urine samples will be collected for clinical safety laboratory analytes (hematology, chemistry, coagulation, urinalysis, and viral serology), and a pregnancy test. Parameters for assessment are listed in Table 4 for hematology, chemistry, coagulation, and urinalysis.

For any laboratory test value outside the reference range that the Investigator considers clinically significant, the Investigator will follow the instructions in Section 7.4.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. All other laboratory tests will be conducted at the central laboratory. Local laboratory data may be used in place of central lab data, in such instances where the central laboratory is unable to analyze the data (ie, central lab sample coagulated, sufficient volume of sample not collected or available for analysis, etc.).

Fasting is not required prior to clinical laboratory assessments.

Table 4: Clinical Laboratory Safety Assessments

Test	Analytes
Hematology	Absolute neutrophil count, hemoglobin, hematocrit, MCH, MCV, MCHC, white blood cells, red blood cells, platelet count, and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
Chemistry (serum or plasma)	Sodium, potassium, chloride, calcium, glucose, bicarbonate, albumin, total protein, creatinine, HbA1C, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, phosphorous, total bilirubin (direct and indirect), amylase, cholesterol (total, LDL, HDL), triglycerides, uric acid, creatine phosphokinase, lactate dehydrogenase, magnesium, C-reactive protein. Thyroid-stimulating hormone, folic acid, vitamin B12, and viral serology (HIV-1 or HIV-2 antibody and antigen, hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, HCV antibody/RNA) will also be assessed at screening only.
Coagulation	Prothrombin time with INR, activated partial thromboplastin time
Urinalysis	Dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic analysis in the event of abnormal dipstick results (urinary sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria).
Pregnancy (WOCBP only)	Serum pregnancy test, urine pregnancy test.

HbA1C=hemoglobin A1C; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL=low-density lipoprotein; MCH=Mean Corpuscular Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration; MCV=Mean Corpuscular Volume; WOCBP=woman of childbearing potential.

6.5.11. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed regularly throughout the study through participant completion of the C-SSRS. The C-SSRS is an interview-based instrument used to assess baseline incidence of suicidal ideation and behavior and to prospectively assess suicidal ideation and behavior at post-baseline visits. Post-baseline assessments will assess suicidal ideation and behavior since the previous visit. The C-SSRS is administered to the participant and measures 5 subtypes of suicidal ideation and behavior thought by the FDA to be important to capture in a prospective assessment of suicidality (FDA 2012).

Any change in the C-SSRS score indicating the presence of suicidality should be immediately evaluated by the Investigator and reported to the Medical Monitor. Participants who are suicidal on the basis of C-SSRS will be referred for appropriate psychiatric evaluation and management per local clinical practice. When the psychiatric evaluation verifies suicidal ideation or behavior, this should be recorded as an AE.

6.5.12. Magnetic Resonance Imaging

Brain MRI, including but not limited to 3DT1, FLAIR, and T2-weighted GRE sequences, will be performed to provide pharmacodynamic imaging biomarker measurements, provide the structural basis for PET registration, and to detect brain abnormalities including treatment-emergent ARIA.

In Part 1, on Day 15 and 43, a brain MRI will be performed. Participants with MRI evidence of ARIA will not be eligible to receive further administration of study drug. Additionally, on Day 43, an ophthalmological examination, neurological examination, and an LP will be performed. Participants in Part 1 with ARIA after Day 43 will be managed according to the guidelines in Section 7.11.

All new cases of ARIA-E and/or new cases of ARIA-H will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or ARIA-H has stabilized without new findings. An Amyloid PET scan may also be requested after the first occurrence of ARIA-E and/or ARIA-H for those participants who have opted-in to have longitudinal Amyloid PET performed. An unscheduled LP for CSF analysis may be requested after any occurrence of ARIA-E and/or ARIA-H.

In Part 2, Surveillance for treatment-emergent ARIA will be accomplished with post-randomization MRI scans as follows: MRIs to be performed 5-10 days before Dose 2 (Day 29), Dose 3 (Day 57), and Dose 4 (Week 13), and 5-10 days before doses at all subsequent visits with MRI (Weeks 25, 49, 73, 97) (see Section 14.1). The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

If new or worsening ARIA is observed on any of these post-randomization MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 7).

Participants with new or worsening radiographic evidence of ARIA on post-baseline MRI scans should be evaluated for neurological signs or symptoms during an unscheduled visit.

All new cases of ARIA-E and/or new cases of ARIA-H in Part 2 will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or ARIA-H has stabilized without new findings. An Amyloid PET scan may also be requested after the first occurrence of ARIA-E and/or ARIA-H for those participants who have opted-in to have longitudinal Amyloid PET performed. An unscheduled LP for CSF analysis may be requested after any occurrence of ARIA-E and/or ARIA-H.

All MRIs will be read for brain abnormalities within 5 days by blinded independent radiologists at a central MRI reader with Brain MRI Worksheets (BMWs) provided to the clinical sites and Sponsor.

See Section 7.11 for a description of radiographic severity, resolution, and stabilization of ARIA findings, MRI surveillance for ARIA, and expectations for investigator review of BMW reports. In addition to the MRI assessments prescribed in the Schedules of Assessments (Section 14.1) and in Section 7.11, the Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

Specific information regarding the collection and processing of MRI images will be provided in a separate Imaging Procedures Manual.

6.5.13. PrecivityAD™-Aβ Blood Test

This study will utilize an PrecivityAD™-Aβ blood assessment prior to assessment via PET or CSF. The participant must be amyloid positive by the PrecivityAD™-Aβ blood test (ie, have a high or an intermediate APS) prior to proceeding with either the Amyloid PET or CSF studies for confirmation of cerebral Aβ pathology. Confirmation of cerebral amyloid pathology by

Amyloid PET or CSF pTau/Aβ42 ratio is required for all participants. Participants with a positive historical Amyloid PET scan that has been collected ≤24 months prior to the start of screening and meets the acceptable criteria for a historical Amyloid PET scan outlined in Inclusion Criterion 1 will not be tested by PrecivityAD™-Aβ blood test (see Section 4.1). Participants with a validated, positive historical Amyloid PET scan are considered positive for cerebral Aβ pathology without further testing. Participants with a positive historical CSF measurement may forego the PrecivityAD™-Aβ blood test and confirmatory Amyloid PET or CSF pTau/Aβ42 measurement, if approved by the Medical Monitor. Participants with a low APS are not eligible.

6.5.14. Amyloid and Tau Positron Emission Tomography

Participants who are enrolled using Amyloid PET evaluation will be assessed by PET imaging at screening and must have a positive Amyloid PET scan by central visual read. Refer to the Study Design (Section 3.1) and the inclusion criteria (Section 4.1) for details regarding Amyloid PET evaluation.

If a prospective participant has received a positive Amyloid PET scan within 24 months before the start of screening as part of their prior medical care, this prior scan may be used to determine eligibility if all of the following requirements are met:

- The prior Amyloid PET scan must have been conducted in accordance with the specifications outlined in the PET Imaging Procedures Manual. If the scan specifications are not available or cannot be verified, the prior scan is not considered valid.
- Relevant prior data must be the original, reconstructed PET images themselves, not the resulting clinical reading. Images need to be sent to the imaging vendor for central review (see instructions for transferring in the PET Imaging Procedures Manual).
- Images must be presented to the central imaging reader(s) in the same format and undifferentiated in any way from images that would result from a newly acquired scan in this study.

The central imaging reader(s) must conduct a new, independent reading of the prior Amyloid PET scan, following the same process as for a newly acquired scan, to determine eligibility. The study reader(s) should not reference any prior reading of a previously acquired scan.

Participants in countries where local regulations allow may participate in an optional exploratory assessment to evaluate changes in the brain as measured by longitudinal Amyloid PET imaging. In addition to the scan obtained at the screening or Predose Baseline Visit, an additional Amyloid PET scan would be obtained at the Week 49 Visit, and a third Amyloid PET at the EFU or ET visit, if applicable. Please see the Schedules of Assessments in Section 14.1 for details. Only participants who obtain a new Amyloid PET scan at screening or the Predose Baseline Visit will be eligible for longitudinal Amyloid PET scanning.

During screening, participants will consent to the optional longitudinal Amyloid PET imaging assessment. If the participant is eligible, the participant must agree and provide consent separately for the optional assessment as defined in Section 10.3. Refer to the PET Imaging Procedures Manual for further details.

Participants in countries where local regulations allow may participate in an optional exploratory assessment to evaluate changes in the brain as measured by [^{18}F]MK-6240 Tau PET imaging. Participants may travel to select imaging sites to undergo Tau PET imaging at the Predose Baseline Visit and at 1 or more subsequent timepoints (please see the Schedules of Assessments [Section 14.1] for details).

During screening, participants will consent to the optional Tau PET imaging assessment. If the participant is eligible, agrees, and provides consent separately for this optional assessment as described in Section 10.3, additional safety assessments and Tau PET imaging procedures will be performed at the imaging site, as detailed in the PET Imaging Procedures Manual.

Participants who undergo the optional Tau PET imaging assessment will receive [^{18}F]MK-6240 and undergo a PET scan on multiple occasions as described in the Schedules of Assessments in Section 14.1. Refer to the Study Design (Section 3.1) for details regarding the circumstances when Tau PET scans must be performed. The Schedule of Assessments (Section 14.1) specifies when a final Tau PET scan should be performed if a participant discontinues from the study, provided that local radiation limits have not been exceeded.

If occurring at the same visit, Amyloid PET scans or Tau PET scans must be performed after administration of COAs. If occurring at the same visit, Amyloid PET and Tau PET scans must occur on different calendar days. If occurring at the same visit, Amyloid PET scans or Tau PET scans must be performed after MRI. PET scans should be performed only if the Investigator has determined that the total past and planned annual radiation exposure does not exceed local guidelines.

6.5.14.1.1. Positron Emission Tomography Imaging Procedures

The Sponsor, in conjunction with the imaging vendor, will prepare and distribute a detailed PET Imaging Procedures Manual for image acquisition, reconstruction procedures, and parameters for each center prior to the start of the study. All imaging data will be transferred to the imaging vendor for quality control and image analysis as documented in the PET Imaging Procedures Manual.

Detailed methodology, including scanning procedures, is included in the PET Imaging Procedures Manual.

6.6. Efficacy Assessments

The primary objective of this study is to evaluate the efficacy of AL002 in participants with Early AD in delaying disease progression compared to placebo. The primary efficacy endpoint and the secondary efficacy endpoints for the study are presented in Section 2.

Timing and frequency of all efficacy assessments are presented in the Schedules of Assessments (Section 14.1). Adaptations to visits and procedures under the exceptional circumstance of the COVID-19 pandemic are detailed in Section 14.4.

6.6.1. Clinical Outcome Assessments–- Neurocognitive and Functional Tests

The following neurocognitive and functional tests (described in Section 14.2) will be performed. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (eg, blood collections, LPs, imaging).

- CDR
- MMSE
- RBANS-Update
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13)
- Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment Scale (ADCS-ADL-MCI)
- WLSA (optional)

If a participant is taking intermittent or short-term regimens of medications known to impair consciousness or cognition, such medication must be stopped 2 days or less, or 5 half-lives (whichever is longer) prior to any cognitive or behavioral assessment. Use of cannabinoids (other than cannabidiol [CBD]) is prohibited within 72 hours prior to any cognitive or behavioral assessment.

6.7. Pharmacokinetic Assessments

The secondary PK endpoints for this study are presented in Section 2.

PK blood, CSF (mandatory for Part 1 participants for all visits through study completion; optional for Part 2 participants), and ADA collections will be performed, and AL002 concentrations will be measured.

On the dosing visits for study Weeks 1, 5, 9, 13, 25, and 49, serum PK samples will be collected predose, within 15 minutes after the end of infusion, and within 60 to 90 minutes after the end of infusion. Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at 4 and 8 and 24 or 48 hours after the end of infusion at one of the following: Week 25 or 37 or 49. On all other dosing visits, serum PK samples will be collected predose and within 15 minutes after the end of infusion. The end of infusion is defined as the end of the line flush.

On non-dosing visits, serum PK samples may be collected at any time during the visit.

Timing and frequency of all PK assessments and study drug administration are presented in the Schedules of Assessments (Section 14.1). The actual collection time of each sample must be recorded in the source data, on the collection tube, and in the eCRF and provided to the bioanalytical laboratory.

The bioanalytical laboratory will be unblinded to allow for analysis of the PK samples. Serum PK sample analysis will be performed using validated procedures and methods.

Blood samples will be collected for ADA monitoring and will be analyzed at an assigned bioanalytical laboratory for the presence of AL002 ADA using a validated bridging immunoassay. Additional samples for ADA assessment will be collected in participants with

signs and symptoms of infusion-related reactions. In such cases, a corresponding additional PK sample will be obtained at the same timepoint as the observed infusion-related reaction.

6.8. Pharmacodynamic Biomarker Assessments

6.8.1. Exploratory Pharmacodynamic Biomarker Assessments

The exploratory PD biomarker endpoints for this study are presented in Section 2.

The PD biomarker assessments will consist of, but are not limited to, blood-based biomarkers, CSF-based biomarkers (when available), and imaging biomarkers, as follows:

Blood-based biomarkers:

- sTREM2 in plasma
- Plasma biomarkers relevant to AD (eg, Aβ42, Aβ40, total tau [tTau], pTau, neurofilament light [NfL])
- Other exploratory PD biomarkers which may include transcriptional analysis of whole blood following PAX gene extraction of cellular RNA to assess TREM2 expression as well as other genes of interest.

CSF-based biomarkers (CSF collections apply to participants in Part 1 and those participants in Part 2 who consent to the optional LPs only):

- sTREM2 in CSF
- CSF biomarkers relevant to AD (eg, Aβ42, Aβ40, tTau, pTau, NfL) and to microglia function (eg, chitinase 3-like 1 (YKL-40), osteopontin)
- Other exploratory PD biomarkers

Imaging biomarkers:

- MRI imaging measures
- Optional longitudinal Amyloid PET imaging measures
- Optional Tau PET imaging measures

Timing and frequency of all PD biomarker assessments are presented in the Schedules of Assessments (Section 14.1).

6.9. Genomic Assessments and Genetic Disclosure

A blood sample will be collected at screening for DNA extraction to genotype *APOE* variants. Participants will be stratified during randomization based on *APOE* e4 status (carrier vs noncarrier).

Blood samples will be collected at baseline (or the next available visit) for DNA extraction to enable analysis of targeted genomic variants and WGS analysis to identify common and rare genetic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with safety findings, or can increase the knowledge and

understanding of disease biology. WGS samples will be collected where acceptable by local regulations.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of larger datasets will assist in identification of important pathways, guiding the development of new targeted agents.

Targeted genomic assessments will include, but not limited to, the following:

- *APOE* e4 allele; and
- TREM2 variants, sialic acid-binding Ig-like lectin 3 (CD33) variants, transmembrane protein 106b (TMEM106b) variants, and CLUSTERIN variants.

Study sites will follow their local guidelines and regulations regarding disclosure and supportive genetic counseling.

6.10. Unscheduled Visits

Unscheduled visits may occur at any time while the participant is enrolled in the study.

6.11. Study Completion and Early Termination

Participants are considered to have completed the study if they engage in all procedures and visits as outlined in the Schedules of Assessments. Participants can also be considered completers even if they discontinue study drug but choose to complete all of the remaining visits as outlined in the Schedules of Assessments. This includes all associated procedures up through and including Week 97 (if applicable), and well as the subsequent SFU (8 weeks after the end of the treatment period).

If it is not possible to keep the participant in the study, or if continued participation is not acceptable to the participant or Investigator, the participant may be withdrawn. It is recommended that the Investigator consults with the Medical Monitor prior to removing a participant from the study for any reason except participant withdrawal of consent, DLAE, or other protocol-mandated discontinuation. Participants are considered to be withdrawn or ET when the study drug is discontinued and they refrain from completing further visits as outlined in the Schedules of Assessments (Section 14.1). Please also refer to Section 3.3 and Section 4.3 for additional information.

7. ASSESSMENT OF SAFETY

The Investigator's assessment of the relationship of an AE, SAE, or radiotracer AE to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE/SAE, the event should be reported.

The Investigator is responsible for reporting all AEs/SAEs/AESI that are observed or reported during the study, from the time a participant signs informed consent until the end of study participation, regardless of clinical significance or of the AEs suspected relationship to study drug and/or radiotracer.

Any AESI detected after informed consent signature but prior to the first dose administration of study drug will be considered medical history and recorded as such on the medical history eCRF and electronic data capture (EDC).

7.1. Definition of Adverse Event

AEs are any untoward medical occurrence in a participant enrolled into this study, including side effects, injury, toxicity, sensitivity reaction, intercurrent illnesses, clinically significant physical exam signs, or sudden death, whether or not it is considered related to the study drug. Participants will be instructed to contact the Investigator at any time after informed consent if any symptoms develop. Participants will be instructed to report all AEs to the Investigator. All AEs must be appropriately documented in the participant's original source documents and on the eCRFs. Investigators should report the diagnosis rather than list symptoms, whenever possible.

A treatment-emergent AE is defined as any event not present before exposure to study drug and/or radiotracer, and any event that worsens from baseline after exposure.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported within the established time frames.

An AE does not include the following:

- Elective medical or surgical procedures planned prior to the start of study drug (eg, hip replacement surgery) that did not result from a worsening of a pre-existing condition (ie, prior to signing informed consent). Note: Any serious procedural complication or hospital-emergent conditions (eg, nosocomial infection) that, for instance, prolongs the hospitalization would be reported as an SAE.
- Any medical condition or clinically significant laboratory abnormality that has an onset date before the consent form is signed, and that is not related to a protocol-associated procedure, is not an AE. Findings identified during screening examinations, including events of ARIA identified during MRI performed at screening, are not AEs. Such conditions are considered to be pre-existing and should be documented on the medical history eCRF. A pre-existing condition should be reported as an AE only if its frequency, intensity, or symptoms worsen during the course of the study.

- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for study drug administration per institutional guidelines, elective surgery, social and/or convenience admissions).

Disease progression within expected parameters for the study population is not considered an AE. See Section 7.3.1 for Protocol Specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements.

7.2. Adverse Events of Special Interest

An AESI is a serious or nonserious AE which is of scientific and medical concern specific to a product for which ongoing monitoring and rapid reporting by the Investigator to the Sponsor should occur. AESI for study AL002-2 are defined as the following occurrences:

- ARIA-H
  - There are 3 categories of ARIA-H which are considered separate AESI. See Section 7.11 for additional details.
- ARIA-E
- Uveitis Grade 2 or higher

For AESI, the most appropriate diagnosis should be recorded on the AE eCRF and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event) as an AESI, regardless of whether the AESI is deemed to have a possible relationship to the study drug or not.

Management of ARIA is described in Section 7.11.

Uveitis (Grade 2 or higher) should be managed by an ophthalmologist and the Medical Monitor.

The reporting of an AESI will trigger an auto notification email alert from EDC to the Medical Monitor.

In the event that EDC is not functioning, the Investigator should utilize the back-up paper process described below for SAE reporting and clearly indicate if the event is nonserious or serious, and related or not related to study drug in the opinion of the Investigator, and that the event is assessed as an AESI.

7.2.1. Recording of ARIA-H and ARIA-E as Adverse Events of Special Interest

Findings of ARIA-E or ARIA-H on MRI are determined by the MRI Central Reader (see Section 6.5.12 for more detail). Once confirmed by the BMW report, ARIA-H and ARIA-E will be captured as such on the AE eCRF and marked as AESI. For definitional details of ARIA-H and ARIA-E see Section 7.11. For details on how to enter AESI of ARIA in the AE eCRF, please see the CRF Completion Guidelines.

7.3. Definition of Serious Adverse Events

An SAE is defined as any AE that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not meet one of the above criteria could be considered a SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered "life-threatening" if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

7.3.1. Protocol Specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements

Disease progression in this study is measured via the CDR-SB. Changes in these scores that are consistent with the expected rate of progression of the underlying disease should not be recorded as AEs.

However, symptomatic deterioration or events that are judged by the Investigator to be inconsistent with normal disease progression or are considered related to study drug should be reported as AEs, and if any of the "serious" criteria are met, it must be reported as an SAE.

Please note that the term "disease progression" should not be reported, but rather the clinical manifestation(s) with applicable descriptors should be captured on the AE eCRF page.

7.4. Definition of Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events/Serious Adverse Events

Abnormal laboratory findings (eg, hematology, coagulation, chemistry, and urinalysis) or other abnormal assessments (eg, ECG, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (or recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if applicable).

The Investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the

abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

7.5. Assessment of Adverse Events

7.5.1. Assessment of Adverse Event/Serious Adverse Event Severity

The severity of an AE refers to the extent to which an AE affects the participant's daily activities. Severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 or later. If an AE is not specified within the CTCAE guidelines, then the AE will be graded according to the definitions in Table 5.

Table 5: Adverse Event Grading Criteria

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life-threatening	Hospitalization, or prolongation of hospitalization indicated; disabling, limiting self-care ADL[b]
4	Life-threatening consequences	Urgent intervention indicated
5	Death	Death related to AE

ADL=activities of daily living, AE=adverse event.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note that "severity" is a measure of intensity and that a severe AE is not necessarily an SAE.

Changes in the severity of an AE should be documented to allow assessments of the duration of the events at each level of intensity. AEs characterized as intermittent do not require documentation of onset and end date of each episode. When the intensity of an AE changes more than once a day, the maximum severity for the event should be recorded for that day. If the intensity changes over a number of days, these changes should be recorded separately (eg, as having distinct onset dates on one or more eCRF lines).

7.5.2. Assessment of Causality

The relationship or association of the study drug or radiotracer, in causing or contributing to the AE will be characterized using the following classification and criteria:

Relationship to Study Drug or Radiotracer	Comment
Related	There is reasonable possibility that the event may have been caused by study drug/ radiotracer (eg, there is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies).
Not Related	The event can be readily explained by the participant's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes that it is unlikely that a causal relationship exists between the event and study drug or radiotracer.

AE=adverse event; PET=positron emission tomography.

The Investigator should assess causality by answering either "related" or "not related" to the question "Is there a reasonable possibility that the event may have been caused by the study drug" The following factors may be used in consideration of causality assessment:

- Challenge/rechallenge: Did the event abate after study drug was reduced or interrupted? Did the event reappear after study drug was reintroduced?
- Temporal relationship and time to onset plausibility
- Confounding risk factors
- Amount and duration of study drug exposure
- Concomitant medications

7.6. Recording of Adverse Events

7.6.1. Eliciting and Documenting the Adverse Events

At every study visit after screening, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Please refer to Section 6.5.1 for additional AEs and special situations that require immediate reporting to the Sponsor.

Laboratory test values or investigational findings (eg, findings on ECGs, imaging, or examination) outside the normal reference range are not necessarily AEs. Only those that meet the following criteria should be reported as an AE: (1) is confirmed and the Investigator considers clinically significant, or (2) that requires a participant to be discontinued from the study, or (3) that requires a participant to receive treatment. Abnormal laboratory test values or investigational findings reported as AEs should be followed until satisfactory clinical resolution, participant withdrawal of consent, lost to follow-up, or death, whichever comes first. Specific instructions for recording of ARIA-E and ARIA-H as AESI are specified in Section 7.2.1.

7.6.2. Recording the Action Taken with Study Drug in Response to Adverse Events/Serious Adverse Events

Should the Investigator need to alter the administration of the study drug from the procedure described in the protocol in response to an AE/SAE, then the action taken will be recorded on the AE eCRF page as one of the following options:

- Dose not Changed
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown

7.6.3. Recording the Outcome and Follow-up of Participants Reporting an AE/SAE

Outcome of an AE/SAE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovered/Resolved with Sequelae (with sequelae being a condition that is the consequence of the reported event, and not the event in a lower grade/ severity)
- Not Recovered/Not Resolving
- Fatal
- Unknown

7.7. Reporting Adverse Events

7.7.1. Adverse Events and Serious Adverse Events Reporting

Regardless of cause or relationship to study drug, all AEs/SAEs that occur after a participant signs the informed consent until the end of study participation, regardless of clinical significance or of the suspected relationship of the AE to study drug and/or radiotracer, should be reported by the Investigator. All unresolved AEs and/or SAEs will be followed through their resolution, or until the participant returns to his or her baseline condition, or is lost to follow-up or dies of another cause. Additionally, SAEs considered related to the study drug or radiotracer, which occur at any time during the study, should be reported by the Investigator, regardless of the AE/SAE collection window. Definitions pertaining to AEs are provided in Section 7.1.

Information to be collected includes but is not limited to the following:

- Event term
- Time and date of onset of event
- Investigator-specified assessment of severity and relationship to study drug or radiotracer
- Time and date of the end of the event or the date on which the event changes severity

- All serious criteria (if applicable)
- Any required treatment or evaluations
- Event outcome

In the event of any SAE reported or observed during the study, the site is required to complete the AE eCRF within the EDC system, including the event seriousness criteria, within 24 hours of becoming aware of the event or aware of substantive new information relating to the event.

Please note two additional scenarios requiring 24-hour reporting to the Sponsor:

5. AEs assessed as *related* to the *radiopharmaceutical*, Neuraceq® (florbetaben 18F injection). ***Please note:*** *if the site's imaging facility is located outside of the institutional facility, please ensure the imaging lab is aware of this requirement.*
6. Special situations (eg, overdose, occupational exposure, medication error) associated with Neuraceq® **or** the Alector study drug *regardless of whether the special situation is associated with an AE and regardless of the Investigator's causality assessment of the event to the radiotracer or Alector study drug*.

If the EDC system is not available, a paper Serious Adverse Event Report Form should be used and emailed to [redacted] according to the instructions provided in the Study Specific Regulatory Binder. Once the EDC system becomes available, SAEs reported using a paper Serious Adverse Event Report Form should be entered in the EDC system. The interval for which AEs are reported as described above also applies to SAE reporting.

The participant's condition will be followed by the Investigator or designated Subinvestigator, as described in Section 7.9. If unscheduled visits are required, the participant will be asked to return to the study site for further follow-up. As additional information becomes available, such as hospital discharge notes and participant medical records, the Investigator or designee will update the SAE eCRF and other relevant documentation pertaining to the SAE, and these updates will be submitted to the Sponsor within 24 hours of knowledge.

- Alector is responsible for notifying applicable regulatory agencies of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, Alector must notify the applicable regulatory agencies and all participating Investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after Alector determines that the information qualifies for reporting.
- It is the Investigator's responsibility to report all SAEs to Alector (covered in Section 11.6) in compliance with current regulations and it is Alector's responsibility to ensure all safety reporting obligations are carried out in compliance with current legislation for expedited reporting of SAEs (including suspected unexpected serious adverse reactions).

The MedDRA Version 23.0 or later will be used by Alector to code all AEs.

7.8. Safety Monitoring

For medical emergencies, contact Sponsor's Medical Monitor or designee:

PPD Safety Hotline

- North America: [redacted]
- Europe, Middle East, and Africa/Asia-Pacific Region: [redacted]

The Medical Monitor will review AE reports, compiled by Data Management, as described in the Medical Monitoring Plan. The Medical Monitor will review blinded study data on enrollment, abnormal laboratory results and protocol deviations. These reports will collectively be known as the Medical Monitoring Report.

7.9. Follow-Up of Adverse Events and Serious Adverse Events

All AEs, SAEs, and AESI that are deemed related, possibly related, or probably related to study drug must be followed until resolution, the condition stabilizes, the event is otherwise explained, the participant dies of another cause, or is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations that may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE/AESI. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during the protocol-defined follow-up period, the cause of death should be reported as a SAE and the Sponsor should be provided with a copy of any postmortem findings, including histopathology.

All AEs, AESI, and SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed up until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value is available.
- The participant withdraws consent.
- The participant dies.
- The event can be attributed to agents other than the study drug, [^{18}F]MK-6240 radiotracer, or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant lost to follow-up or medical records are not received after demonstration of due diligence with follow-up efforts).

After the protocol-defined follow-up period, if the Investigator becomes aware of any SAE that is assessed as related to an Alector study drug or radiotracer, the SAE must be reported to Alector within 24 hours of site awareness.

7.10. Infusion Reactions

Signs or symptoms of AEs during the infusion will be carefully monitored and treated according to standard of care. In addition, in the event of an infusion reaction, serum samples of PK and ADAs should be obtained, as well as a plasma sample for cytokine, etc. See Section 14.3 for information on the management of infusion-related reactions.

7.11. Amyloid-Related Imaging Abnormalities

Amongst the brain abnormalities detected on MRI are ARIA which are believed to reflect leakage of proteinaceous fluid or other blood products into the leptomeninges or brain parenchyma. The term ARIA was originally coined to describe specific brain abnormalities seen on MRI in anti-amyloid clinical trials. Although MRI findings potentially caused by AL002 may or may not be related to disruption/mobilization of, or a reaction to, amyloid species in the brain parenchyma or vasculature, the term ARIA will be used in this protocol to describe such findings until the biological mechanism is better understood. Specifically, according to the convention developed to describe ARIA occurring in clinical trials of anti-amyloid immunotherapies, ARIA-E will refer to MRI findings of vasogenic edema and leptomeningeal/sulcal effusion, and ARIA-H will refer to MRI findings of cerebral microhemorrhages, leptomeningeal hemosiderosis (also known as superficial siderosis of the CNS) and cerebral macrohemorrhages.

For the purpose of this protocol, four categories of ARIA will be tracked (see Section 7.2.1 for recording of AESIs of ARIA). These categories are ARIA-E, ARIA-H cerebral microhemorrhages, ARIA-H leptomeningeal hemosiderosis, and ARIA-H cerebral macrohemorrhages. Symptoms associated with ARIA-H and ARIA-E will be captured as separate AEs on the AE eCRF and linked to the applicable ARIA AE line number. All clinical signs and symptoms that are identified as associated with an ARIA finding will be entered as separate AEs on the AE eCRF. Based on evaluation of the participant for signs and symptoms, and review of safety findings by the Sponsor that possibly indicates the presence of ARIA, the Sponsor may request an unscheduled MRI be obtained.

To maintain consistency of reporting across clinical sites, findings of ARIA-E or ARIA-H on MRI are determined by the MRI Central Reader by radiologists with expertise in assessing for ARIA and other abnormalities on brain MRI. ARIA-E, ARIA-H and other findings are documented on and reported to the sites with the BMW report (see Section 6.5.12). The BMW provided by the Central Reader after each MRI examination scores ARIA-E (parenchymal vasogenic edema, leptomeningeal/sulcal effusion) according to: extent, location, number of sites involved, radiographic severity (mild, mild+, moderate, moderate+, severe) (Table 6) and changes since prior MRI exams. ARIA-E findings typically resolve radiographically and will be noted as such on the BMW of follow-up MRI scans. The BMW also documents occurrence and characteristics (location, size, number) of ARIA-H (parenchymal microhemorrhages and leptomeningeal hemosiderosis and macrohemorrhages).

Overall, ARIA-H radiographic severity is defined as the worst individual radiographic severity for microhemorrhages, leptomeningeal hemosiderosis or macrohemorrhages (eg, if there are

4 incident microhemorrhages, 1 incident areas of leptomeningeal hemosiderosis and no macrohemorrhages, then ARIA-H is rated as “Moderate”) (Table 6).

Table 6: ARIA-E and ARIA-H Radiographic Severity Scales

ARIA-E Characterization:	**Severity/Grade**		
<5 cm monofocal	Mild (Grade 1)		
<5 cm multifocal	Mild+ (Grade 2)		
5-10 cm monofocal	Moderate (Grade 3)		
5-10 cm multifocal	Moderate+ (Grade 4)		
>10 cm monofocal/multifocal	Severe (Grade 5)		
Incident ARIA-H:	**Mild**	**Moderate**	**Severe**
microhemorrhages	1-4	5-9	10 or more
Areas of leptomeningeal hemosiderosis	NA	1	2 or more
macrohemorrhages	NA	NA	1 or more

ARIA-E=amyloid-related imaging abnormalities-edema; ARIA-H=amyloid-related imaging abnormalities-hemosiderin deposits; NA=not applicable.

ARIA-H findings very rarely resolve radiographically; it is more typical for ARIA-H findings to stabilize radiographically. Radiographic stabilization of an ARIA-H finding is defined as when a follow-up MRI scan shows no increase in number/size/extent of previously seen cerebral microhemorrhages, leptomeningeal hemosiderosis and cerebral macrohemorrhages.

7.11.1.1. Schedule of MRI Surveillance for ARIA

Surveillance for treatment-emergent ARIA will be accomplished with post-randomization MRI scans as follows: MRIs to be performed 5-10 days before Dose 2 (Day 29), Dose 3 (Day 57), and Dose 4 (Week 13), and 5-10 days before doses at all subsequent visits with MRI (Weeks 25, 49, 73, 97) (see Section 14.1). The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

If new or worsening ARIA is observed on any of these post-randomization MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 7).

7.11.1.2. Participant Follow-up for ARIA Events

Participants with new or worsening radiographic evidence of ARIA on post-baseline MRI scans should be evaluated for neurological signs or symptoms during an unscheduled visit.

Investigators should comprehensively review the BMW for the presence of ARIA or other abnormalities. When ARIA has been detected, follow-up BMWs should be reviewed for radiographic evolution/resolution/stabilization of findings. Investigators suspecting ARIA that has not been detected by the MRI Central Reader should contact the Medical Monitor. For instance, if a local radiologist detects a faint area of vasogenic edema or microhemorrhage, which was not documented in the BMW, the Investigator should contact the Medical Monitor.

If participants are determined to have ARIA-related symptoms or signs, the Medical Monitor should be contacted within 48 hours. Investigators should be aware of the symptoms most commonly observed in participants with symptomatic ARIA. ARIA-related symptoms are typically non-localizing such as headache, confusion, visual changes, dizziness, nausea, and gait difficulty. However, in some cases, focal neurological deficits (eg, visuospatial difficulty, aphasia, and apraxia) may occur. Serious ARIA symptoms can include encephalopathy, stupor, seizures, and status epilepticus (Cummings 2023, Cogswell 2022).

Participants with asymptomatic ARIA-E may be observed; for participants with mild or moderate symptomatic ARIA-E, the use of oral or IV steroids may be considered (see Table 7). In the case of severe symptomatic ARIA-E, it is recommended to hospitalize the participant for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent.

All new cases of ARIA-E and/or new cases of ARIA-H will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved and/or until ARIA-H has stabilized without new findings. In addition, the Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

An Amyloid PET scan should be requested after the first occurrence of ARIA-E and/or ARIA-H for those participants who have opted-in to have longitudinal Amyloid PET performed. An unscheduled LP for CSF analysis and plasma may be requested, if not contraindicated, after any occurrence of ARIA-E and/or ARIA-H.

Participants in Part 1 with MRI evidence of ARIA at the Day 15 or Day 43 MRI will be discontinued from study drug administration. Participants in Part 1 with ARIA after Day 43 and participants in Part 2 with MRI evidence of ARIA at any visit will be managed according to the guidelines in Table 7.

Table 7: Dosing Guidelines for ARIA

Finding	Asymptomatic/Symptomatic	Action
Mild[a] ARIA-E	Asymptomatic or Symptomatic	Suspend dosing until resolution of ARIA-E or stabilization of ARIA-H. After resolution (ARIA-E) and/or stabilization (ARIA-H), if participant dosing is restarted, they must receive the same dose they received immediately prior to the ARIA-E/ARIA-H findings and continue on that dose for the remainder of the study. After resuming dosing, 5-10 days before their second post-resumption dose, participants must undergo an unscheduled MRI that must be assessed by the Central Reader for ARIA-E/H before the next dose is administered. For mild or moderate symptomatic ARIA-E the use of oral or IV steroids can be considered. For severe symptomatic ARIA-E it is recommended to hospitalize the participant for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent.
Moderate[b] ARIA-E	Asymptomatic or Symptomatic	
Severe ARIA-E	Asymptomatic or Symptomatic	
Mild or Moderate ARIA-H	Asymptomatic	
Mild or Moderate ARIA-H	Symptomatic	Permanently discontinue treatment
Severe ARIA-H	Asymptomatic or Symptomatic	Permanently discontinue treatment
Serious[c] ARIA-E or Serious ARIA-H	Symptomatic	Permanently discontinue treatment
Serious[c] ARIA-E or Serious ARIA-H	Asymptomatic	Suspend dosing until resolution of ARIA-E or stabilization of ARIA-H. After resolution (ARIA-E) and/or stabilization (ARIA-H), if participant dosing is restarted, they must receive the same dose they received immediately prior to the ARIA-E/ARIA-H findings and continue on that dose for the remainder of the study. After resuming dosing, 5-10 days before their second post-resumption dose, participants must undergo an unscheduled MRI that must be assessed by the Central Reader for ARIA-E/H before the next dose is administered.
A second occurrence of ARIA-E after full resolution of a prior occurrence of ARIA-E	Asymptomatic or Symptomatic	Permanently discontinue treatment

ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposits; MRI=magnetic resonance imaging.

[a] Mild includes 'mild' and 'mild+', as scored on the BMW from the Central Reader.

[b] Moderate includes 'moderate-' and 'moderate+', as scored on the BMW from the Central Reader.

[c] Meets criteria for a SAE.

7.12. General Safety Monitoring

7.12.1. Special Situations

Special situations are non-standard medical conditions that provide valuable information about an investigational product. All special situations associated with an AE or SAE should be recorded in the EDC system in the AE eCRF. Special situations must be reported within 24 hours of becoming aware.

Special situations are defined as below:

- Overdose: An overdose is any dose of study drug given to a participant or taken by a participant that exceeds the dose described in the protocol. There is no known treatment for AL002 overdose, and all participants should be monitored for AEs.
- Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information. It's the use of a pharmaceutical drug for an unapproved indication or in an unapproved age group, dosage or route of administration.
- Misuse: This refers to situations where the IP is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or within legal status of its supply.
- Abuse: This corresponds to the persistent or sporadic, intentional excessive use of IP, which is accompanied by harmful physical or psychological effects.
- Medication error: A medication error is any dose of study drug given to a participant or taken by a participant that differs from the dose described in the protocol. Medication errors are not likely in the study, as the study drug is administered by IV infusion by trained personnel under the supervision of the Investigator or their designee.
- Occupational exposure: This corresponds to an IP for human use as a result of one's occupation.
- Lack of efficacy/effect: Efficacy is the ability of a drug, biologic, or device to produce desired therapeutic effect independent of potency (amount of the product needed for desired effect). Lack of efficacy/effect, therefore, is the evidence of less than the expected effect of a product. There might be subpopulations that have a higher risk for lack of efficacy/effect; in order to identify such cases, one needs to consider types of events that may be reported in such situations for the specific product and indications.

7.12.2. Pregnancy

Female participants must be instructed to discontinue all study drugs and inform the Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy within 24 hours of becoming aware of it using the paper Pregnancy Report Form. Follow-up information documenting the pregnancy outcome should be reported on the paper Pregnancy Report Form. The site should email the Pregnancy

Report Form to [redacted] according to the instructions provided in the Study Specific Regulatory Binder.

The participant must be immediately discontinued from study drug and/or optional Tau PET imaging procedure. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed until a final outcome is known.

Pregnancies are captured if they occur in female participants or in the sexual partners of male participants from the time the participant is first exposed to the study drug or radiotracer until the SFU visit.

Any congenital abnormalities associated with a pregnancy that occurred during study participation are considered SAEs. The outcome of any pregnancy and complete health information regarding the baby will be recorded in the source documentation and reported to Pharmacovigilance.

Any SAE occurring in association with a pregnancy must be reported to Pharmacovigilance regardless of whether the events are considered related to study drug.

7.12.3. Breastfeeding

Adverse events which occur in infants following exposure to an investigational product from breastmilk should be reported.

8. STATISTICAL METHODS AND ANALYSIS PLAN

All data for each participant will be listed as collected. The statistical analysis plan (SAP) for interim analysis will be finalized prior to the first interim analysis (if applicable). The SAP for final analysis will be finalized prior to the final database lock. The SAP will provide further details regarding the planned analysis methodology, to address all study objectives. Statistical analysis analyses will be performed using Statistical Analysis System (SAS) software Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina, USA).

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25% quartile, 75% quartile], minimum, and maximum) unless otherwise specified in the SAP. Categorical data will be summarized using counts and percentages, unless otherwise specified in the SAP.

For analysis, Day 1 is defined as the day of the first study drug administration. The preceding day is Day -1. Baseline is the last non-missing assessment (scheduled or unscheduled) obtained prior to the first study drug administration, unless otherwise specified in the SAP. Baseline for endpoints that have more than one component is calculated from the individual component baselines, whether or not they were assessed during the same visit, unless otherwise specified in the SAP.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP. Any changes to the data summaries and analyses outlined in this section will be documented in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate. Any deviations from the analysis planned in the SAP will be justified and recorded in the final clinical study report (CSR).

Study endpoints are provided in Section 2.

8.1. Sample Size Calculations

The primary analysis model is a proportional mixed effect model with repeated measurements (pMMRM) which estimates an average treatment effect over all the post-baseline visits. Our proposed model estimates the weighted average across the time varying components. The model provides a clinically meaningful estimation of the treatment benefit averaged across the full duration of the clinical trial, rather than focusing on a single timepoint at the last visit, which may be a random high/low assessment.

To assess the power of the proposed pMMRM, a simulation experiment was conducted using the planned common close design with CDR-SB assessments at baseline and month 6, 12, 18, and 24. Data on the CDR-SB from clinical trials for AD, that are part of a master dataset, were used as the basis for assumptions for the simulations. A total of 441 patients with a global baseline CDR score of 0.5 and 1.0 were selected from this master dataset and the mean and covariance matrix were estimated using a mixed-effects model for repeated measures (MMRM) model. The mean and covariance were then used in simulations to estimate the power of the study. The following table shows the power based on the planned primary analysis method (pMMRM), for different sample sizes per group and different treatment effect assumptions, under the common close design using a two-sided 10% significance level. Under the common close design, we have assumed that 22% (per visit), 27% (per visit), 44% (total), and 58% (total) of participants will be

missing CDR-SB data at month 6, 12, 18, and 24, respectively, due to dropout and the common close nature of the study design. A total of 5,000 simulations were run per scenario.

Sample Size	Assumed Treatment Effect		
	0%	**30% Reduction**	**40% Reduction**
60/group	<10%	59%	78%
70/group	<10%	64%	83%

Power based on a two-sided 10% significance level. A total of 5000 simulations were run per scenario.

Based on the above power calculations, 70 participants per group will provide approximately 83% power to detect at least a 40% reduction in the CDR-SB score between any one dose group and the placebo group. To account for an additional 15 participants who discontinued the study drug prematurely because of the removal of the *APOE* e4-homozygous genotype carriers, 6 participants who were randomized but never received any dose administration, and 27 participants who prematurely discontinued from the study (Section 4.3.3), a total of 82 participants per group is planned to be randomized. The planned total sample size is therefore approximately 328 participants (approximately 82 participants per group).

8.2. Analysis Sets

The following sets of participants will be used in the statistical analyses. The Full Analysis Set (FAS) and the Per-Protocol Analysis Set (PPS) exclude the participants who are *APOE* e4-homozygous genotype carriers. The protocol was modified to stop enrolling and to discontinue study drug for participants who are *APOE* e4-homozygous genotype carriers. These participants are now excluded from the main study objectives/estimands and so will not be included in these analysis sets to address these. Data from these participants will be listed and summarized separately in the CSR.

All Randomized Set: the All Randomized Set will include every participant randomized.

Safety Set: the Safety Set will include all participants who received study drug.

Full Analysis Set (FAS): the FAS will consist of all participants who were randomly assigned and received any amount of double-blind study drug and had baseline and at least one post-baseline CDR-SB assessment and is not an *APOE* e4-homozygous genotype carrier.

Per-Protocol Analysis Set (PPS): the PPS will consist of all participants in the FAS without any major protocol violation that would impact the assessment of efficacy. All major protocol violations will be reviewed for defining the PPS and agreed on prior to database lock. This analysis set will be used for supportive efficacy analyses.

PK Set: the PK Set will include all participants in the Safety Set who had adequate assessments for determination of at least 1 PK parameter.

APOE Non-e4-Homozygous Genotype Carriers: this subset will include all randomized and dosed participants who are not *APOE* e4-homozygous genotype carriers.

APOE e4-Homozygous Genotype Carriers: this subset will include all randomized participants who are *APOE* e4-homozygous genotype carriers.

8.3. Statistical Analysis Methodology

8.3.1. General Analyses

Unless specified otherwise in the SAP, general analyses will be applied to All Randomized Set, FAS, and Safety Set.

8.3.1.1. Disposition of Participants

Disposition will be summarized, presenting the numbers of participants, reasons for study discontinuation, reasons for study drug discontinuation, and the number of participants in each analysis set.

8.3.1.2. Protocol Deviations

A protocol deviation occurs when the participant, Investigator, or Alector (or designee) fails to adhere to protocol requirements.

8.3.1.3. Demographics and Other Baseline Characteristics

Summary statistics will be provided for demographics, medical history, PE, social history, and risk factor variables at baseline, using the All Randomized and FAS populations. Risk factors will include duration of AD, severity of disease, and age at time of diagnosis.

8.3.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO DD, March 2020 or later. A medication will be considered as "prior" if the stop date and time of administration are before the start of the first study drug administration on Day 1. A medication will be considered "concomitant" if the stop date and time of administration is after the start of study drug administration. If the date and time of administration contains partial information such that the attribution of concomitant administration cannot be ruled out, then it will be considered as concomitant.

Prior medications, concomitant medications, exposure to blinded treatment and compliance with treatment will be summarized.

8.3.2. Efficacy Analyses

All efficacy analyses will combine data from all participants in Part 1 and Part 2. The FAS analysis set will be used for all efficacy analyses and participants will be analyzed according to their randomized treatment group.

8.3.2.1. Analyses of Primary Efficacy Endpoint

The primary analysis will use the FAS. The primary estimand for the primary efficacy endpoint is defined as:

- Treatment condition: while on treatment (hypothetical strategy) regardless of other interventions (treatment policy strategy).

- Target population: adult patients with Early AD as defined by the protocol inclusion/exclusion criteria.
- Primary endpoint: change from baseline in CDR-SB score to Weeks 25, 49, 73, and 97.
- Accounting for intercurrent events: A composite strategy will be used to handle intercurrent events
  - hypothetical strategy for handling premature study drug discontinuation for any reason;
  - treatment policy strategy for handling all other intercurrent events.
- Population-level summary: the percent reduction relative to placebo decline (the proportional treatment effect), comparing each dose level to placebo.

The primary analysis will use a pMMRM approach. A pMMRM models the treatment effect as a single proportional difference at each post-baseline visit. The treatment effect is defined as a percentage reduction of the placebo group clinical decline (eg, increase in CDR-SB). As the effect of AL002 may not be seen in the early stages of the trial, the pMMRM model will only assume the treatment effect is proportional from the analysis visits of Week 25 through Week 97, and use the timepoints of Week 25, 49, 73 and 97, to estimate the treatment effect (θ). Analysis visits will be defined in the SAP.

The following hypothesis will be tested using a 1-sided 5% significance level:

- H_0 (null): $\theta <= 0$, indicating that treatment does not slow disease progression relative to placebo control
- H_1 (alternative): $\theta > 0$, indicating that treatment slows disease progression relative to placebo control

If a participant is missing data because they missed a scheduled visit or because they drop out from the study and are no longer followed, their data will be assumed to be missing at random (MAR) and likelihood based mixed-effects models will be used as the primary analysis methodology to compare treatment groups, as these are the most appropriate model choice for a primary analysis (Mallinckrodt 2003). Additional sensitivity analyses using pattern mixture models will be conducted to assess the assumption of MAR.

A supportive analysis for the rate of change in the primary efficacy endpoint will include a linear mixed-effects model assuming change from baseline in CDR-SB following a linear relationship overtime. The model will use change from baseline in CDR-SB as dependent variable and include baseline CDR-SB score, continuous time and the time-by-treatment interaction term as fixed effects. An unstructured covariance matrix will be assumed to model the within-participant errors. If there is a convergence problem with the unstructured covariance matrix, alternative covariance structures will be examined (heterogeneous Toeplitz structure, Autoregressive (1), etc.) and the one with the best fit will be used. The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The p-value for the equality of slopes will be used to test the hypothesis of no treatment difference in the rate of change.

A supportive analysis for the treatment benefit across all timepoints will be based on an MMRM to compare the difference at Weeks 25, 49, 73, and 97 between each treatment group and placebo. The model will include baseline CDR-SB score, categorical treatment, categorical visits (ie, Week 25, 49, 73, and 97) and visit-by-treatment interaction terms as fixed effects. An unstructured covariance matrix will be assumed to model the within-participant errors. This variance-covariance matrix will be estimated across treatment groups. If there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be examined (heterogeneous Toeplitz structure, Compound Symmetry, etc.) and the one with the best fit will be used. The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The least squares mean (LS-mean) averaged across all timepoints and at each analysis visit will be estimated for each treatment group. The LS-mean treatment difference between each treatment group and placebo, averaged across all timepoints and at each analysis visit, along with the corresponding confidence intervals for the LS-mean treatment difference and the p-value for the treatment difference, will be reported.

Analyses based on a supportive estimand for the primary efficacy endpoint will be performed. The supportive estimand for the primary efficacy endpoint is defined with the same attributes as in the primary estimand for the primary efficacy endpoint except that a treatment policy strategy will be used to handle all intercurrent events, except death. All on-study data will be included regardless of whether an intercurrent event occur or not. Hypothetical strategy will be used for handling death.

8.3.2.2. Analysis of Secondary Efficacy Endpoints

The same methods as described for the primary endpoint will be applied to each of the secondary endpoints.

8.3.3. Multiplicity Adjustment

For the primary efficacy endpoint (a percentage reduction of the placebo group clinical decline as measured by change in CDR-SB), each dose of AL002 will be compared to placebo. To adjust for multiplicity among the multiple doses for the primary endpoint, a fixed testing order will be used starting with the highest dose, followed by the next lower dose, and then the next lower dose after that.

For all secondary endpoints and exploratory PD endpoints, no adjustment for multiplicity will be made and nominal p-values will be presented.

8.3.4. Safety Analyses

Safety analyses will be performed based on the Safety Set and participants will be assigned according to treatment actually received. If a participant is randomized to placebo and receives any amount of AL002, they will be included in the AL002 dose group based on the dose received.

All safety analyses at the completion of the study will be presented with data from Parts 1 and 2 combined. AEs will be coded using the MedDRA Version 23.0 or later. They will be summarized by system organ class and preferred term. Severity of the AEs, their relationships to treatment, SAEs, events leading to study drug withdrawal will be summarized similarly.

The following endpoints will be summarized:

- Incidences of AEs, AESI, SAEs, AEs leading to study drug withdrawal, and death
- Changes from baseline in clinical laboratory tests over time, as appropriate
- Changes from baseline in 12-lead ECG results
- Incidences of MRI safety findings
- Incidences of physical, ophthalmological, and neurologic examination abnormalities
- Changes from baseline in vital signs over time and incidence of abnormal vital signs
- Incidences of suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, as determined using the C-SSRS
- Immunogenicity as assessed by incidence of ADAs during the study relative to the prevalence of ADAs at baseline, and impact upon safety, efficacy, and PK findings
- ECGs being read centrally will be analyzed and reported in a separate report

8.3.5. Pharmacokinetic Analyses

All PK analyses will be performed on the PK set. Individual and mean serum AL002 concentration-time data will be tabulated and plotted by study day and treatment group. As applicable, the serum PK of AL002 will be summarized by estimation of C_{max} and observed trough concentration on the basis of results obtained following multiple doses of AL002 by study day and treatment group. When available, the individual and mean CSF AL002 concentration-time data will be tabulated, plotted, and summarized similarly.

Potential correlations of serum and/or CSF PK data with demographics, safety (including QT changes), efficacy, and PD measures may be explored, as data allow. Additional modeling, including population PK analysis and/or PK/PD analysis to characterize these correlations may be performed. The results of such additional analyses may be reported separately from the CSR.

8.3.6. Exploratory Pharmacodynamic Biomarker Analyses

The exploratory PD biomarkers (including but not limited to, sTREM2, NfL, brain atrophy, Aβ42, pTau Tau PET, longitudinal Amyloid PET), and their changes from baseline, will be summarized over time using descriptive statistics. Comparisons between treatment groups will be explored using MMRM models.

The relationships between serum, plasma and/or CSF PK concentrations of AL002 and efficacy or PD biomarker endpoints will be explored.

The relationships between PD biomarkers at baseline, including common and rare genetic variants, identified through WGS performed on DNA extracted from blood, and safety, PK, activity, immunogenicity, or other PD biomarker endpoints including RNA, will be explored.

8.3.7. Interim Analyses

Up to 3 interim analyses for the purposes of planning for future clinical studies may be conducted. There is no plan to stop the study early for overwhelming efficacy based on the

results of the interim analyses. Details of the interim analyses will be provided in a separate SAP. All site personnel, participants and members involved in the day-to-day activities of study conduct (Alector or CRO) will remain blinded throughout the study.

9. DATA QUALITY ASSURANCE

This study will be conducted according to the ICH E6(R2) quality and risk processes described in the applicable procedural documents. The quality and risk management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current GCP, the protocol, and applicable SOPs. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and study site personnel. eCRFs and EDC will be utilized. The EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11 and applicable local regulations for GxP systems. Each person involved with the study will have an individual identification code and password that allows for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

9.1. Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, recorded data from automated instruments, medical progress notes, email correspondence, and ECG strips.

A separate device will be used for the WLSA (optional assessment where available under local regulations; for participants from English-, French-, or German-speaking countries). All data collected by the Winterlight application will be stored securely on the device and queued for upload to Winterlight Lab's secure servers.

The Investigator will adhere to Good Documentation Practice, and investigative site personnel will enter participant data into the eCRF. The analysis datasets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical Data Management will be performed in accordance with applicable standards, and data cleaning procedures to ensure the integrity of the data, eg, identifying errors and inconsistencies in the data. AE terms will be coded using the MedDRA Version 23.0 or later, an internal validated medical dictionary, and concomitant medications will be coded using the WHO Drug Dictionary, March 2019 or later.

After database lock, each study site will receive a digital file containing all of their site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a digital copy of all of the study site's data from the study will be created and sent to Alector for storage. The CRO will maintain a duplicate digital file copy for their records. In all cases, participant initials will not be collected or transmitted to Alector.

10. ETHICS

10.1. Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or the participant's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH E6(R2): GCP will be maintained by the site and will be available for review by Alector or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must promptly supply Alector or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

10.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

10.3. Participant Information and Consent

A written informed consent in compliance with US Title 21 CFR Part 50 and any other applicable local health authority regulations shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by Alector to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent will be reviewed by Alector or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants (or legally authorized representative) must sign the revised form.

Before recruitment and enrollment, each prospective participant or his/her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study by signing the ICF. The participant's study partner will also be asked to give consent to participate in the study by signing an ICF.

If the study participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB/IEC. Where not permitted by local regulations,

participants deemed not competent to provide consent by the Investigator will not be enrolled. If the study participant becomes incompetent over the course of the study, a legally authorized representative will need to be identified and the participant will need to provide assent.

Prior to agreeing to samples being retained for future testing outside of the main study, participants will provide informed consent in accordance with the SOPs of the investigational sites.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the participant or legal guardian.

Optional LP for CSF collection

If the participant is eligible, agrees, and provides additional consent for these optional assessments, in accordance with SOPs of sites, additional LP for CSF collection will be performed.

Optional Tau PET imaging assessments

If the participant is eligible, agrees, and provides additional consent for these optional assessments, in accordance with SOPs of sites, additional safety assessments and PET imaging procedures will be performed at the imaging site, as detailed in the PET Imaging Procedures Manual.

Optional Amyloid PET imaging assessments

If the participant is eligible, agrees, and provides additional consent for these optional assessments, in accordance with SOPs of sites, additional safety assessments and PET imaging procedures will be performed at the imaging site, as detailed in the PET Imaging Procedures Manual.

Optional WLSA

If the participant is eligible, agrees, and provides additional consent for these optional assessments, in accordance with SOPs of sites, additional speech assessment procedures will be performed, as detailed in the applicable WLSA Manual.

11. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be participant to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

11.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant's legal guardian), except as necessary for monitoring and auditing by Alector, its designee, the US FDA, other health authorities, or the IRB/IEC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Alector or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Alector to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the Investigator must provide to Alector a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Alector (or delegate) is not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, Alector (or delegate) is not financially responsible for further treatment of the participant's disease.

11.3. Investigator Documentation

Prior to beginning the study, the Principal Investigator will be asked to comply with ICH E6(R2) 8.2 and US Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval.
- Original Investigator-signed Investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572, or an equivalent form capturing this information.
- Curriculum vitae for the Investigator and each Subinvestigator listed on Form FDA 1572 (or equivalent to Form FDA 1572).

- Financial disclosure information to allow Alector to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the Investigators must provide to Alector a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant or legal guardian.
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with US Title 42 CFR 493.

11.4. Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

11.5. Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

11.6. Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to Alector and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

11.7. Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Alector and regulatory authority(ies) with any reports required.

11.8. Records Retention

Essential documents should be retained until at least 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 study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Alector. It is the responsibility of Alector to inform the Investigator/institution as to when these documents no longer need to be retained. The trial master file will be created during the implementation phase of a study, maintained on an ongoing basis throughout the duration of the project and collated at the end of the study.

11.9. Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, Alector will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Alector has final approval authority over all such issues.

Data are the property of Alector and cannot be published without prior authorization from Alector, but data and publication thereof will not be unduly withheld.

12. STUDY MANAGEMENT

12.1. Monitoring

12.1.1. Independent Data Monitoring Committee

The administrative structure will include an unblinded external iDMC, which will oversee participant safety in the study. All further details with regard to the composition, purpose, and duties of the iDMC are provided in a separate iDMC charter. After approximately 20 participants have completed their Day 43 visit, the iDMC will perform the first safety review of all available safety and tolerability data (including from the MRI and neurological and ophthalmological examinations) from all participants up to that timepoint in an unblinded manner. The iDMC will recommend whether (a) the study will continue without changes or (b) the study should be modified for safety reasons.

A second safety review will be made by the iDMC after approximately 40 (minimum of 32 in case higher than expected discontinuation rate) participants have completed the Day 43 visit. The iDMC will review all available safety and tolerability data (including from the brain MRI and neurological and ophthalmological examinations), and PK data from all participants up to that timepoint in an unblinded manner. Based on this second iDMC assessment, the iDMC will recommend that (a) the study may continue without changes or (b) the study should be modified for safety reasons. Randomization may be paused to allow the iDMC to review data prior to Part 2 commencing.

After the first two initial reviews, cumulative safety data will be reviewed by the iDMC approximately every 6 months. The iDMC may convene on an ad-hoc basis, as required, to review cumulative safety data.

The iDMC will act in an advisory capacity to the Sponsor. The iDMC responsibilities will be detailed in a charter and will include but not be limited to the following:

- Review the following documents before commencing activities as an iDMC: draft iDMC charter, IB, study protocols, template informed consent form, blank case report forms, and data monitoring plans
- Evaluate the progress of the study; timeliness and quality of the data; participant recruitment, accrual, and retention; risk versus benefit to participants; and other factors that might affect the outcome of the study
- Consider relevant information that may have an impact on participant safety or the ethics of the study
- Make recommendations to the Sponsor concerning continuation, termination, or other modifications to the study based on their observations of the study and its data
- Conduct routine review of data according to a preplanned schedule

Further details will be included in the iDMC charter.

12.1.2. Monitoring of the Study

The clinical monitor, as a representative of Alector, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel. In addition, under the exceptional circumstances of the COVID-19 Pandemic, the monitor may follow the study closely through remote monitoring and/or remote conduct of Investigator and study site visits, as allowed per local regulations. Refer to Section 14.4 for additional details on remote source document verification as a result of the COVID-19 pandemic.

All aspects of the study will be carefully monitored, by Alector or its designee, for compliance with applicable government regulation with respect to current GCP and current SOPs.

12.1.3. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow Alector, representatives of Alector, and/or a regulatory agency access to all study records.

The Investigator should promptly notify Alector and the CRO of any audits scheduled by any regulatory authorities. Dependent upon the scope of the regulatory authority audit, Alector may elect to assist the site in preparation or support. The Investigator should promptly forward copies of any audit reports received to Alector.

12.2. Study Termination

Although Alector has every intention of completing the study, Alector reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (includes SFU visit).

12.3. Final Report

Whether the study is completed or prematurely terminated, Alector will ensure that the CSR is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the CSR in marketing applications meets the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, Alector will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

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14. APPENDICES

14.1. Appendix 1: Schedules of Assessments

Table 8: Schedule of Assessments – Part 1 Only

Study Period	Screening[gg] (Days -78 to -23)	Predose Baseline[b] (Days -22 to -1)	Treatment				
Study Week[a]			1 (D1)	2 (D8)	3 (D15)	5 (D29)	7 (D43)[c]
Visit Window				±2d	±2d	±2d	±2d
Informed consent[d]	x						
Demographic data	x						
Medical history, social history and baseline conditions	x						
Viral serology[e]	x						
Height and weight[f,g]	x		x			x	
Vital signs[h,i]	x	x[p]	x	x	x	x	x
Complete PE[g,j]	x						
Neurological examination[g]	x						x
Ophthalmological examination[g]	x						x
Concomitant medications[i,k]	x	x[p]	x	x	x	x	x
Randomization[l]		x	x				
Study drug administration			x			x	
Adverse events[i,m]	x	x[p]	x	x	x	x	x
ECG (triplicate)[i,n]	x		x			x	
Pregnancy test (if applicable)[o]	x	x[p]					
Thyroid function	x						
Folic acid and vitamin B12 levels	x						
Hematology[g,q], chemistry[g,r], and urinalysis[g,s]	x		x		x	x	x
Coagulation[g,t]	x					x	

Table 8: Schedule of Assessments – Part 1 Only (Continued)

Study Period	Screening[gg] (Days -78 to -23)	Predose Baseline[b] (Days -22 to -1)	Treatment				
Study Week[a]			1 (D1)	2 (D8)	3 (D15)	5 (D29)	7 (D43)[c]
Visit Window				±2d	±2d	±2d	±2d
C-SSRS[g]			x				
MRI (safety, PD)[g,ee]	x[u]				x[ff]		x
CDR[g,v]	x						
MMSE[g,v]	x						
ADAS-Cog13[g,v]			x				
RBANS-Update[g,v]	x						
ADCS-ADL-MCI[g,v]			x				
Serum sample for ADA[g,w]			x		x	x	x
Serum PK sample(s)[i,w]			x	x	x	x	x
Plasma sample for PD biomarkers[g]	x		x	x	x	x	x
PrecivityAD™-Aβ Blood Test[x]	x						
Whole blood sample for mRNA[g]			x		x	x	
Blood sample for WGS[g]			x				
APOE e4 testing	x						
Whole blood sample for other targeted genomic variants[g,y]			x				
Amyloid PET [z,ee]	x						
LP for CSF pTau/Aβ42[aa,ee]	x						
LP for CSF[aa,ee]	x[bb]						x
Longitudinal Amyloid PET (optional)[ee,gg]	x	x					
Tau PET (optional)[p,cc,ee]		x					
WLSA (optional)[v,dd]		x				x	

Aβ=amyloid beta; Aβ42=amyloid beta 1-42; ADA=anti-drug antibodies; ADAS-Cog13=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS=Alzheimer's Disease Composite Score; ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment Scale; AE=adverse event; AESI=adverse event of special interest; *APOE* e4=apolipoprotein E epsilon4; BP=blood pressure; CD33=sialic acid-binding Ig-like lectin 3; CDR=Clinical Dementia Rating; COA=clinical outcome assessment; COVID-19-coronavirus disease 2019;CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; d or D=day; ECG=electrocardiogram; ET=early termination; HIV=human immunodeficiency virus; Ig=immunoglobulin; LP=lumbar puncture; MMSE=Mini-Mental State Examination; mRNA=messenger RNA; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PE=physical examination; PET=positron emission tomography; PK=pharmacokinetic(s); pTau=phosphorylated tau; RBANS-Update=Repeatable Battery for the Assessment of Neuropsychological Status-Update; RDVF=Research Diagnostic Verification Form; SAE=serious adverse event; SFU=safety follow-up; TMEM106b=transmembrane protein 106b; TREM2=triggering receptor expressed on myeloid cells 2; WGS=whole genome sequencing; WLSA=Winterlight Labs Speech Assessment; WOCBP=woman of childbearing potential.

[a] Study Day number and Study Week number begin with 1 on the day of the first administration of study drug.

[b] The Predose Baseline Visit for Part 1 adds up to 21 days to the duration of study participation for those participants participating. This visit will be performed for (1) participants participating in the optional Tau PET imaging procedures in order to schedule and perform PET imaging prior to Day -1 or WLSA, and for (2) participants who do not receive an LP for CSF sampling during the screening period for eligibility, in order to schedule and perform an LP prior to Day -5 and/or the

optional longitudinal Amyloid PET imaging procedure where Amyloid PET was not performed during screening in order to schedule and perform PET imaging prior to Day 1. Part 1 participants must have LP during screening.

[c] Part 1 assessments for the remainder of treatment and follow-up are in Table 9.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Viral serology panel includes: HIV (-1 or -2 antibody and antigen), hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, and hepatitis C antibody/RNA. Participants with a positive hepatitis C virus antibody will be allowed if hepatitis C RNA is negative.

[f] Height and weight will be measured at screening; weight will also be measured at all other indicated timepoints.

[g] Perform/collect prior to dosing.

[h] Vital signs include temperature, respiratory rate, pulse rate, and systolic and diastolic BP while the participant is at rest in a supine position for at least 3 minutes. Heart rate and BP measurements should be obtained with a validated digital monitoring device where available and an appropriately sized cuff. The same arm should be used for all BP measurements if possible. Heart rate and BP should not be measured unless 15 minutes have passed since the last blood draw.

[i] Perform/collect prior to dosing and at the end of the infusion. Vital signs will be collected and concomitant medications and AEs documented prior to and at the end of infusion. Triplicate ECGs will be performed at screening, and predose and 60 to 90 minutes after the end of infusion on Day 1 and Week 5. On dosing visits, serum PK samples will be collected predose, within 15 minutes after the end of infusion, and 60 to 90 minutes after the end of infusion. On non-dosing visits, serum PK samples may be collected at any time during the visit.

[j] Complete PE includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, rectal, and genitourinary exams should be performed as clinically indicated.

[k] Includes any medication (eg, prescription drugs, herbal or homeopathic products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications) used by a participant from 14 days prior to initiation of study drug to the SFU/ET visit.

[l] Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit and Day 1 Visit. Participants who have provided consent to participate in the optional Tau PET imaging, optional longitudinal Amyloid PET imaging (if applicable), optional LP for CSF collection (if applicable) and/or optional WLSA will be randomized prior to the Predose Baseline Visit. Participants who will not be participating in the optional assessments will be randomized prior to the Day 1 Visit.

[m] AEs, AESI, and SAEs will be assessed after the participant signs the informed consent until the end of study participation. Any unresolved AEs, AESI, and SAEs will be followed up through resolution or return to baseline. Additionally, SAEs considered related to study drug, [^{18}F]MK-6240 radiotracer which occur at any time during the study will be reported until resolution, participant withdrawal of consent, loss to follow-up, or death, whichever is applicable. Definitions describing what is and is not considered an AE are provided in Section 7.1.

[n] Triplicate 12-lead ECGs will be obtained approximately 1-3 minutes apart and before blood draws (predose) on appropriate days. Each ECG must be performed after the participant has been resting (supine) for at least 10 minutes.

[o] A WOCBP must have a negative serum pregnancy test at screening. Additional blood or urine tests will be performed for further confirmation of nonchildbearing potential if required by local regulations, guidelines, or the institutional review board/independent ethics committee.

[p] Urine pregnancy test (for WOCBP only) and vital signs will be performed and concomitant medications and AEs will start being collected at the Predose Baseline Visit and subsequent visits for those participants participating in a Tau PET scan.

[q] Hematology includes hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cells, red blood cells, platelet count, and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils, other cells).

[r] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, calcium, glucose, bicarbonate, albumin, total protein, creatinine, hemoglobin A1c, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, phosphorus, total bilirubin (direct and indirect), amylase, cholesterol (total, low-density lipoprotein, high-density lipoprotein), triglycerides, uric acid, creatine phosphokinase, lactate dehydrogenase, magnesium, and C-reactive protein.

[s] Urinalysis: dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic analysis in the event of abnormal dipstick results (urinary sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria).

[t] Coagulation panel includes prothrombin time with international normalized ratio and activated partial thromboplastin time.

[u] Screening MRI is to occur as close to the beginning (Day -78) of the screening window as possible and at least 10 days prior to randomization. Confirmation of COA scores for eligibility must be received prior to performing the MRI.

[v] Perform COAs prior to any potentially stressful procedure (eg, blood collections, LPs, imaging). The ADCOMS is not a scale that is administered; it is a composite measurement that combines items from the MMSE, ADAS-Cog13, and CDR.

[w] Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A corresponding additional PK sample should be obtained at the same timepoint.

[x] Participant must have a high or intermediate score on the PrecivityAD™-Aβ blood test prior to proceeding with either the Amyloid PET or CSF studies for confirmation of cerebral Aβ pathology. Confirmation of amyloid pathology by Amyloid PET or CSF pTau/Aβ42 ratio is required, as described in Inclusion Criterion 1 (see Section 4.1). Participants with a positive historical Amyloid PET scan that has been collected ≤24 months prior to the start of screening and meets the acceptable

criteria for a historical Amyloid PET scan as outlined in Inclusion Criterion 5 will not be tested by PrecivityAD™-Aβ blood test. Participants with a validated, positive historical Amyloid PET scans are considered positive for cerebral Aβ pathology without further testing. Participants with a positive historical CSF measurement may forego the PrecivityAD™-Aβ blood test and confirmatory Amyloid PET or CSF pTau/Aβ42 measurement, if approved by the Medical Monitor.

[y] Other targeted genomic variants will include TREM2 variants, CD33 variants, TMEM106b variants, and CLUSTERIN variants.

[z] Screening for amyloid positivity. Positivity on either Amyloid PET or CSF pTau/Aβ42 is sufficient. Confirmation of COA scores for eligibility must be received prior to performing Amyloid PET scans.

[aa] An LP should not be performed on the same day when COAs are performed. Participants will be required to stay in the clinic or hospital for a minimum of 30 minutes after the procedure for SFU. LPs performed during screening or will be performed at least 5 days prior to the expected D1 dosing visit or randomization (whichever is sooner). Confirmation of COA scores for eligibility must be received prior to performing the LP.

[bb] Part 1 participants must have LP during screening.

[cc] For participants in countries where local regulations allow, baseline (optional) Tau PET imaging should be performed prior to Day -1 only after a participant has demonstrated eligibility for study participation, based on completion of all other screening assessments. Participants who receive an optional Tau PET scan at baseline will receive 1 or more repeated scans after beginning study drug. PET imaging is allowed outside of the standard visit window by ±14 days.

[dd] Optional WLSA Assessments (for English-, French-, Spanish-, or German-speaking participants who agree to participate in the optional assessments) will be administered at the clinic during the Predose Baseline Visit, every 24 weeks following commencement of dosing, and at the end of study (or the ET visit). For participants who consent to at-home WLSA, all other assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments). At-home WLSA assessments will be conducted within the 7 days prior to a treatment assessment visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the final visit.

[ee] If an LP and an MRI are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements. If an LP and a PET scan are performed in the same visit, either (a) the LP should be performed first or (b) the LP should be performed at least 12 hours after the PET scan. Participants who undergo both Tau PET and Amyloid PET exams at a given study visit must receive these exams on different calendar days. Participants who are electing to undergo longitudinal Amyloid PET imaging will require a new Amyloid PET at screening or at the Predose Baseline Visit; historical Amyloid PET scans may not be used for as part of longitudinal Amyloid PET imaging. Tau PET scans or Amyloid PET scans should not be performed if local restrictions for radiation exposure would be exceeded; if applicable, the site should contact the Sponsor to discuss alternative timing of Tau PET or Amyloid PET exams.

[ff] If a participant has not yet reached Week 3 (Day 15), the MRI should be conducted at the Day 15 visit. If the participant has passed Week 3 (Day 15) the MRI should be conducted at an unscheduled visit at least 5 days before the second dose at Week 5. MRI results must be received from the central imaging vendor prior to dose administration at Week 5. Participants with MRI evidence of ARIA will be discontinued from study drug administration but should remain in the study for future study visits. If a participant opts into longitudinal Amyloid PET imaging, only a single Amyloid PET exam should be performed prior to dosing on Day 1. A screening Amyloid PET scan may be used both for study inclusion and as the baseline scan for longitudinal Amyloid PET imaging only if the screening Amyloid PET scan was not a historical Amyloid PET scan. If the screening Amyloid PET scan was historical and collected prior to the screening period, the participant will be required to undergo a new Amyloid PET scan at the screening or Predose Baseline Visit. PET imaging is allowed outside of the standard visit window by ±14 days. Visits may be conducted over 2 consecutive days.

[gg] At the discretion of the Sponsor the screening period may be extended to accommodate delays for reasons including but not limited to COVID-19, laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.

Table 9: Schedule of Assessments – Part 1 (Study Week 9 and Following) and Part 2 (All Visits)

Study Period	**Screening (Days -78 to -23)[ss]**	**Predose Baseline (Days -22 to -1)**	**Treatment**																									**Follow-up**		
Study Week[a]			**1 (D1)**	**3 (D15)**	**5 (D29)**	**9 (D57)**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65 and 69**	**73**	**77**	**81**	**85**	**89 and 93**	**97**	**EFU/4 weeks[qq]**	**SFU/8 weeks[d]**	**ET[c]**
Visit Window[oo]			**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**
	Part 2 only		**For participants randomized under Parts 1 and 2**																										
Informed consent[e]	x																												
Demographic data	x																												
Medical history, social history and baseline conditions	x																												
Viral serology[f]	x																												
Height and weight[g,h]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Vital signs[i,j]	x	x[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[l]	x	x[l]
Complete PE[h,m]	x																											x	x
Limited PE[h,m,n]							x				x						x						x						
Neurological examination[h]	x						x				x						x						x					x	x
Ophthalmological examination[h]	x							x				x				x					x							x	x
Concomitant medications[j,o]	x	x[k]	x	x	x	x	x[rr]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[l]	x	x[l]
Randomization[p]		x	x																										

Table 9: Schedule of Assessments – Part 1 (Study Week 9 and Following) and Part 2 (All Visits) (Continued)

Study Period	**Screening (Days -78 to -23)[ss]**	**Predose Baseline (Days -22 to -1)**	**Treatment**																									**Follow-up**		
Study Week[a]			**1 (D1)**	**3 (D15)**	**5 (D29)**	**9 (D57)**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65 and 69**	**73**	**77**	**81**	**85**	**89 and 93**	**97**	**EFU/4 weeks[qq]**	**SFU/8 weeks[d]**	**ET[c]**
Visit Window[oo]			**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**
	Part 2 only					**For participants randomized under Parts 1 and 2**																								
Study drug administration			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Adverse events[j,q]	x	x[k]	x	x	x	x	x[rr]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[l]	x	x
ECG (triplicate)[j,r,pp]	x		x		x		x			x						x							x					x	
Pregnancy test (if applicable)[s]	x	x[k]														x[k]					x[k]						x[t]	x[t]	x[t]
Thyroid function	x																													
Folic acid and vitamin B12 levels	x																													
Hematology[h,u] and chemistry[h,v]	x		x				x				x			x			x							x				x	x
Coagulation[h,w]	x														x					x[nn]									x
Urinalysis[h,x]	x		x								x						x						x					x	x
C-SSRS[h]			x							x						x					x		x			x	x[y]	x	x[y]
MRI (safety, PD)[h,ll]	x[z]				x	x	x			x						x					x					x			
CDR[h,aa]	x									x						x					x					x	x[y]		x[y]
MMSE[h,aa]	x									x						x					x					x	x[y]		x[y]

Table 9: Schedule of Assessments – Part 1 (Study Week 9 and Following) and Part 2 (All Visits) (Continued)

Study Period	Screening (Days -78 to -23)[ss]	Predose Baseline (Days -22 to -1)	Treatment																									Follow-up		
Study Week[a]			1 (D1)	3 (D15)	5 (D29)	9 (D57)	13	17	21	25	29	33	37	41	45	49	53	57	61	65 and 69	73	77	81	85	89 and 93	97	EFU/4 weeks[qq]	SFU/8 weeks[d]	ET[c]
Visit Window[oo]			±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
	Part 2 only		For participants randomized under Parts 1 and 2																										
ADAS-Cog13[h,aa]			x							x						x					x					x	x[y]		x[y]
RBANS-Update[h,aa]	x									x						x					x					x	x[y]		x[y]
ADCS-ADL-MCI[h,aa]			x							x						x					x					x	x[y]		x[y]
Serum PK sample(s)[j, bb]			x	x	x	x	x	x		x			x			x			x		x			x		x		x	x
Serum sample for ADA[h,bb]			x	x		x		x		x			x			x			x		x			x		x		x	x
Plasma sample for PD biomarkers[h]	x		x	x	x	x	x	x		x			x			x			x		x			x		x		x	x
PrecivityAD™-Aβ blood test[kk]	x																													
Whole blood sample for mRNA[h]			x	x						x						x										x			x
Blood sample for WGS[h]			x																											
APOE e4 testing	x																													
Whole blood sample for other targeted genomic variants[h,cc]			x																											

Table 9: Schedule of Assessments – Part 1 (Study Week 9 and Following) and Part 2 (All Visits) (Continued)

Study Period	Screening (Days -78 to -23)[ss]	Predose Baseline (Days -22 to -1)	Treatment																									Follow-up		
Study Week[a]			1 (D1)	3 (D15)	5 (D29)	9 (D57)	13	17	21	25	29	33	37	41	45	49	53	57	61	65 and 69	73	77	81	85	89 and 93	97	EFU/4 weeks[qq]	SFU/8 weeks[d]	ET[c]
Visit Window[oo]			±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
	Part 2 only		For participants randomized under Parts 1 and 2																										
Amyloid PET[dd,ll,mm]	x																												
LP for CSF pTau/Aβ42[ff,ll]	x																												
LP for CSF (mandatory for Part 1; optional for Part 2 participants)[ff,ll,mm]		x[gg]														x					x						x[ee]		x[ee]
Tau PET (optional)[k,hh,ll]		x														x					x						x[ii]		x[ii]
Longitudinal Amyloid PET (optional)[k,ll,mm]	x	x														x											x[ii]		x[ii]
WLSA[ij,aa] (optional)		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[l]		x[l]

Aβ=amyloid beta; AB42=amyloid beta 1-42; ADA=anti-drug antibody (-ies); ADAS-Cog13=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS=Alzheimer's Disease Composite Score; ADCS ADL-MCI=Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment Scale; AE=adverse event; AESI=adverse event of special interest; APOE e4=apolipoprotein E epsilon4; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CD33=sialic acid-binding Ig-like lectin 3; CDR=Clinical Dementia Rating; COA=clinical outcome assessments; CSF=cerebrospinal fluid; d or D=day; ECG=electrocardiogram; ET=early termination; EFU=efficacy follow-up; FU=follow-up; Ig=immunoglobulin; LP=lumbar puncture; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; mRNA=messenger RNA; PD=pharmacodynamic(s); PE=physical examination; PET=positron emission tomography; PK=pharmacokinetic(s); pTau=phosphorylated tau; RBANS-Update=Repeatable Battery for the Assessment of Neuropsychological Status-Update; RDVF=Research Diagnostic Verification Form; SAE=serious adverse event; SFU=safety follow-up; TMEM106b=transmembrane protein 106b; TPTD=treatment period termination date; TREM2=triggering receptor expressed on myeloid cells 2; WGS=whole genome sequencing; WLSA=Winterlight Labs Speech Assessment; WOCBP=woman of childbearing potential.

[a] Study Day number and Study Week number begin with 1 on the day of the first administration of study drug.

[b] The Predose Baseline Visit for Part 2 is optional and will add up to 21 days to the duration of study participation for those participants participating. This visit will be performed for (1) participants participating in the optional Tau PET imaging procedures in order to schedule and perform PET imaging prior to Day -1 or WLSA assessment, and for (2) participants who do not receive an LP for CSF sampling (optional) during the screening period for eligibility, but who still wish to provide CSF samples, in order to schedule and perform an LP prior to Day -5 and/or the optional longitudinal Amyloid PET imaging procedure where Amyloid PET was not performed during screening in order to schedule and perform PET imaging prior to Day -1. For Part 1, please see footnote b in Table 8 or details. Participants who will not participate in the optional Tau PET imaging assessments, optional longitudinal Amyloid PET imaging assessments (where applicable) or in the optional WLSA will not have a Predose Baseline Visit. Note: participants who have consented to the optional WLSA may complete the baseline measurement either at the Predose Baseline Visit or prior to dosing on Day 1.

[c] Participants who are withdrawn from the study prior to the TPTD and who will not complete any further study procedures will return to the study for an ET visit.

[d] Participants who complete the planned treatment period will be asked to return to the study site for an SFU visit, unless the participants enroll in the AL002-LTE study. A SFU visit is not needed if a participant enrolls in the AL002-LTE study. Participants who discontinue study drug prematurely should continue attending all visits as outline in the Schedule of Assessments including the EFU (if needed) and the SFU.

[e] Informed consent must be documented before any study specific screening procedure is performed.

[f] Viral serology panel includes: human immunodeficiency virus (-1 or -2 antibody and antigen), hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, and hepatitis C antibody/RNA. Participants with a positive hepatitis C virus antibody will be allowed if hepatitis C RNA is negative.

[g] Height and weight will be measured at screening; weight will also be measured at all other indicated timepoints.

[h] Perform/collect prior to dosing. For all post-screening MRIs, the MRI should occur at least 5 days prior to the next dose administration and no more than 10 days prior to the next dose administration, with results received from the central imaging vendor prior to dosing. Note that the central imaging vendor typically requires 5 business days after receipt of the MRI before sending a BMW to the site. MRIs may be scheduled outside of the prescribed window, with approval from the Medical Monitor. The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA. Participants with MRI evidence of ARIA should be managed according to instructions provided in Table 7.

[i] Vital signs include temperature, respiratory rate, pulse rate, and systolic and diastolic BP while the participant is at rest in a supine position for at least 3 minutes. Heart rate and BP measurements should be obtained with a validated digital monitoring device where available and an appropriately sized cuff. The same arm should be used for all BP measurements if possible. Heart rate and BP should not be measured unless 15 minutes have passed since the last blood draw.

[j] Perform/collect prior to dosing, and at the end of the infusion. Vital signs will be collected and concomitant medications and AEs documented prior to and at the end of infusion. Triplicate ECGs will be performed predose and 60 to 90 minutes after the end of infusion on Day 1, Weeks 5, 13, 25, and 49. On dosing visits, serum PK samples will be collected predose and within 15 minutes after the end of infusion. On the dosing visits for Day 1 and Weeks 1, 5, 9, 13, 25, and 49 serum PK samples will also be collected 60 to 90 minutes after the end of infusion. On non-dosing visits, serum PK samples may be collected at any time during the visit.

[k] Urine pregnancy test (WOCBP only) and vital signs will be performed and concomitant medications and AEs will start being collected at the Predose Baseline Visit and subsequent visits for those participants participating in a Tau PET scan or Amyloid PET scan

[l] Assessment is to be completed only if visit is conducted for another reason (eg, COAs).

[m] Complete PE includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, rectal, and genitourinary exams should be performed as clinically indicated. Limited exams should include cardiovascular, respiratory, and gastrointestinal systems. Symptom-directed PEs may also include any other pertinent system as required.

[n] Perform a limited, symptom-directed PE at specified timepoints or as clinically indicated.

[o] Includes any medication (eg, prescription drugs, herbal or homeopathic products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications) used by a participant from 14 days prior to initiation of study drug to the final study visit.

[p] Participants will be randomized prior to undergoing procedures or assessments at the Predose Baseline Visit and Day 1 Visit. Participants requiring a Predose Baseline Visit will be randomized prior to the Predose Baseline Visit. All other participants will be randomized prior to the Day 1 Visit.

[q] AEs, AESI, and SAEs will be assessed after the participant signs the informed consent until the end of study participation. Any unresolved AEs, AESI, and SAEs will be followed up through resolution or return to baseline. Additionally, SAEs considered related to study drug, [^{18}F]MK-6240 radiotracer which occur at any time during the study will be reported until resolution, participant withdrawal of consent, loss to follow-up, or death, whichever is applicable. Definitions describing what is and is not considered an AE are provided in Section 7.1.

[r] Triplicate 12-lead ECGs will be obtained approximately 1-3 minutes apart and before blood draws (predose) on appropriate days. Each ECG must be performed after the participant has been resting (supine) for 10 minutes.

[s] A WOCBP must have a negative serum pregnancy test at screening. Additional blood or urine tests will be performed for further confirmation of nonchildbearing potential if required by local regulations, guidelines, or the institutional review board/independent ethics committee.

[t] Urine pregnancy test (for WOCBP only) is to be completed only if optional Tau PET imaging is completed at this visit.

[u] Hematology includes hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cells, red blood cells, platelet count, and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils, and other cells).

[v] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, calcium, glucose, bicarbonate, albumin, total protein, creatinine, hemoglobin A1c, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, phosphorus, total bilirubin (direct and indirect), amylase, cholesterol (total, low-density lipoprotein, high density lipoprotein), triglycerides, uric acid, creatine phosphokinase, lactate dehydrogenase, magnesium, and C-reactive protein.

[w] Coagulation panel includes prothrombin time with international normalized ratio, activated partial thromboplastin time. If the lumbar puncture is required for the EFU, the coagulation panel will be performed at the visit immediately preceding the EFU visit within 4 weeks ±5 days.

[x] Urinalysis: Dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic analysis in the event of abnormal dipstick results (urinary sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria).

[y] If COAs have not been performed within 12 weeks, they should be performed at this visit. This applies to the EFU or ET visits.

[z] Screening MRI is to occur as close to the beginning (Day -78) of the screening window as possible and at least 10 days prior to randomization. Confirmation of COA scores for eligibility must be received prior to performing the MRI.

[aa] Perform COAs prior to any potentially stressful procedure (eg, blood collections, LPs, imaging). The ADCOMS is not a scale that is administered; it's a composite measurement that combines items from the MMSE, ADAS-Cog13, and CDR.

[bb] Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A corresponding additional PK sample should be obtained at the same timepoint. Additional optional blood samples for PK will be collected from approximately 64 participants in Part 2 at 4, 8 and 24 (or 48) hours after the end of infusion at Week 25 or 37, or 49.

[cc] Other targeted genomic variants will include TREM2 variants, CD33 variants, TMEM106b variants, and CLUSTERIN variants.

[dd] Screening for amyloid positivity. Positivity on either Amyloid PET or CSF pTau/Aβ42 is sufficient. Confirmation of COA scores for eligibility must be received prior to performing Amyloid PET scans.

[ee] If CSF has been drawn within 12 weeks, it should not be drawn at this visit. This applied to the EFU or ET visits. Participants who discontinue due to ARIA may be requested to have an LP per Investigator discretion. LP should be performed at the SFU visit if needed.

[ff] LP should not be performed on the same day when COAs are performed. Participants will be required to stay in the clinic or hospital for a minimum of 30 minutes after the procedure for SFU. LPs performed during screening will be performed at least 5 days prior to the expected D1 dosing visit or randomization (whichever is sooner). LP should not be performed unless results from coagulation laboratory assessments were within clinically acceptable limits within 4 weeks±5 days.

[gg] Part 2 participants who do not receive a LP during the screening period for eligibility, but agree to participate in the optional CSF sampling, a Predose Baseline Visit will occur to schedule and perform an LP prior to Day -5. Confirmation of COA scores for eligibility must be received prior to performing the LP.

[hh] For participants in countries where local regulations allow, baseline (optional) Tau PET imaging should be performed prior to first dosing with study drug only after a participant has demonstrated eligibility for study participation, based on completion of all other screening assessments. In some cases, the initial (baseline) Tau PET scan may be performed after study drug has commenced. Sponsor agreement will be needed for baseline Tau PET scans occurring after dosing has commenced. Participants who receive an optional Tau PET scan at baseline will receive 1 or more repeated scans after beginning study drug.

[ii] If Tau PET has been performed within 24 weeks, it should not be repeated at this visit. If Amyloid PET has been performed within 24 weeks, it should not be repeated at this visit. This applies to both the EFU and ET visits.

[jj] Optional WLSA Assessments (for English-, French-, Spanish-, or German-speaking participants who agree to participate in the optional assessments) will be administered at the clinic during the Predose Baseline Visit, every 24 weeks following commencement of dosing, and at the end of study (or the ET visit). For participants who consent to at-home WLSA, all other assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments). At-home WLSA assessments will be conducted within the 7 days prior to a treatment assessment visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EFU visit.

[kk] Participant must be amyloid positive by the PrecivityAD™-Aβ blood test prior to proceeding with either the Amyloid PET or CSF studies for confirmation of cerebral Aβ pathology. Confirmation of amyloid pathology by Amyloid PET or CSF pTau/Aβ42 ratio is required, as described in Inclusion Criterion 1 (see Section 4.1). Participants with a positive historical Amyloid PET scan that has been collected ≤24 months prior to the start of screening and meets the acceptable criteria for a historical Amyloid PET scan as

outlined in Inclusion Criterion 1b will not be tested by PrecivityAD™-Aβ blood test. Participants with validated, positive historical Amyloid PET scans are considered positive for cerebral Aβ pathology without further testing. Participants with a positive historical CSF measurement may forego the PrecivityAD™-Aβ blood test and confirmatory Amyloid PET or CSF pTau/Aβ42 measurement, if approved by the Medical Monitor.

[ll] If an LP and an MRI are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements. If an LP and a PET scan are performed in the same visit, either (a) the LP should be performed first or (b) the LP should be performed at least 12 hours after the PET scan. Participants who undergo both Tau PET and Amyloid PET exams at a given study visit must receive these exams on different calendar days. Participants who are electing to undergo longitudinal Amyloid PET scanning will require a new Amyloid PET at screening or at the Predose Baseline Visit; historical Amyloid PET scans may not be used for as part of longitudinal Amyloid PET scanning. Tau and Amyloid PET imaging is allowed outside of the standard visit window by ±35 days. Extensions for PET imaging beyond that window may be permitted, at the discretion of the Sponsor. Tau PET scans or Amyloid PET scans should not be performed If local restrictions for radiation exposure would be exceeded; if applicable, the site should contact the Sponsor to discuss alternative timing of Tau PET or Amyloid PET exams.

[mm] If a participant opts into longitudinal Amyloid PET imaging, only a single Amyloid PET exam should be performed prior to dosing on Day 1. A screening Amyloid PET scan may be used both for study inclusion and as the baseline scan for longitudinal Amyloid PET imaging only if the screening Amyloid PET scan was not a historical Amyloid PET scan. If the screening Amyloid PET scan was historical and collected prior to the screening period, the participant will be required to undergo a new Amyloid PET scan at the screening or Predose Baseline Visit. PET imaging is allowed outside of the standard visit window by ±14 days.

[nn] Only required at Week 69

[oo] Visits may be conducted over 2 consecutive days

[pp] Triplicate ECG tracings from Day 1 and Week 25 or Week 49 for approximately 100 consecutive participants will be read by a core ECG laboratory (Note: Central ECG reads may not occur in real time; thus, these results will not be used for safety assessments during study conduct.). Results from centrally read ECG's will not be captured in the eCRF.

[qq] Participants who complete the planned treatment period, whether dosing was completed, prematurely discontinued or paused, may return to the study site for an EFU visit, unless the participants enroll in the AL002-LTE study. An EFU visit is not needed if a participant enrolls in the AL002-LTE study.

[rr] All participants will receive a phone call around Day 43 (between the second and third dose) and around Day 71 (between the third and fourth dose) and be assessed open-endedly for AEs and any concomitant medication. Based on emerging data, the titration schedule may be modified; if the titration schedule is modified, the AE phone call visits may be modified to appropriately monitor for ARIA and potential symptoms. Based on AE assessment, further follow-up may be needed, including an unscheduled visit, to assess for subtle symptoms or neurological signs

[ss] At the discretion of the Sponsor, the screening period may be extended to accommodate delays for reasons including but not limited to COVID-19, laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.

14.2. Appendix 2: Clinical Outcome Assessments - Neurocognitive and Functional Tests

14.2.1. Clinical Dementia Rating

Washington University's CDR is a global assessment instrument that yields a global score, which is weighted towards memory (eg, CDR-GS). The CDR-SB score is a quantitative general index that provides more precision than the CDR-GS in participants with mild dementia (O'Bryant 2010). The CDR characterizes 6 domains of cognitive and functional performance applicable to AD and related dementias: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the participant and a reliable informant or collateral source (the study partner). Details of the CDR, including the algorithm used to compute the CDR-GS, can be found at the website: http://knightadrc.wustl.edu/cdr/aboutcdr.htm.

14.2.2. Mini-Mental Status Examination

The MMSE (Folstein 1975) is a brief test used to screen for cognitive impairment. It is routinely used for estimating the severity of cognitive impairment and tracking cognitive changes in an individual over time. The MMSE assesses orientation (time and place), registration, attention and calculation, recent memory, language (naming, comprehension, and repetition), and constructional praxis (copying a figure). The maximum total score is 30, with a higher score indicating better cognitive performance.

14.2.3. Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS-Update (Randolph 1998) is a collection of 12 subtests representing 5 neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The raw scores from each subtest within a domain are converted to a summary score, or Index Score, for the domain by consulting normative data tables. The RBANS-Update also provides an overall Index Score that summarizes the participant's overall level of performance on this measure.

14.2.4. Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-Cog is one of the most frequently used tests to measure cognition in clinical trials for AD. The ADAS-Cog13 is a 13-item version of the test that assesses immediate and delayed memory, confrontational naming, ability to follow commands, ideational and constructional praxis, orientation, language, and attention.

14.2.5. Alzheimer's Disease Cooperative Study-Activities of Daily Living – Mild Cognitive Impairment Scale

The ADCS-ADL-MCI assesses the competence of participants with AD in basic, instrumental, and complex activities of daily living; this scale is administered to the study partner.

14.2.6. Alzheimer's Disease Composite Score

The Alzheimer's Disease Composite Score (ADCOMS) (Wang 2016) is a composite measure comprising 4 items from the ADAS-Cog13, 2 items from the MMSE, and the 6 individual domain scores from CDR (Wang 2016). The ADCOMS has shown improved sensitivity to clinical decline in the Early AD dementia populations. The ADCOMS score will be derived from the scores on other COAs described in this section; there is no separate scale to administer to participants or study partners. Details of the ADCOMS can be found at the website: https://www.ncbi.nlm.nih.gov/pubmed/27010616.

14.2.7. Optional Winterlight Lab Speech Assessment

The optional WLSA is for all participants who are proficient in and from an English-, French-, German-, or Spanish-speaking country and who agree and are eligible to participate in these optional assessments. Participants may opt in to at-home and in-clinic assessments, or in-clinic only.

If the participant and study partner are eligible, agree to, and provide consent for this optional assessment, WLSA procedures will be performed at-home and/or in-clinic, as detailed in the Schedules of Assessments (Section 14.1).

14.2.7.1. Winterlight Lab Speech Assessment Overview

The WLSA was developed to evaluate speech, language, and cognition using short samples of speech. Winterlight's software decomposes a speech sample into over 500 individual markers. These markers quantify both the acoustic and linguistic properties of the speech. Acoustic markers describe properties of the sound wave itself such as tone, speaking rate, pausing (both filled and unfilled), pitch, and spectral power. Linguistic markers are extracted from the content of speech (eg, transcripts) and include the frequency of different parts of speech (such as nouns, verbs, pronouns, and prepositions) as well as more global measures of discourse coherence and the complexity of syntax and grammar.

To standardize the content of each speech sample and ensure that sufficient speech is collected, the WLSA records participants' responses to a series of standard speech and language tasks. While these tasks provide consistent participant matter, they also provide their own task-specific indices of performance. The WLSA leverages both these task-specific outcomes as well as task-independent markers to evaluate an individual's cognitive performance.

The WLSA is administered using a device that presents assessment questions and records audio of the participant. It is composed of various established aspects from paper/interview-based assessments, including picture description, story recall, and object recognition.

Assessments will be administered at the clinic during the Predose Baseline Visit, every 24 weeks following the commencement of dosing, and at the end of study (ET visit). Assessments will be conducted at home every 4 weeks (with the exception of the predefined in-clinic assessments), within 7 days prior to a treatment administration visit. Assessments will be supervised by the study partner.

14.3. Appendix 3: Management of Infusion-Related Reactions

Monoclonal antibodies such as AL002 may be associated with the potential risk for infusion-related reactions. Acute infusion-related reactions typically occur within 24 hours of infusion and may manifest as erythema, pruritis, fever, or chills and progress to an anaphylactic-type reaction. Clinical sites should be prepared to manage any acute hypersensitivity or hypersensitivity-like events. All participants will be monitored for infusion reactions or injection reactions during the infusion/injection and immediately afterwards.

Table 10 provides guidelines on management of acute infusion reactions as well as management of subsequent dosing instructions.

Table 10: Guidelines for Management of Acute Infusion-Related Reactions

CTCAE Toxicity Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Stop infusion and monitor symptoms. If symptoms resolve without intervention, the infusion may be restarted at 50% of the original infusion rate.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, and antipyretics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve following supportive treatment, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. If IRR occurs during titration (ie, at first or second dose) next dose should be administered at 50% of the original infusion rate. Participants who develop Grade 2 toxicity despite adequate premedication and infusion rate reduction should be permanently discontinued from further trial treatment administration.	Participant should be premedicated prior to next dose of study drug with antihistamine (eg, diphenhydramine 50 mg po) and antipyretic (eg, acetaminophen / paracetamol 500-1000 mg po).
Grades 3 or 4 Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequalae Grade 4: Life-threatening consequences; urgent intervention indicated	Stop infusion and increase monitoring of vital signs as medically indicated. Additional appropriate medical therapy may include but is not limited to IV fluids, IV steroids (eg, hydrocortisone 100-200 mg or corticosteroid equivalent), IV antihistamines, vasopressors, and antipyretics. Hospitalization may be indicated. Participants with signs or symptoms that may be consistent with cardiac etiology should be assessed by ECGs, cardiac enzymes (eg, creatinine-MB isoenzyme, troponins, brain natriuretic peptide) to rule out myocardial infarction, and echocardiogram should be performed unless cardiac failure is ruled out by preceding investigations. Participant is permanently discontinued from further trial treatment administration.	Any participant with a serious Grade 3 or any Grade 4 event will not be permitted to re-dose. Any subsequent redosing of nonserious Grade 3 events must be discussed and approved by the Medical Monitor.

CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; IRR=Infusion-related reaction; IV=intravenous; MB=myocardial band; NSAIDs=non-steroidal anti-inflammatory drugs; po=orally.

14.4. Adaptation of Trial Protocol During COVID-19 Pandemic

14.4.1. Background

The COVID-19 pandemic has caused significant disruption, globally. The public health emergency will have an impact on the conduct of global clinical research activities. The safety and well-being of study participants, personnel involved in clinical studies, and colleagues across the globe is of primary importance. Alector is closely monitoring the situation and will continue to align clinical study execution with guidance from the World Health Organization and the US Centers for Disease Control as appropriate, conducting ourselves in accordance with all applicable national, regional, and local government and public health authority requirements.

Alector made a decision to initiate and continue patient participation in the AL002-2 study at the discretion of the Principal Investigator, and in accordance with current health authority guidelines and recommendations for each site's region/country regarding the COVID-19 pandemic. The safety of the participants and site staff continue to be paramount in their continuation within the study.

An ongoing collaborative risk review which includes analysis of COVID-19 restrictions as they impact participant safety, study and data integrity, and impact on program timelines continues to be assessed. The review has been and will continue to be conducted regularly and will take into consideration any new information regarding the pandemic and ongoing, continuous assessment of adverse events reported.

14.4.2. Implementation of COVID-19 Procedures

The implementation of adaptations to visits and procedures detailed within this appendix only apply under the exceptional circumstance of the COVID-19 pandemic. Procedures apply to those sites which have been impacted by the pandemic through restrictions to movement, study site restrictions and where the safety of the participant may be impacted through attendance at hospital for on-site visits.

The implementation will be determined on a site-by-site basis dependent on local requirements and will be reviewed on a regular basis with the Sponsor to confirm the continued need for implementation. Every effort should be made to follow the Clinical Study Protocol; however, for clarity additional instructions are provided below. Where applicable, study specific instructions will be communicated separately.

14.4.3. Study Screening Period

Every effort should be made to complete the screening assessment per the Schedules of Events detailed in Table 8 and Table 9. At the discretion of the Sponsor the screening period may be extended to accommodate delays for reasons including but not limited to COVID-19, laboratory delays, and difficulties scheduling MRI or PET scans. Sponsor approval must be obtained for all screening extensions and the Sponsor will determine whether any screening tests must be repeated.

14.4.4. Essential On-Site Assessments and Remote Visits (Via Phone or Video)

Continuation of the study during the pandemic does, and may continue to, impact the ability of some sites to conduct all protocol assessments per the Schedules of Assessments detailed in Section 14.1. This is due to reduced time for on-site visits, limited or no availability of some services at site, or the need to conduct visits remotely via telephone or via televisit (if approved locally).

The primary objective with any change to the study schedule is to ensure ongoing monitoring of participant safety.

14.4.4.1. On-site Essential Assessments

Where possible, all protocol assessments and treatments should be completed.

To accommodate reduced time on site during study visits, the following reduced assessments schedule should be completed as a minimum:

- Vital signs, weight, physical, ophthalmological and neurological examinations
- Phlebotomy and urinalysis, including pregnancy test
- ECGs
- Collection of AEs and concomitant medications
- C-SSRS
- Study drug administration
- MRI
- PET imaging
- Biofluid collection for PD Biomarkers (CSF or blood). In the case of LPs for CSF collection, a normal coagulation result must be available prior to taking the lumbar puncture.

14.4.4.2. Remote Essential Assessments (Telemedicine or Televisits)

If participants or raters are not able to come to the study site for a visit, the following assessments should be completed by telephone or video (if locally approved/allowed):

- Review of AEs and concomitant medications
- Review of medical history
- The COAs listed below can be completed remotely via telephone by qualified raters:

1. **Clinical Dementia Rating – Sum of Boxes (CDR-SB)**
   While it is strongly preferred that participants and caregivers receive administration of the CDR-SB in person, it is understood that remote administration might be required due to extenuating circumstances. The CDR-SB can be administered telephonically or by locally approved video conference capabilities.
   - **Recommendation:** Remote administration by phone has been validated for the 6 domains of the CDR-SB (Randolph 2014).
   - In the circumstance that the primary rater is remote, and the participant and back-up rater are on site, scales can still be administered by the primary rater. The primary rater should call in to the visit to administer the CDR-SB questions over the phone. The back-up rater should observe the participant while they are answering the questions, and then provide observations of the participant behavior to the primary rater. Missing data from direct observation, which cannot be provided by the primary rater, can be completed by the back-up rater, as long as they are appropriately trained on the scale. Final observational assessments should be made by the primary rater.
2. **Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment Scale (ADCS-ADL-MCI)**
   - **Recommendation:** As a clinician-administered interview with the caregiver, the ADCS-MCI-ADLI can be administered in person in the clinic, in home, or telephonically.
   - In the circumstance that the primary rater is remote, and the participant and back-up rater are on site, scales can still be administered by the primary rater. The primary rater should call in to the visit to administer the ADCS-ADL-MCI questions over the phone. The back-up rater should observe the caregiver (study partner) while they are answering the questions, and then provide observations of caregiver behavior to the primary rater. Missing data from direct observation, which cannot be provided by the primary rater, can be completed by the back-up rater, as long as they are appropriately trained on the scale. Final observational assessments should be made by the primary rater.
3. **Columbia-Suicide Severity Rating Scale (C-SSRS)**
   - **Recommendation:** This assessment can be administered to the participant by a clinician via phone.

The remote assessments would be administered by the qualified site staff authorized to perform the procedures above. The following general guidelines for administering scales telephonically or by video conference should be followed:

- Always record on the notes page of the scale or in your source documents when a certain assessment was administered remotely and describe any accommodations made.

- Ensure that scale administration guidelines indicated in the scale manual and tutorial are carefully followed when adapted for use via telephone.
- Raters are encouraged to consider and address possible distractions which could affect performance during an assessment. This includes forms of distraction that may not be obvious or visible (eg, sight, sound, and smell). Consider the quality of the telecommunication technologies being used and the hardware requirements needed in order to conduct the specific assessment (eg, a telephone with speakerphone).
- Always use the speaker phone for the scales that should be recorded for Independent Review.
- Scales should be administered as if informant (rater) and/or participant/caregiver were face-to-face with the rater and should be administered in a quiet, distraction-free interview environment.
- Generally, patient reported outcomes and observer reported outcomes cannot be administered over the telephone unless they are used in your study as "Clinician Read".
- There may be situations in which study partners or raters are remote. In these cases, the following guidance should be followed:
  - If the study partner/caregiver is remote and the participant is on site, scales can be administered per procedure, with study partner/caregiver providing answers to the site rater.
  - If the primary rater is remote, and the participant and back-up rater are on site, scales can still be administered by the primary rater. The back-up rater can be used to provide observational information to the primary rater, provided that they are trained on the scale. Refer to additional guidance under CDR, ADCS-ADL-MCI, and C-SSRS sections.

Please note that some scales requiring participant performance, like drawing or writing, are not validated for remote administration and **may not be administered via telephone** (ie, ADAS-Cog13, MMSE, and RBANS-Update).

14.4.5. On-Site Assessments Unable to be Completed at Scheduled Visits

In the event that a scheduled assessment is unable to be completed at site, eg, limited availability/restriction of equipment (eg, MRI), participant limited time on site or because a remote visit was completed, the following assessments may be completed at the **next** scheduled on-site visit:

- Clinical laboratory assessments, including urinalysis
- ECGs
- COAs not approved for remote administration
- MRI
- PET imaging

- Biofluid collection for PD Biomarkers (CSF or blood). In the case of LPs for CSF collection, a normal coagulation result must be available prior to taking the lumbar puncture.

The approval of the Medical Monitor must be obtained prior to completion of these moved assessments.

14.4.6. COVID-19 Reporting

In the event where a study participant is diagnosed with COVID-19 infection, the local health authority recommendations regarding treatment should be followed and the event should be reported as an AE/SAE depending on the severity of infection and diagnosis. Refer to Section 7 of the protocol.

14.4.7. Remote Consent

Sponsor will provide a simple downloadable consent that will enable qualified site staff to consent a participant to complete televisits. Where it is allowed by country/site regulations, a remote eConsent will be provided that allows a participant to be remote from the site and participate in the consent process.

14.4.8. Remote Source Document Verification

Remote source document verification will be employed **only** in the following circumstance:

- National law, Regulatory Authorities and IRB/IEC permit this process and approval is obtained.
- On-site clinical research associated (CRA) visits are not permitted due to continued COVID-19 restrictions.
- There is a need to complete source document verification for the following reasons:
  - Study Data assessment review of critical study milestones (eg, database lock)
  - Participant safety.
  - A significant backlog of data monitoring that could impact data integrity or participant safety.

Prior to commencing remote source document verification, the following documentation must be completed:

- The Site CRA will complete a confidentiality agreement committing to securely destroy any copies of documents received from sites (paper or electronic), nor take any recording during video access.
- Remote SDV will only be completed for participants who have consented to allow access to their health records remotely.

Document Approvals

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Approval Task Verdict: Approve	Gary Romano, [redacted] Management Approval 23-Jun-2023 19:34:57 GMT+0000