A MULTICENTER, LONG-TERM EXTENSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF AL002 IN PARTICIPANTS WITH ALZHEIMER'S DISEASE

Protocol Number:	AL002-LTE
Current Version Number:	2.0
Replaces Version Number, Date:	1.0, 30 August 2022 (Global) 1.1, 25 August 2023 (European Union [EU]/ European Economic Area [EEA] Only)
Name of Investigational Product:	AL002
Developmental Phase of Study:	Phase 2
Indication:	Alzheimer's Disease (AD)
Sponsor:	Alector, Inc. 131 Oyster Point Blvd, Suite 600 South San Francisco, CA 94080 US
IND Number:	136758
EudraCT Number:	2022-002987-57
EU CT Number:	2023-506872-29-00
Approval Date:	12 January 2024

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

PROTOCOL SIGNATURE PAGE

A Multicenter, Long-Term Extension Study to Evaluate the Safety, Tolerability, and Efficacy of AL002 in Participants with Alzheimer's Disease

Study Number: AL002-LTE

Version: 2.0

Date of Issue: 12 January 2024

Signature of Approval for Protocol (AL002-LTE Version 2.0)

Name	Signature	Date
Gary Romano, MD, PhD [redacted] Alector, Inc. 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 Multicenter, Long-Term Extension Study to Evaluate the Safety, Tolerability, and Efficacy of AL002 in Participants with Alzheimer's Disease".

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol AL002-LTE Version 2.0, dated 12 January 2024, 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, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Herein is a summary of the changes made to Version 1.0 of the protocol, dated 30 August 2022, and reflected in the amended Version 2.0 of the protocol, dated 12 January 2024.

Amended Protocol Sections	Summary of Change(s)	Rationale
Throughout	• Revised date and version. • Other typographical, formatting corrections, minor administrative changes, and minor text clarifications. • Updates to the Table of Contents, List of Tables, List of Abbreviations, and References.	Minor changes made to correct errors, conform to revised style standards, and/or reflect updates to the content for version control.
Throughout	• Removed all content related to participant randomization.	Content was inaccurate - participants will not be randomized in this study.
Throughout	• Removed all content related to the Winterlight Labs Speech Assessment and whole genome sequencing.	Assessments will no longer be utilized in this study.
Throughout	• Revised Medical Dictionary for Regulatory Activities (MedDRA) from Version [redacted] • Revised the World Health Organization Drug Dictionary (WHO DD) from March 2019 to September 2022 version.	Revised to most recent versions of regulatory guidance documents.
Throughout	• Revised term "investigational medicinal product (IMP)" to either AL002 or study drug depending on context.	Revised for standardization with parent study protocol, AL002-2.
Throughout	• Previously, triplicate 12-lead electrocardiograms (ECGs) were required; this has now been modified to a single 12-lead ECG.	Revised to reduce patient testing burden.
Title Page	Added EudraCT number and European Clinical Trial Register (EU CTR) number.	Revised for standardization with regulatory requirements.
Synopsis	Reorganization and revision of synopsis.	Revised for clarity and alignment with updated protocol body text.
Section 1.1	• Added content related to approval of Leqembi® (lecanemab) and lack of marketing authorization for AL002. • Content reorganization.	Revised to include availability of new AD therapy with additional reorganization for clarity and for compliance with European Clinical Trials Regulation (EU CTR) for trials conducted in the European Union (EU) and European Economic Area (EEA).

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 1.5	Refinements to content to remove clinical activity information.	Revised for clarity.
Section 2, Section 3.1	• Primary endpoint revised to co-primary endpoints including assessment of dose titration on amyloid-related imaging abnormalities (ARIA) to objectives. • Secondary objectives and endpoints added and now include evaluation of pharmacokinetic (PK) parameters and clinical outcome assessments (COAs). • Exploratory objectives and endpoints were refined, and the COAs are now secondary objectives and endpoints (as noted above). • Added content related to approval of Leqembi® (lecanemab). • Content added to indicate participants were not directly involved in the study design.	Revisions to objectives and endpoints for robustness and accuracy of study outcomes and assessments and compliance with EU CTR for trials conducted in EU/EEA.
Section 3.2	• Expanded content related to Screening/Baseline Visit, with an emphasis on transition from AL002-2 parent study. • Expanded and reorganized content related to treatment period. • Expanded content related to the Early Termination (ET) Visit. • Content added to indicate that no additional care is expected to be required after the study has ended.	Revised for clarity and to provide additional details related to transition of participants from parent study AL002-2 and for compliance with EU CTR for trials conducted in EU/EEA.
Section 4 (Initial Paragraphs)	Removal of redundant content that is now included in Section 3.2.	Revised for clarity and to eliminate redundancy.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 4.1, Section 4.2	• Revised to include detailed criteria for inclusion of female participants in relation to childbearing and contraception and male participants in relation to contraception. • Revised to include criteria related to weight and body mass index (BMI). • Participation in optional assessments removed as inclusion criteria. • Participants taking anticoagulation medications are now excluded from the study. • Participant agrees not to receive any investigational treatment, other than AL002, during the study. • Participants taking any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline are excluded from the study.	Revised for safety and clarity.
Section 4.3.1, Section 4.3.2	Section 4.3.1 is now "Withdrawal from Study Drug" and a new section has been added, "Section 4.3.2 Withdrawal from Study." Criteria for withdrawal were further clarified and placed in the appropriate sections. In addition, content was added to indicate that participants who discontinue will not be replaced and duplicate content re: electronic case report from (eCRF) reporting was eliminated.	Revised for clarification and accuracy of criteria for study drug as well as study withdrawal and participant replacement.
Section 5.1	Content related to the Titration Cohort was revised to indicate that evaluation of dosing and its relationship to safety and ARIA within the Titration Cohort will occur only by unblinded study personnel and the unblinded safety management team at Alector. ARIA monitoring and management will be consistent with the procedures outlined in the parent study.	Revised for clarification and accuracy of evaluation of the Titration Cohort.
Section 5.2.3	Content related to the radiotracer [^{18}F]flutametamol (Vizamyl) was removed.	Will no longer be utilized in the study.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 5.2.4	Content was added to summarize investigational and auxiliary medicinal products used in this study and their authorization status.	Content added for compliance with EU CTR for trials conducted in the EU/EEA.
Section 5.3.5	Content related to storage and disposal was added for the Tau PET radiotracer [^{18}F]MK-6240.	Content added for compliance with EU CTR for trials conducted in the EU/EEA.
Section 5.4.1, Section 5.4.2	Content was revised to indicate that blinding to treatment assignments will be maintained throughout the LTE study by those who are conducting the efficacy assessments, the Investigator, the study staff at the site, study participants, participant study partners, clinical site monitors, CRO, and the Sponsor except in specific circumstances. Minor corrections were also made to Section 5.4.2.	Revised for clarity and accuracy, and to enhance robustness of research outcomes.
Section 6, Section 10.3	Content was added to indicate that some participants may become incompetent during the study due to progression of disease.	Content added for clarity.
Section 6.1	Section now entitled, “Timing of Study Drug Administration and Procedures.”	Revised for clarity and accuracy and to align with Schedule of Assessments.
Section 6.3.3	Years of education will not be collected.	Data not required for study analysis.
Section 6.3.9, Section 14.1	Content related to core ECG laboratory readings have been eliminated.	Revised to align with updated study procedures.
Section 6.5	Section now entitled, “Pharmacokinetic and Anti-Drug Antibody Assessments” and content was reorganized.	Title and content revised for clarity.
Section 6.6	Section now entitled, “Biomarker Assessments” and includes new subsections and reorganized content for “Fluid Biomarker Assessments” and “Imaging Assessments.”	Revised to maintain all content related to biomarkers in a specific location in the protocol for clarity and accuracy.
Section 7 (Initial Paragraph)	Content revised to eliminate statement that any adverse event of special interest (AESI) detected after informed consent but prior to administration of study drug will be considered medical history.	Revised to ensure all safety data is accurately assessed and recorded.
Section 7.1	Content revised to eliminate statement that events of ARIA detected during magnetic resonance imaging (MRI) performed at screening are not adverse events (AEs).	Revised to ensure all safety data is accurately assessed and recorded.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 7.6.5, Section 7.12	Content added for AESI of [redacted]	Information added for monitoring and accurate recording of [redacted].
Section 7.11.2	Table 8 revised to provide additional detail related to specific actions required for monitoring of ARIA.	Revised for accuracy and to ensure participant safety.
Section 8.1	Content added related to slower dose titration has its potential to substantially decrease the incidence of ARIA.	Revised to provide additional detail and clarity related to ARIA and sample size calculations.
Section 8.3.1	Content added to indicate protocol deviations will be summarized.	Revised for clarity and accuracy of evaluations.
Section 8.3.3	Content added to indicate that the effect of dose titration on ARIA will be evaluated.	Revised for clarity and accuracy of evaluations.
Section 8.3.4	Revisions to pharmacokinetic (PK) analyses.	Revised for clarity and accuracy of evaluations.
Section 8.3.6	Section was added detailing methods for immunogenicity analyses.	Revised to provide additional detail and clarity.
Section 8.3.7	Revisions to details regarding the interim analysis.	Revised to provide additional detail and clarity.
Section 9, Section 9.2	Section 9 is now entitled, “Data Quality Assurance and Protection” due to new section added entitled, “Data Protection.”	Revised to add information specifically related to participant data protection for compliance with EU CTR for trials conducted in the EU/EEA.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 14.1	• Serum pharmacokinetic (PK) and plasma samples for biomarkers eliminated at Week 13. • Serum sample for anti-drug antibodies (ADAs) added at Week 5. • Lumbar puncture (LP) will now be performed at [redacted] vs. [redacted] Visit. Per revised footnotes z and aa following the Screening/Baseline Visit, if a participant has an Early Termination (ET) Visit an LP should be performed at that visit. If not, LP should be performed at [redacted]. • Ophthalmological examinations will no longer be required Weeks 9, 25, and 41. • Footnote c revised to provided additional detail for collection of clinical outcome assessments (COAs), LP, and ophthalmological examinations. • Footnote d revised to include information related to examinations required for [redacted] • Footnote i updated to remove ECG information for relocation to footnote p. • Footnote i and w revised to include updated details re: PK blood sample collection. • Footnote l revised to include more detailed information related to neurological examination. • Footnote bb revised to include details related to performance prior to dosing on Day 1/Week 1 unless obtained within 24 weeks before Day 1/Week 1 in study AL002-2. • Footnote cc and dd revised to include clarifying information related to requirements for new Amyloid and Tau PET scans and use of historical/existing scans.	Revised to reduce patient burden and provide clarification.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 14.5	Appendix with "Country-Specific Requirements" was added and includes Germany-specific protocol differences.	Revised to add information specifically related to study conduct in other countries and for compliance with EU CTR for trials conducted in the EU/EEA.

PROTOCOL SYNOPSIS

Protocol Title: A Multicenter, Long-Term Extension Study to Evaluate the Safety, Tolerability, and Efficacy of AL002 in Participants with Alzheimer's Disease

Protocol Number: AL002-LTE

Phase: 2

Indication: Alzheimer's disease (AD)

Objectives and Endpoints:

Primary Objectives	**Primary Endpoints**
To evaluate the long-term safety and tolerability of AL002 in participants with AD	• Incidence of AEs, including AESIs and SAEs • Vital signs, clinical laboratory results, and incidence of findings from physical, neurological, ophthalmological examinations, and ECG • C-SSRS • MRI abnormalities
To evaluate the effect of dose titration on ARIA	• Incidence and severity of ARIA in participants undergoing titration
Secondary Objective	**Secondary Endpoints**
To evaluate the PK of AL002 in participants with AD	• Serum PK concentrations of AL002 and relevant PK parameters
To evaluate the effects of AL002 on COAs in participants with AD	• CDR®-SB • MMSE • RBANS-Update • ADAS-Cog13 • ADCS-ADL-MCI • ADCOMS
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effects of AL002 on biomarkers in participants with AD	• Levels of sTREM2 in CSF and/or plasma • Levels of biomarkers related to microglia function in CSF and/or plasma (eg, CSF1R, IL1RN, osteopontin, YKL40) • Levels of biomarkers related to AD pathology in CSF and/or plasma (eg, Aβ40, Aβ42, pTau, tTau) • Levels of neurodegeneration biomarkers in plasma and/or CSF (eg, NfL) • Brain volume, assessed by volumetric MRI • Brain pathological Tau burden as assessed by longitudinal Tau PET for participants who agree to participate in the optional assessment only

	• Brain amyloid burden as assessed by longitudinal Amyloid PET scanning for participants who agree to participate in the optional assessment only
To evaluate immunogenicity of AL002 in participants with AD	• Incidence of ADAs

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; ARIA=amyloid-related imaging abnormality; 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; YKL-40=chitinase 3-like 1.

Note: All participants who consent to the optional lumbar puncture (LP) will have optional CSF collection. In addition, CSF will be collected as needed in participants with ARIA.
Longitudinal amyloid and Tau PET imaging applies to those participants who consent and participate in the optional exploratory biomarker assessment.

Summary of Study Design:

This is a Phase 2, parallel-group, long-term extension (LTE), dose-blind, global, multicenter study to evaluate the long-term safety and efficacy of AL002 in participants with Alzheimer's disease (AD). The study will enroll participants who completed the planned treatment period in AL002-2 (parent study).

Objectives and Endpoints

The primary objectives of this Phase 2-LTE study (see Table 1) are to evaluate the long-term safety and tolerability of AL002 at 3 possible doses (ie, 15 mg/kg, 40 mg/kg, and 60 mg/kg) and to assess the effect of a slower dose titration on the incidence and severity of amyloid-related imaging abnormality (ARIA). The secondary objectives include the evaluation of pharmacokinetics (PK) of AL002 as well as clinical outcome assessments (COAs) in participants with AD. The exploratory objectives of this AL002-LTE study are to evaluate biomarkers and further assess the immunogenicity of AL002 in participants with AD.

Safety will be assessed through monitoring of adverse events (AEs) (including adverse events of special interest [AESIs] and serious adverse events [SAEs]), changes in laboratory and vital sign values, incidence of findings from physical, neurological, electrocardiogram (ECG), magnetic resonance imaging (MRI), ophthalmological examinations, and reports of suicidal ideation or behavior. Incidence and severity of ARIA will be assessed in participants undergoing titration. Participants' serum PK will be assessed for investigation of exposure-response and exposure-safety relationships. Blood samples for assessment of anti-drug antibodies (ADA) will be taken throughout the study. Biomarkers will be assessed from fluid (blood/plasma, cerebrospinal fluid (CSF)), and imaging (MRI, optional tau positron emission tomography (PET) with tau radiotracer fluorine-18 MK-6240 ([^{18}F]MK-6240), and Amyloid PET). Longitudinal CSF, Tau PET and Amyloid PET will be assessed for all participants who consent to these optional assessments. Those who did not previously opt-in to these procedures in AL002-2 may choose to either opt-in or opt-out in this AL002-LTE study.

Investigational Plan

The first dose of the AL002-LTE study should be within the 4-week ±5-day window of the last dose of the parent study, to maintain continuity of study treatment. Delays of the first AL002-LTE dose beyond that window will constitute protocol deviations.

Surveillance for treatment-emergent ARIA will be accomplished with post-baseline MRI scans as described in the Schedule of Assessments (see Table 9). Additional Baseline MRIs are required if the last MRI occurred more than 90 days prior to the first dose on Day 1/Week 1 of AL002-LTE.

Participants who were randomized to active treatment in the parent study will remain at their previously assigned dose. AL002 will be administered every 4 weeks for up to 48 weeks. Dosing duration may be extended beyond this time through a protocol amendment, within the context of emerging favorable safety data.

Those who are conducting the efficacy assessments, including study staff, the Investigator, and Sponsor will remain blinded to dose assignments throughout the duration of the AL002-LTE study. The Titration Cohort refers to the participants who were randomized to placebo in the parent study AL002-2. They will receive an initial starting dose of [redacted] mg/kg that will be increased to reach the target dose of [redacted] mg/kg per Titration Algorithm 1:

Titration Algorithm 1: Starting Dose: [redacted] mg/kg (See Table 2)

Week	[redacted]	[redacted]	[redacted]	[redacted]
AL002 Dose	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg

The evaluation of dosing and its relationship to safety and ARIA within the Titration Cohort will occur only with the unblinded pharmacist, the unblinded pharmacy monitor, the unblinded clinical research organization (CRO) staff, and unblinded safety management team at Alector. ARIA monitoring and management will be consistent with the procedures outlined in the parent study. Additional information about ARIA safety monitoring is described in Section 7.6.4 and Section 7.11.

If emerging data suggests that Titration Algorithm 1 is not effectively reducing the incidence or severity of ARIA, a lower starting dose of [redacted] mg/kg may be considered upon determination of the safety management team. In the event that a decision is made to lower the starting dose, all subsequent participants previously randomized to placebo in the parent study AL002-2 entering this AL002-LTE study will be treated with an initial starting dose of [redacted] mg/kg and will be administered AL002 every 4 weeks by intravenous (IV) infusion using an up-titration algorithm to reach the target dose of [redacted] mg/kg per Titration Algorithm 2:

Titration Algorithm 2: Starting Dose: [redacted] mg/kg (See Table 3)

Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AL002 Dose	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg

Independent Data Monitoring Committee

The iDMC will perform the safety review of all available safety and tolerability data (including from the MRI, neurological, and ophthalmological examinations) from all participants in an unblinded

manner approximately every 6 months. The iDMC may convene on an ad-hoc basis, as required, to review cumulative safety data.

Description of Study Periods and Visits:

Screening/Baseline Period: Prior to AL002-LTE Study Entry (from Day -28 to Day -1)

As described in the sections above, the participant and/or their study partner may sign the informed consent/assent for AL002-LTE during the final dosing visit of the parent study. This will mark the beginning of the screening/baseline period for AL002-LTE. Required safety and/or eligibility assessments may be obtained at any time prior to dosing on Day 1/Week 1. The screening/baseline period may also be utilized to obtain any efficacy assessments (eg, COAs) that were not collected from the parent study in the last 12 weeks prior to Day1/Week 1. For those participating in the amyloid or Tau PET sub-studies in the AL002-2 trial, a new longitudinal amyloid and Tau PET imaging will be required if the last timepoint from the parent study was taken more than 24 weeks prior to Day 1/Week 1. Baseline MRIs are required if the last MRI occurred more than 90 days prior to the first dose on Day 1/Week 1 of AL002-LTE. For those participating in optional CSF sampling, an optional LP will need to be collected prior to Day 1/Week 1 if it has been more than 12 weeks since the last evaluation. The C-SSRS must be completed during the screening/baseline period.

Once eligibility is confirmed and the appropriate safety assessments have been collected, enrollment can occur any time after signing the informed consent and prior to the AL002-LTE first dose on Day 1/Week 1.

Participants will be offered the opportunity to consent for the optional exploratory biomarker assessments (CSF sampling, longitudinal Amyloid PET and Tau PET) even if they did not previously agree in the parent study. Details for the optional PET imaging assessments including objectives, eligibility criteria, sample collection, and imaging specifications are provided in the PET Imaging Procedures Manual. Consent for the optional assessments will be documented. Participation in the optional PET imaging procedures will be allowed according to local country regulations. The screening/baseline period can be utilized to capture the initial timepoint, which will serve as the participant's baseline and will not be used to determine eligibility.

Treatment Period (Day 1/Week 1 to Week 49)

All participants will be treated for 48 weeks. Dosing duration may be extended via a protocol amendment based on emerging data and upon consultation with both the Principal Investigator and Sponsor. AL002 will be administered via IV infusion at the site on Day 1/Week 1 and every 4 weeks thereafter. To further mitigate ARIA risks, all participants who were previously receiving placebo in the AL002-2 study will be dosed according to Titration Algorithm 1 (Table 2) with a starting dose of [redacted] mg/kg. Based on review of the safety data, Titration Algorithm 2 (Table 3) may be implemented with a starting dose of [redacted] mg/kg to attempt to further reduce ARIA risk. Assessments will be performed at Day 1/Week 1 and throughout the treatment period until the end of study (EOS) participation. The full Schedule of Assessments is provided in Table 9.

ARIA Monitoring and Management

Surveillance for treatment-emergent ARIA will be accomplished with post-baseline MRI scans as described in the Schedule of Assessments (see Table 9). To maintain the blind to participants' original treatment assignment in the AL002-2 study, all post-baseline MRIs are required for all participants, regardless of whether they received AL002 or placebo in the AL002-2 study. 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-baseline MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 8).

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. An unscheduled LP for CSF analysis may be requested after any occurrence of ARIA-E and/or ARIA-H.

End of Study (EOS) Visit

When a participant completes all study visits and procedures up to and including the last visit of their planned treatment period, an EOS Visit will follow 8 weeks after this final treatment period visit. All outstanding assessments will be completed within the specified timepoints as indicated in Table 9.

Early Termination (ET) Visit

An ET Visit is performed only in cases where the participant is prematurely discontinued from the study for any reason. If the participant withdraws or is discontinued from the study for any reason, the ET must be completed no longer than 4 to 8 weeks after the last administered dose. All safety evaluations, efficacy, biomarker, PK and ADA assessments must be completed at this visit. See Table 9 footnotes for additional information.

Study Sites:

Multicenter study with sites in North America, Australia, Europe, and Argentina.

Planned Number of Participants:

All participants who have completed the planned treatment period in the parent study, AL002-2, are invited to participate in this LTE study. Enrollment is optional and participation may be offered at the discretion of the Investigator.

Participant Selection:

Eligibility for study inclusion will be limited to participants who completed the planned treatment period in the parent study AL002-2. Participants must consent to this AL002-LTE study and complete all outstanding assessments from AL002-2 prior to Day 1/Week 1 of the AL002-LTE study.

Criteria for Inclusion and Exclusion:

Inclusion Criteria

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

1. The participant has completed the planned treatment period in the AL002-2 study. Completion of the planned treatment period is defined as any participant who did not prematurely and permanently discontinue the study drug in the AL002-2 study.
2. The participant is willing and able to give informed consent. 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 or independent ethics committee.
3. 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.

4. 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.
5. Participant weighs ≤120 kg; body mass index (BMI) is between 18.5 and 34.9 kg/m^2 inclusive.
6. The participant has availability of a person ("study partner") who, in the Investigator's opinion, has frequent and sufficient contact with the participant (eg, at least 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, and to have the same study partner as in the parent study.
7. The participant and study partner are fluent in the language of the tests used at the study site as assessed by site personnel.
8. The participant is willing and able to complete all aspects of the study (including MRI). The participant should be capable of completing assessments either alone or with the help of the study partner. Participants whose disease has progressed such that they cannot complete the efficacy assessments may participate in the study for assessment of safety.
9. The 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).
10. 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 in the optional Tau PET imaging assessment with [^{18}F]MK-6240 only:

11. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
12. [^{18}F]MK-6240 is available to the PET imaging center based on manufacturing distribution network and local regulations.

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

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

Exclusion Criteria

Participants are excluded who meet any of the following exclusion criteria:

1. Participants deemed not able to provide consent or assent by the Investigator or by local regulations.
2. Participants who were prematurely and permanently discontinued from treatment in the parent study for safety reasons.
3. The 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.
    d. Participants who have an increase in their number of microbleeds, since the previous screening/ baseline MRI in the AL002-2 study and >5, should be discussed with the Medical Monitor.
    e. Participants who have developed ARIA-E and ARIA-H in the parent study and who were permitted to continue dosing according to the ARIA management guidelines, will not be excluded from participation in the AL002-LTE, on the basis of microbleeds or hemosiderosis.
4. 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. Participants taking any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline.
6. Participation in the AL002-LTE is deemed inappropriate for any reason per Investigator discretion.
7. Participant agrees not to receive any investigational treatment, other than AL002, during the study.

Clinical Outcome Assessments – Neurocognitive and Functional Tests:

The following neurocognitive and functional tests (described in Section 14.2) will be performed according to the guidelines set forth in the Site Rater Manual. 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). Blood collection can be considered a stressful procedure for a participant, according to the Investigator's clinical judgment.

- Clinical Dementia Rating (CDR®)
- Mini-Mental Status Examination (MMSE)
- Repeatable Battery for the Assessment of Neuropsychological Status – Update (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)

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) is prohibited within 72 hours prior to any cognitive or behavioral assessment.

Safety Assessments:

Safety assessments will consist of monitoring incidence of AEs, changes in vital signs and clinical laboratory results, incidence findings of physical, neurological, and ophthalmological exams, ECGs, suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS), and MRI abnormalities (see Schedule of Assessments in Table 9).

This study will also evaluate the effect of a slower titration regimen starting at a lower dose than in the parent study on the incidence and severity of ARIA in those participants who were assigned to placebo in the AL002-2 study.

Biomarker Assessments:

The exploratory biomarker endpoints for this study are presented in Section 2 and Section 6.6.

The biomarker assessments will consist of, but are not limited to, blood-based biomarkers, CSF-based biomarkers, 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, amyloid beta 1-42 [Aβ42], amyloid beta 1-40 [Aβ40], total tau [tTau], phosphorylated tau [pTau], neurofilament light [NfL])

CSF-based biomarkers (those participants 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 biomarkers

Imaging biomarkers:

- MRI measures
- Optional longitudinal amyloid and Tau PET imaging measures

Timing and frequency of all biomarker assessments are presented in the Schedule of Assessments (Table 9).

Pharmacokinetic and Anti-drug Antibody Assessments:

PK blood collection will be performed, and AL002 concentrations will be measured. Blood samples for assessment of ADA will be taken throughout the study.

Statistical Methods:

All data for participants will be listed as collected. Analyses may combine the data of the parent study with the data of this AL002-LTE study. Missing data will not be imputed, unless otherwise specified in the statistical analysis plan (SAP). The SAP will provide further details regarding the analysis sets and planned analysis methodologies to address all study objectives. Continuous data will be summarized using an [redacted] unless otherwise specified in the SAP. Categorical data will be summarized using ([redacted]), unless otherwise specified in the SAP. For additional information, see Section 8.

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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
AMP	auxiliary medicinal product
APOE	apolipoprotein E
APOE e4	apolipoprotein E epsilon4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality – edema
ARIA-H	amyloid-related imaging abnormality – hemosiderin deposits
AUC	area under the concentration-time curve
BMW	Brain MRI Worksheet
BP	blood pressure
CDR®	Clinical Dementia Rating
CDR®-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	clinical research organization
CSF	cerebrospinal fluid
CSF1R	colony stimulating factor 1 receptor

Abbreviation	Term or Definition
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLAE	dose-limiting AE
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
EOS	End of Study
ET	early termination
EU	European Union
EU CTD	European Clinical Trial Directive
EU CTR	European Clinical Trials Regulation
FDA	(US) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRE	gradient-recalled echo
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
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous(ly)
LP	lumbar puncture
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term or Definition
MMSE	Mini-Mental Status Examination
MRI	magnetic resonance imaging
mCi	millicurie
mSv	millisievert
NfL	neurofilament light
NIA-AA	National Institute on Aging/Alzheimer's Association
NOAEL	no-observed-adverse-effect level
[redacted]	[redacted]
PD	pharmacodynamic(s)
PE	physical examination
PET	positron emission tomography
PK	pharmacokinetic(s)
pTau	phosphorylated tau
QTcF	QT interval by Fredericia
RBANS-Update	Repeatable Battery for the Assessment of Neuropsychological Status – Update
SAE	serious adverse event
SAS	Statistical Analysis System
SAP	statistical analysis plan
SOP	standard operating procedures
sTREM2	soluble triggering receptor expressed on myeloid cells 2
TREM2	triggering receptor expressed on myeloid cells 2
tTau	total tau
US	United States
WHO DD	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential
YKL-40	chitinase 3-like 1 protein

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, AD 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. Leqembi® was converted to full approval by the FDA in July 2023. Usage of these therapies is not yet widespread outside of confirmatory clinical trials.

Tau protein has also been identified as one of the key pathological features of AD (Grundke-Iqbal 1986; Kosik1986; 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). However, anti-tau disease-modifying therapies have not demonstrated success in slowing cognitive decline in Phase 3 clinical trials thus far.

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 the 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, known as 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 associated with increased pathology (Cheng-Hathaway 2018). Similarly, Wang et al (Wang 2015) showed that in the 5xFAD transgenic 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, 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 also regulates microglial chemotaxis and phagocytosis. In the context of AD pathology, TREM2 expression positively impacts tau hyperphosphorylation and aggregation and reduces 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 slow cognitive decline under pathological conditions.

Alector's approach is to utilize a TREM2 agonistic antibody to activate the innate immune system, thereby improving the clearance and sequestration of the molecular factors causing AD pathology. 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 the study drug can effectively suppress AD pathology in animal models.

AL002 is currently in development and does not have marketing authorization in any country. Per the European Medicines Agency (EMA), a Pediatric Investigational Plan Class Waiver is in effect for all classes of medicinal products for treatment of AD.

1.2. Summary of Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

The pharmacology, pharmacokinetic (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 intravenous (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 cerebrospinal fluid (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 was 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 multidose 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 ICH Tripartite EMA 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 this AL002-LTE 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 pharmacodynamics (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.

AL002 was studied in 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 AL002-1 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 multiple dosing part. 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. In this study, there were no deaths, no DLAEs, no treatment-related serious adverse events (SAEs), and no adverse events of special interest (AESIs). 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 experienced adverse events (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.

In the ongoing, randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study, AL002-2, the AL002 is administered for up to 96 weeks via IV infusion every 4 weeks. To

further mitigate potential risks associated with dosing, enrolled participants are titrated to their assigned dose (15 mg/kg over 1 dose, 40 mg/kg over 2 doses, or 60 mg/kg over 3 doses). Amyloid-related imaging abnormality – edema (ARIA-E) and amyloid-related imaging abnormality – hemosiderin deposits (ARIA-H) have been observed in Study AL002-2, with 3 cases associated with serious and severe symptoms. Because the serious and severe symptomatic cases were in participants with an apolipoprotein E epsilon4/epsilon4 (APOE e4/e4) genotype (APOE e4/e4) genotype, participants with this genotype are no longer participating in this trial. For additional information regarding these cohorts, please refer to Section 5 of the IB.

AL002-LTE is an extension of the ongoing AL002-2 study for all participants who have completed the planned treatment period, who are medically stable, and who consent to dosing for an additional 49 weeks. Participants who received active treatment in the parent study will remain on their current dose in the AL002-LTE study, and participants who received placebo in the parent study will be titrated to [redacted] mg/kg as described in Section 5.1. AL002 will be administered to study participants and all procedures related to the study will be performed by qualified persons at investigational sites from the parent study (ie, AL002-2). The Investigator, the study staff at the site, study participants, participant study partners, and the clinical site monitors will remain blinded to the dose of AL002 participants are receiving throughout the AL002-LTE study as well as which study drug (AL002 vs. placebo) and dose they received in the AL002-2 study.

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 preventing, slowing, or curing 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 [redacted] (for additional information, please see Section 4.3 of the IB). Because of these findings, [redacted] has been added as a potential risk to treatment with AL002, and all treated participants will be monitored by an eye specialist (see Section 6.4 of the IB and Section 6.3.7 in this protocol). In the Phase 1 study (Study AL002-1), eye-related AEs have been limited to mild and transient events.

ARIA-E and ARIA-H have been observed in Study AL002-2, with 3 cases associated with serious and severe symptoms as of 15 April 2022. 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 amyloid-related imaging abnormality (ARIA) have been updated (Table 8) in addition to the Schedule of Assessments (Table 9). Because the serious and severe symptomatic cases occurred in participants with an APOE e4/e4 genotype, participants with this genotype are no longer eligible to participate in the parent study AL002-2

and are not eligible to participate in this AL002-LTE. MRI surveillance monitoring will be conducted for all participants at the beginning of this study to maintain the blind during the dose titration.

For this Phase 2 LTE study, AL002 will be administered for up to 48 weeks via IV infusion and is expected to be generally safe and well tolerated. To further mitigate ARIA risks, those who were previously on placebo will receive a lower starting dose ([redacted] mg/kg) than in the parent trial and will slowly titrate up to [redacted] mg/kg as described in Table 2: Titration Algorithm 1 (Starting Dose: [redacted] mg/kg) (Titration Algorithm 1). MRI surveillance of ARIA will occur, and determination of the absence of incident ARIA will be made before escalating to the next higher dose level. If ARIA is observed, a lower [redacted] mg/kg starting dose may be implemented at the Sponsor's discretion and communicated to all clinical sites (see Section 5.1).

Potential risks associated with AL002 administration include [redacted], infusion-related reactions, and immunogenicity (see Section 6.4 of the IB). Identified risks associated with AL002 include MRI findings of ARIA-E and ARIA-H (Section 7.2; also see Section 6.4.1 of the IB, Version 7.0, Addendum 2). To minimize risks to study participants, careful monitoring of each participant will be conducted at time points throughout the study to detect any AEs or safety signals through physical, neurological, and ophthalmological examination, and assessment of electrocardiogram (ECG) findings, MRI findings, 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 Schedule of Assessments (Table 9). Based on the monitoring of AEs, the Sponsor may request an additional unscheduled MRI be performed to determine whether symptoms may be due to ARIA or ensure early identification of ARIA. Samples to assess the development of ADAs will be collected prior to and throughout the treatment period of the study. For more detail on potential and identified risks, and overall benefit risk evaluation associated with AL002, 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.

Suicidality will be assessed with regular participant interviews using the Columbia-Suicide Severity Rating Scale (C-SSRS). Brain MRI (including, but not limited to, 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 and the Schedule of Assessments (Table 9) for a description of ARIA risk mitigation steps and management guidelines.

1.4. AL002 Dosage Determination

In this AL002-LTE study, participants who were previously assigned to active treatment in the 15 mg/kg, 40 mg/kg, and 60 mg/kg arms of the AL002-2 parent study will remain on the same dose. Those who were previously on placebo will receive a lower starting dose (ie, [redacted] mg/kg) than in the parent trial and will slowly titrate up to [redacted] mg/kg. A reduced starting AL002 dose of [redacted] mg/kg may be considered based on emerging safety data and upon consultation with the unblinded teams, the Investigator, and the Medical Monitor. For justification of the target treatment doses of 15 mg/kg, 40 mg/kg, and 60 mg/kg, please refer to the AL002-2 study protocol.

The emergence of ARIA with AL002 in the parent study is consistent with findings from anti-amyloid trials, with most moderate to severe cases occurring in those who are APOE e4/e4 homozygotes. There also appears to be a dose-dependent association in anti-amyloid trials, and a higher incidence of ARIA occurring early in the treatment course and a subsequent reduction with continued dosing. While the mechanism behind AL002 and the development of ARIA has yet to be fully elucidated, there is some evidence to suggest that it maybe a result of the downstream effects of TREM2 on microglial activation along with the rapid and abundant clearance of amyloid within the perivascular spaces (Ostrowitzki 2012). To mitigate the risk of ARIA and to further inform the development plan of AL002, a titration regimen will be employed in this AL002-LTE study such that participants who were randomized to the placebo arm of the AL002-2 trial will receive a target dose of [redacted] mg/kg employing a slow up-titration (See Section 5.1).

1.5. Participant Population

Eligibility for study inclusion will be limited to participants who completed the planned treatment period in the parent study AL002-2. Participants must consent to this AL002-LTE study and complete all outstanding assessments from AL002-2 prior to Day 1/Week 1. Participants from the parent study AL002-2 met all inclusion criteria at the time of enrollment for that study, including a diagnosis of Stages 2 and 3, or early Stage 4 AD as defined in the 2018 National Institute on Aging/Alzheimer's Association (NIA-AA) Research Framework (Jack 2018).

2. OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
To evaluate the long-term safety and tolerability of AL002 in participants with AD	• Incidence of AEs, including AESIs and SAEs • Vital signs, clinical laboratory results, and incidence of findings from physical, neurological, ophthalmological examinations, and ECG • C-SSRS • MRI abnormalities
To evaluate the effect of dose titration on ARIA	• Incidence and severity of ARIA in participants undergoing titration
Secondary Objective	**Secondary Endpoints**
To evaluate the PK of AL002 in participants with AD	• Serum PK concentrations of AL002 and relevant PK parameters
To evaluate the effects of AL002 on COAs in participants with AD	• CDR®-SB • MMSE • RBANS-Update • ADAS-Cog13 • ADCS-ADL-MCI • ADCOMS
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effects of AL002 on biomarkers in participants with AD	• Levels of sTREM2 in CSF and/or plasma • Levels of biomarkers related to microglia function in CSF and/or plasma (eg, CSF1R, IL1RN, osteopontin, YKL 40) • Levels of biomarkers related to AD pathology in CSF and/or plasma (eg, Aβ40, Aβ42, pTau, tTau) • Levels of neurodegeneration biomarkers in plasma and/or CSF eg, NfL • Brain volume, assessed by volumetric MRI • Brain pathological tau burden as assessed by longitudinal Tau PET for participants who agree to participate in the optional assessment only • Brain amyloid burden as assessed by longitudinal Amyloid PET scanning for participants who agree to participate in the optional assessment only
To evaluate immunogenicity of AL002 in participants with AD	• Incidence of ADAs

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 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; YKL-40=chitinase 3-like 1.

Note: All participants who consent to the optional lumbar puncture (LP) will have optional CSF collection. In addition, CSF will be collected as needed in participants with ARIA.
Longitudinal amyloid and Tau PET imaging applies to those participants who consent and participate in the optional exploratory biomarker assessment.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase 2, parallel-group, long-term extension (LTE), dose-blind, global multicenter study to evaluate the long-term safety and efficacy of AL002 in participants with AD. The study will enroll participants who completed the planned treatment period in AL002-2 (parent study). Study sites are located in North America, Australia, Europe, and Argentina.

Participants who were randomized to active treatment in the parent study will remain on their previously assigned dose. Participants who were previously on placebo in the parent study will be assigned to the Titration Cohort, which will initiate with a starting dose of [redacted] mg/kg with the potential of escalating to [redacted] mg/kg per the Titration Algorithm described in Section 5.1.

The primary objectives of this Phase 2-LTE study are to evaluate the long-term safety and tolerability of AL002 at 3 possible doses (ie, 15 mg/kg, 40 mg/kg, and 60 mg/kg) and to assess the effect of a slower dose titration on the incidence and severity of ARIA (see Study Objectives/Endpoints Table 1).

The secondary objectives include the evaluation of the PK of AL002 as well as clinical outcome assessments (COAs) in participants with AD. A battery of COAs (Section 14.2) will be administered as secondary assessments over the course of the study. Efficacy assessments will be made during the pre-specified time points throughout the 49-week treatment period and at an end of study (EOS)/Week 57 or early termination (ET) Visit if needed (Table 9).

The exploratory objectives of this AL002-LTE study are to evaluate biomarkers, and the immunogenicity of AL002 in participants with AD. Exploratory fluid (blood/plasma and CSF), imaging (MRI, Tau positron emission tomography (PET) with the tau radiotracer fluorine-18 MK-6240 ([^{18}F]MK-6240) and Amyloid PET) biomarker measures will be assessed. Optional biomarker assessments include: CSF collection, Tau PET and Amyloid PET imaging.

Participants who did not previously opt-in to these exploratory PET and CSF assessments in AL002-2 may choose to either opt-in or opt-out in this LTE study. Those who did not previously consent to these optional assessments in AL002-2 may be required to complete these procedures during the screening/baseline period in order to establish a baseline before their AL002-LTE Day 1/Week 1 AL002 dose, if they choose to participate in these assessments in this study. Please see sections related to study visits in this protocol and the footnotes in the Schedule of Assessments (Table 9) for details.

Safety assessments will be performed upon signing of informed consent and throughout the treatment period until the EOS participation. Safety will be assessed through monitoring of AEs (including AESIs and SAEs), changes in laboratory and vital sign values, incidence of findings from physical, neurological, ECG, MRI, ophthalmological examinations, and reports of suicidal ideation or behavior. In addition, CSF (optional) AL002 concentrations will be measured. Blood samples for assessment of ADA will be taken throughout the study. PK and PD (CSF, imaging, and blood) assessments will be performed during the pre-specified time points throughout the treatment period, and at the EOS or ET Visit. The full Schedule of Assessments is provided in Table 9.

Participants were not directly involved in the design of the AL002-LTE clinical trial.

3.2. Description of Study Periods and Visits

3.2.1. Screening/Baseline Period

After signing the Informed Consent Form (ICF) at the final dosing visit of the parent study, participants enter a screening/baseline period of up to 4 weeks to confirm eligibility and to obtain outstanding assessments. A Screening/Baseline Visit could occur any time in the screening/baseline period. It is preferred to obtain informed consent and initiate the screening/baseline activities for this AL002-LTE study at the conclusion of the final dosing visit of the parent study AL002-2. If the assessments (see Schedule of Assessments in Table 9) were collected at that visit, they will not have to be repeated prior to Day 1/Week 1 of this AL002-LTE study. The C-SSRS must be collected during the screening/baseline period.

This period can also be utilized to schedule and perform optional biomarker assessments prior to dosing on Day 1/Week 1 for those participants who consented to these procedures as follows:

- For participants who did not have amyloid and/or Tau PET imaging assessments completed in study AL002-2 in the 24 weeks preceding Day 1/Week 1, a visit will be performed to schedule PET imaging prior to Day 1/Week 1. Participation in the optional amyloid and/or Tau PET procedures may not be permitted in some countries.
- For participants who did not complete the optional CSF collection in study AL002-2 in the 12 weeks preceding Day 1/Week 1, an lumbar puncture (LP) must be performed 5 days prior to the first dose on Day 1/Week 1.

If the COAs or LP were collected in the 12 weeks preceding Day 1/Week 1, or if the amyloid and/or Tau PET scan(s) was done in the 24 weeks preceding Day 1/Week 1, these assessments will not have to be collected during the screening/baseline period for the AL002-LTE study.

For the participants who do not need to have additional assessments collected after the final dosing visit in the parent study AL002-2 and who provide consent on the same day of the final dosing visit in the parent study AL002-2, the Screening/Baseline Visit of this LTE study could coincide with the final dosing visit in the parent study AL002-2, ie, on the same day. If the assessments (as outlined in Table 9) were collected at the final dosing visit in the parent study AL002-2, they will not have to be repeated at the Screening/Baseline Visit of this LTE study.

3.2.2. Treatment Period

The planned duration of study treatment extends from Day1/Week 1 to Week 49 (Table 9). Dosing duration may be extended beyond this time through a protocol amendment, within the context of emerging favorable safety data. AL002 will be administered via IV infusion at the study site on Day 1/Week 1 (after all necessary baseline assessments have been completed) and will be repeated subsequently once every 4 weeks throughout the treatment period.

The first dose of the AL002-LTE should be within the 4-week window (±5 days) of the last dose of the parent study, to maintain continuity of study treatment. Delays of the first AL002-LTE dose beyond that window will constitute protocol deviations.

Dosing for any individual participant may be stopped, paused, or reduced based on emerging safety data and/or the development of ARIA-E or ARIA-H. If a participant discontinues the

study prior to the end of their planned treatment period, they will need to return for an ET Visit and that will mark the end of their participation in the study.

At study entry and throughout the treatment period, safety will be assessed through monitoring of AEs (including AESIs and SAEs), changes in laboratory and vital sign values, incidence of findings from physical, neurological, ECG, MRI, ophthalmological exams, and reports of suicidal ideation or behavior. Serum PK will be assessed for investigation of exposure-response and exposure-safety relationships. Blood samples for assessment of ADA will be taken throughout the study.

The COAs, PK assessments, and biomarker assessments (fluid collection and imaging) will be performed prior to dosing and at specific time points during the treatment period and at EOS/ET if needed. Please see the Schedule of Assessments (Table 9) as well as details regarding the required and optional assessments needed throughout the treatment period.

3.2.3. Unscheduled Visits

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

3.2.4. End of Study/Week 57 Visit

Participants are considered to have completed the study if they engage in all procedures and visits as outlined in Table 9. The EOS Visit is defined as the final study visit at Week 57 which is 8 weeks after the last AL002 administration.

All outstanding assessments will be completed within the specified timepoints as indicated in Table 9. For a detailed list of procedures, please refer to Table 9.

No additional care is expected to be required for participants after participation in the AL002-LTE study has ended because of their participation in this clinical trial.

3.2.5. Early Termination Visit

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 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 Table 9. Please also see Section 4.3. (Withdrawal of Participants from Study) and Table 9 for additional information regarding discontinuation of participants from study drug and/or withdrawal from the study.

An ET Visit is performed only in cases where the participant is prematurely discontinued from the study for any reason. If the participant withdraws or is discontinued from the study for any reason, the ET must be completed no longer than 4 to 8 weeks after the last administered dose. All safety evaluations, efficacy, biomarker, PK and ADA assessments must be completed at this visit. COAs that were collected in the 12 weeks preceding the ET Visit will not have to be collected at the ET Visit. C-SSRS is to be collected at the ET Visit regardless of the last collection date. Please see Table 9 schedule and footnotes for additional information.

If a participant is not able to return to the site for the ET Visit, then certain assessments may be performed remotely, similar to situations involving COVID-19 (Appendix 14.4.2).

If the participant is discontinued or withdrawn from treatment related to an AE (see Section 7), they must be followed until resolution or stabilization of the event, or as deemed no longer necessary by the Investigator or Medical Monitor, and the ET Visit should not occur until resolution of the event. A participant is considered lost to follow-up if the Investigator has not had contact with them or their study partner after 3 attempts. Efforts to contact the participant must be made in more than one modality, including, but not limited to, a telephone call, mailing, or other means of communication, and this should be documented accordingly.

4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

All participants who have completed the planned treatment period in the parent study, AL002-2, are invited to participate in this study. Enrollment is optional and participation may be offered at the discretion of the Investigator.

Eligibility for study inclusion will be limited to participants who completed the planned treatment period in the prior AL002-2 study. Participants must consent to this dose-extension study and complete all outstanding assessments from AL002-2 prior to Day1/Week 1 of AL002-LTE. Participants with the APOE e4/e4 genotype who were previously enrolled and permanently discontinued from study drug are excluded from participation.

4.1. Inclusion Criteria

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

1. The participant has completed the planned treatment period in the AL002-2 study. Completion of the planned treatment period is defined as any participant who did not prematurely and permanently discontinue the study drug in the AL002-2 study.
2. The participant is willing and able to give informed consent. 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 or independent ethics committee.
3. 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.
4. 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.

5. Participant weighs ≤120 kg; body mass index (BMI) is between 18.5 and 34.9 kg/m^2 inclusive.
6. The participant has availability of a person ("study partner") who, in the Investigator's opinion, has frequent and sufficient contact with the participant (eg, at least 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, and to have the same study partner as in the parent study.
7. The participant and study partner are fluent in the language of the tests used at the study site as assessed by site personnel.
8. The participant is willing and able to complete all aspects of the study (including MRI). The participant should be capable of completing assessments either alone or with the help of the study partner. Participants whose disease has progressed such that they cannot complete the efficacy assessments may participate in the study for assessment of safety.
9. The 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).
10. 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 in the optional Tau PET imaging assessment with [^{18}F]MK-6240 only:

11. Participant has not had excessive radiation exposure prior to enrollment in the trial, as defined by local standards.
12. [^{18}F]MK-6240 is available to the PET imaging center based on manufacturing distribution network and local regulations.

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

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

4.2. Exclusion Criteria

Participants are excluded who meet the following any of the following exclusion criteria:

1. Participants deemed not able to provide consent or assent by the Investigator or by local regulations.
2. Participants who were prematurely and permanently discontinued from treatment in the parent study for safety reasons.
3. The 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.
   d. Participants who have an increase in their number of microbleeds, since the previous screening/ baseline MRI in the AL002-2 study and greater than 5, should be discussed with the Medical Monitor.
   e. Participants who have developed ARIA-E and ARIA-H in the parent study and who were permitted to continue dosing according to the ARIA management guidelines, will not be excluded from participation in the AL002-LTE, on the basis of microbleeds or hemosiderosis.
4. 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. Participants taking any passive immunotherapy (eg, immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline.
6. Participation in the AL002-LTE is deemed inappropriate for any reason per Investigator discretion.
7. Participant agrees not to receive any investigational treatment, other than AL002, during the study.

4.3. Withdrawal of Participants from 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. Participants who discontinue the study drug will be withdrawn from this study. 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. Pregnancy
6. Discretion of the Investigator
7. Death
8. Early termination of the study by Sponsor for any reason

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.

Reasonable attempts will be made by the Investigator to contact the participant prior to deeming the study participant as lost to follow-up (refer to Section 3.2.5 for details).

The reason for the participant's withdrawal from the 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 at any time if the participant, the Investigator, or Alector feels that it is not in the participant's best interest to continue. Participants who discontinue the study drug will be withdrawn from this study. The following is a list of possible reasons for study 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
5. Pregnancy
6. Discretion of the Investigator
7. Death
8. Early termination of the study by Sponsor for any reason

All participants who discontinue the study should come in for the ET Visit according to the Schedule of Assessments (Table 9), unless they were lost to follow-up, withdrew consent or died. Participants who discontinue from the study will not be replaced.

Reasonable attempts will be made by the Investigator to contact the participant prior to deeming the study participant as lost to follow-up (refer to Section 3.2.5 for details).

The reason for the participant's withdrawal from the study will be specified in the participant's source documents and on the eCRF.

5. STUDY DRUG

5.1. Method of Assigning Participants to Treatment Groups

Participants in the active treatment group in the parent study will remain at their assigned dose.

The Titration Cohort refers to participants who were randomized to placebo in the parent study AL002-2. They will receive an initial starting dose of [redacted] mg/kg that will be increased to reach the target dose of [redacted] mg/kg per Titration Algorithm 1 (Table 2). The dose escalation consists of:

- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg begin on [redacted], and this dose continues until the final dosing visit.

Table 2: Titration Algorithm 1 (Starting Dose: [redacted] mg/kg)

Week	[redacted]	[redacted]	[redacted]	[redacted]
AL002 Dose	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg

The evaluation of dosing and its relationship to safety and ARIA within the Titration Cohort will occur only with the unblinded pharmacist, the unblinded pharmacy monitor, the unblinded clinical research organization (CRO) staff, and unblinded safety management team at Alector. ARIA monitoring and management will be consistent with the procedures outlined in the parent study. Additional information about ARIA safety monitoring is described in Section 7.6.4 and Section 7.11.

If emerging data suggests that Titration Algorithm 1 is not effectively reducing the incidence or severity of ARIA, a lower starting dose of [redacted] mg/kg may be considered. In the event that a decision is made to lower the starting dose, all subsequent participants previously randomized to placebo in the parent study AL002-2 entering this AL002-LTE study will be treated with an initial starting dose of [redacted] mg/kg and will be administered AL002 every 4 weeks by IV infusion using an up-titration algorithm to reach the target dose of [redacted] mg/kg per Titration Algorithm 2 (Table 3). The dose escalation includes:

- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted],
- [redacted] doses of [redacted] mg/kg: [redacted] on [redacted] and [redacted] on [redacted]
- [redacted] doses of [redacted] mg/kg begin on [redacted], and this dose continues through the final dosing visit.

Table 3: Titration Algorithm 2 (Starting Dose: [redacted] mg/kg)

Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AL002 Dose	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg	[redacted] mg/kg

The evaluation of dosing and its relationship to safety and ARIA within the Titration Cohort are specified in Section 5.4.

MRIs are performed per the Schedule of Assessments (see Table 9). The Sponsor may request that additional unscheduled MRIs be performed for the detection and follow-up of ARIA.

Dosing for the Titration Cohort or any individual participant may be stopped, paused, or reduced based on emerging safety data and/or the development of ARIA-E or ARIA-H.

ARIA monitoring and management will be consistent with the procedures outlined in the parent study. Additional information about ARIA safety monitoring is described in Section 7.6.4 and Section 7.11.

5.1.1. 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 Titration Algorithm 1 for participants who received placebo in the parent study in Table 2. 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 by the participant's weight on the date of AL002-LTE participant screening/baseline (reference weight), unless the participant's current weight changes (increases or decreases) ≥10% from the screening/baseline 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. 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.

5.2. Identity of Study Drug and PET Radiotracers

5.2.1. Study Drug

AL002 is a recombinant humanized monoclonal antibody, which is an agonistic TREM2 monoclonal antibody.

AL002 for infusion will be provided as a [redacted] in a [redacted], with [redacted] and [redacted] with a [redacted]. Each [redacted] will contain at least [redacted] of a [redacted] in [redacted], and [redacted] at a [redacted] of [redacted]. Each vial will contain at least [redacted] mL of AL002 for IV use only.

5.2.1.1. Study Drug 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 will be manufactured for Alector under contractual and quality agreements at a qualified current GMP contract manufacturing organization. The Sponsor will ensure that the products are labeled in accordance with all local regulatory requirements.

5.2.2. [^{18}F]MK-6240 Tau PET Radiotracer

This section is only applicable for those who participate in the optional Tau PET assessments. [^{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 countries where the Tau PET radiotracer is unavailable and/or where it is not part of the approved Clinical Trial Application. [^{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 in millicurie (mCi) units, 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 millisievert (mSv), including radiation from the associated attenuation computerized tomography (CT) scan.

5.2.3. Amyloid PET Radiotracer

This section is only applicable for those who participate in the optional Amyloid PET assessments. 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)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 and 8.0 mSv with Amyvid.

5.2.4. Investigational and Auxiliary Medicinal Products Used in AL002-LTE

The investigational medicinal products (IMPs) and auxiliary medicinal products (AMPs) used in AL002-LTE are listed in Table 4.

Table 4: Comprehensive List of Investigational and Auxiliary Medicinal Products (IMP and AMP) Used in AL002-LTE Study

	Category	Authorization Status
Study Drug (AL002)	IMP	Not authorized for use in any country.
[^{18}F]MK-6240 Tau PET radiotracer	AMP	Not authorized for use in any country. Will only be used in accordance with approved national and/or local standards; Tau PET will not be conducted in those countries where the Tau PET radiotracer is unavailable and/or where it is not part of the approved Clinical Trial Application. Use of the [^{18}F]MK-6240 tracer is justified because this Tau PET tracer has improved tracer characteristics (lower non-specific binding and lower prevalence of off-target binding) as well as the ability to detect lower levels of tau compared to other available tracers, which is important to be able to measure small longitudinal changes in tau levels (Rowe 2022).
[^{18}F]florbetaben (Neuraceq) Amyloid PET radiotracer	AMP	Authorized for use in US, European Union (including Spain, Poland, Italy, France, Germany, and Netherlands), UK, Canada, and Australia. Neuraceq will be used in accordance with the terms of its marketing authorization in all countries in which it is approved and will not be used in any countries where it is not authorized.

	Category	Authorization Status
[^{18}F]florbetapir (Amyvid) Amyloid PET radiotracer	AMP	Authorized for use in US, UK, Spain, Italy, France and Germany; however this radiotracer is only being used in the AL002-LTE study in the US. Amyvid will be used in accordance with the terms of its marketing authorization in all countries in which it is approved and will not be used in any countries where it is not authorized.

5.3. 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.

5.3.1. Study Drug Supply

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

5.3.2. 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.

5.3.3. 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 drugs will be reconciled and retained or destroyed according to applicable local regulations. Please see the Pharmacy Manual for additional instructions.

5.3.4. 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.

5.3.5. Unauthorized AMP Accountability, Return, and/or Disposal

[^{18}F]MK-6240 is the only unauthorized AMP used in this study. If all or a portion of [^{18}F]MK-6240 is unused at the subject's visit, the tracer will not be returned to the production facility. The imaging facility is recommended to wait for the product to decay and then dispose of the vial or syringe according to their internal SOPs. Depending on the method or transportation (car/air), the lead shielded containers used to ship the tracer will need to be returned. For handling the Tau PET radiotracer, only personnel properly trained in the handling and administration of radioactive materials should handle [^{18}F]MK-6240. Usual radiation protection procedures should be used for handling radiotracers, including shielding (lead or tungsten containers/shields), and personal protective equipment including gloves. There are no specific procedures required for the handling of [^{18}F]MK-6240. The expiry of [^{18}F]MK-6240 is 8 hours from the time at end of synthesis.

5.4. Blinding

5.4.1. Blinding of the Parent Study AL002-2 and AL002-LTE

To maintain the blind to the treatment assignments in the parent study AL002-2 and the blind in this LTE study, those who are conducting the efficacy assessments, the Investigator, the study staff at the site, study participants, participant study partners, and the clinical site monitors will remain blinded to treatment assignments throughout the LTE study, except in circumstances described in Sections 5.4.2 and 5.4.3. In addition, the clinical research organization (CRO) and the Sponsor will also remain blinded to the treatment assignments, except in circumstances described in Sections 5.4.2 and 5.4.3 and below.

Upon unblinding of the parent study AL002-2, the personnel at CRO or Sponsor who are unblinded to the treatment assignments (except those described in Sections 5.4.2 and 5.4.3) will no longer have any involvement with the LTE study conduct including but not limited to the management, treatment, or assessment of participants; new personnel who are blinded to the treatment assignments will replace these individuals to support the LTE study conduct.

The evaluation of dosing and its relationship to safety within the Titration Cohort will occur only with the unblinded pharmacist, the unblinded pharmacy monitor, the unblinded CRO staff, and members of the unblinded safety management team at Alector.

The Sponsor may be unblinded to a participant's treatment assignment, if necessary, for safety, even before the time when participants' treatment assignments in the parent study AL002-2 are unblinded to the Sponsor.

5.4.2. Personnel Who Are Unblinded Throughout the Study

The independent Data Monitoring Committee (iDMC) and the independent statistical group supporting the iDMC will be unblinded to treatment assignments for the duration of the study to perform the safety review in an unblinded manner (see Section 12.1.1).

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, pharmacy monitor, and personnel involved in preparation of the study drug dosing solutions for IV infusion
- Interactive web response system setup personnel (CRO)
- 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

5.4.3. Breaking the Blind by the Investigator

A participant's treatment assignment, including dosage, 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 participant's study file. The date on which the code was unblinded, together with the identity of the person responsible, must also be documented.

5.5. Prior and Concomitant Therapy

All concomitant medications used by a participant in AL002-2 must be collected and recorded into each participant's eCRF for this study and coded using the World Health Organization Drug Dictionary (WHO DD), September 2022 or later. The minimum requirement is that the 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/baseline 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/baseline 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 or Medical Monitor.

Use of nonsedating antihistamine medications is 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/baseline and for the duration of the study. Participants may be taking antidepressant medication (eg, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) if on a stable dose at screening/baseline 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.

5.6. 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.

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 (preference is for signing the ICF at the final dosing visit of the planned treatment period of the AL002-2 study) before performing any study procedures for the LTE study. As AD is a progressive neurodegenerative disease, some participants may become incompetent during the course of the study, and it is important to understand if AL002 is safe and effective in these participants. 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 institutional review board/independent ethics committee (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.

Safety assessments will consist of monitoring incidence of AEs, changes in vital signs and clinical laboratory results, incidence findings of physical, neurological, and ophthalmological exams, ECGs, suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS), and MRI abnormalities.

Study visits and timing of assessments and procedures are provided in the Schedule of Assessments (Table 9). Study visits may be conducted on 2 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 and Procedures

Timing of study drug administration are provided in the Schedule of Assessments (Table 9).

Pre-dose study procedures and assessments:

- Height, weight, and vital signs, including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure (BP)
- Physical examination (PE) or limited, symptom-driven examination
- Neurological examination
- Review of concomitant medication(s) (completed before performing COAs to rule out use of medications prohibited within specific time windows)
- Record any AEs, AESIs, and SAEs
- Single 12-lead ECG
- Obtain blood and urine samples for chemistry, hematology, coagulation, viral serology, pregnancy testing, and urinalysis
- Perform C-SSRS

- Perform COAs prior to any potentially stressful procedure (eg, LPs, imaging). Blood draws may be counted as a stressful procedure per the Investigator's clinical judgment.
- Obtain blood samples for ADAs, PK, and biomarkers
- Perform MRI
- Perform optional Tau PET imaging
- Perform optional longitudinal Amyloid PET imaging

Dosing procedures:

- Study drug will be administered to participants per institutional practice and the Pharmacy Manual

Post-dose procedures (Day 1/Week 1 to end of treatment period):

- Obtain blood samples for biomarkers
- Single 12-lead ECG
- Vital signs, including body temperature, respiratory rate, pulse, and systolic and diastolic BP
- Record any AEs and SAEs
- Optional LP

6.2. 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, 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 optional blood or CSF samples may be used for future testing not described in this protocol.

For participants who have provided consent, the samples may be used for testing including the following: further evaluation of 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, biomarker or diagnostic assays).

Timing and frequency of all sample collections are presented in the Schedule of Assessments (Table 9).

6.3. Safety Assessments

Safety endpoints for this study are presented in Section 2. Safety assessments will consist of monitoring incidence of AEs, changes in vital signs and clinical laboratory results, incidence of findings of physical, neurological, and ophthalmological exams, ECGs, suicidality via the C-SSRS, and MRI abnormalities.

Participants with new or worsening radiographic evidence of ARIA on post-baseline MRI scans should be evaluated for neurological signs or symptoms after the initial Day 1/Week 1 dose. ARIA will be managed according to the guidelines in Section 7. Timing and frequency of all safety assessments are presented in the Schedule of Assessments (Table 9).

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

All AEs, AESIs, and SAEs must be collected and recorded, regardless of cause or relationship to AL002, after the participant signs the ICF 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® (florbetaben F18 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 or ongoing AEs, AESIs, and SAEs will be collected and recorded up through resolution, stabilization, 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.

6.3.2. Concomitant Medications

All concomitant medications used by a participant 14 days prior to screening/baseline through study completion/ET Visit will be collected and recorded in the participant's eCRF. Timing and frequency of concomitant medication assessments are presented in the Schedule of Assessments (Table 9).

6.3.3. Demographics

Year of birth, age (calculated), sex, ethnicity, handedness, and race will be collected unless disallowed by local regulatory agencies.

6.3.4. Medical History and Social History

Medical history will not be collected for this study.

Any new event or change in the participant's social history prior to the initial dosing on Day 1/Week 1 will be reported in the relevant social history section of the participant's eCRF. Social history includes the following information, past and current, regarding the participant: marital status, employment status, highest level of education, tobacco use (eg, smoking, vaping, chewing, etc.), alcohol consumption, cannabinoid use, and recreational drug use history.

6.3.5. 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, eye, 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/baseline and at EOS/ET.

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 time points, prior to study drug administration (as specified in the Schedule of Assessments [Table 9]) or as clinically indicated.

Abnormalities observed prior to dosing with 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 time points delineated in the Schedule of Assessments (Table 9).

6.3.6. Neurological Examinations

Neurological examinations will be performed at the time points delineated in the Schedule of Assessments (see Table 9).

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 and/or 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.

6.3.7. Ophthalmological Examinations

Ophthalmological examination will be conducted at the time points delineated in the Schedule of Assessments (see Table 9).

Ophthalmologic exams include the following:

1. [redacted] exam (eg, using a [redacted] chart)
2. [redacted] examination before and after dilation
3. Dilated exam of the [redacted] by [redacted]
4. [redacted] exam, including [redacted] for examination of the [redacted]

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 in the Investigator's judgment. Refer to the Ophthalmological Assessment Manual for further details.

6.3.8. 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. Vital signs will be measured at the time points delineated in the Schedule of Assessments (Table 9).

After the participant signs the ICF, new or worsened clinically significant abnormalities will be recorded on the eCRF. New or worsened abnormalities should be recorded as AEs, AESIs, or SAEs on the AE eCRF if considered clinically significant in the Investigator's opinion.

6.3.9. Electrocardiograms

A single 12-lead ECG will be obtained at screening/baseline (Table 9). A single 12-lead ECG will also be obtained before blood draws (pre-dose) and 60 to 90 minutes after the end of infusion on Day 1/Week 1, and Weeks 5, 13, 25, 49, and EOS/ET (Table 9). The 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 interval, and result interpretation will be captured in the eCRF.

6.3.10. Clinical Laboratory Assessments

Clinical laboratory assessments will be performed as delineated in Table 9. 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 5 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.

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 5: 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/baseline 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; RNA=ribonucleic acid; WOCBP=woman of childbearing potential.

6.3.11. Columbia-Suicide Severity Rating Scale

Suicidality will be assessed regularly throughout the study through participant completion of the C-SSRS (Table 9). The C-SSRS is an interview-based instrument used to assess incidence of suicidal ideation and behavior. 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 considered by health authorities 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 based on the 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 must be recorded as an AE.

6.3.12. Magnetic Resonance Imaging

Safety will be assessed with structural brain MRI at screening/baseline and according to the visits outlined in the Schedule of Assessments (Table 9) to evaluate the presence of ARIA. An MRI must be done at least 5 days and not more than 10 days prior to dose escalation.

All new cases of ARIA-E and/or new cases of ARIA-H will require unscheduled MRI scans every 4 to 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 for those participants who have opted in to have longitudinal Amyloid PET performed.

Surveillance for treatment-emergent ARIA will be accomplished with post-baseline MRI scans as delineated in the Schedule of Assessments (Table 9).

If new or worsening ARIA is observed on any of these post-baseline MRIs, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 8).

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 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 Schedule of Assessments (Table 9) 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.

6.4. Efficacy Assessments

Efficacy will be assessed with COAs. Please see sections related to study visits in this protocol and the footnotes in the Schedule of Assessments (Table 9) for details.

The following neurocognitive and functional tests (described in Section 14.2) will be performed according to the guidelines set forth in the Site Rater Manual. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (eg, blood collection, LPs, imaging). Blood collection can be considered a stressful procedure for a participant, according to the Investigator's clinical judgment.

- Clinical Dementia Rating® (CDR®)
- Mini-Mental State Examination (MMSE)
- Repeatable Battery for the Assessment of Neuropsychological Status-Update (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)

If a participant cannot be evaluated due to disease progression, administration of the informant portion of the CDR® should still be attempted. 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) is prohibited within 72 hours prior to any cognitive or behavioral assessment.

6.5. Pharmacokinetic and Anti-Drug Antibody Assessments

The PK blood collections will be performed, and AL002 concentrations will be measured (see Table 9). Blood samples for assessment of ADA will be taken throughout the study.

6.6. Biomarker Assessments

Blood-based biomarker and MRI biomarker measures will be assessed for all participants. In this study, several optional biomarker assessments will be performed. These include CSF collection, PET imaging with the tau radiotracer [^{18}F]MK-6240, and longitudinal Amyloid PET imaging. Those who did not previously opt-in to these procedures in the AL002-2 study but opt-in for the LTE study may be required to complete these procedures during the screening/baseline period in order to establish a baseline before their Day 1/Week 1 dose. Please see sections related to study visits in this protocol and the footnotes in the Schedule of Assessments (Table 9) for details.

Exploratory Pharmacodynamic Biomarker Assessments

- The exploratory biomarker endpoints for this study are presented in Section 2.
- The biomarker assessments will consist of, but are not limited to, blood-based biomarkers, CSF-based biomarkers, and imaging biomarkers, as follows:

Blood-based biomarkers:

- soluble triggering receptor expressed on myeloid cells 2 (sTREM2) in plasma
- Plasma biomarkers relevant to AD (eg, Aβ42, Aβ40, phosphorylated tau [pTau], neurofilament light [NfL])

Optional CSF-based biomarkers:

- 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 biomarkers

Imaging biomarkers:

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

6.6.1. Fluid Biomarker Assessments

6.6.1.1. Blood Biomarker Sampling

Blood-based biomarker measures will be assessed for all participants. Assessments include evaluation of sTREM2 in plasma and other plasma biomarkers relevant to AD (eg, Aβ42, Aβ40, pTau, NfL).

6.6.1.2. Optional Cerebrospinal Fluid Sampling

For participants who will participate in the optional CSF assessments, LPs should be completed only after the COAs have been administered (eg, Clinical Dementia Rating [CDR®]). As outlined in Table 9, 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 Schedule of Assessments (Table 9) to evaluate PK, and exploratory biomarker measures.

Participants will be required to stay in the clinic or hospital for a minimum of 30 minutes after the LP for safety monitoring. Any treated participant who discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation. Please refer to Section 6.2 for information regarding sample collection.

6.6.2. Imaging Assessments

Imaging biomarkers will be assessed with MRI (all participants) and with optional PET scans using an amyloid tracer and/or the tau tracer [^{18}F]MK 6240 (both optional).

6.6.2.1. Optional PET 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.

6.6.2.1.1. Optional Amyloid PET Imaging

In countries where local regulations allow, participants may either opt-in or opt-out of exploratory assessments to evaluate changes in the brain as measured by longitudinal Amyloid PET imaging.

During screening/baseline, 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.

6.6.2.1.2. Optional Tau PET Imaging with [^{18}F]MK-6240

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]MK6240 Tau PET imaging.

Participants may travel to select imaging sites to undergo Tau PET imaging at the visits outlined in the Schedule of Assessments in Table 9.

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 assessment of correlation of tau pathology with cognitive and functional outcome measures after extended AL002 dosing. 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 mCi (185 megabecquerel) dose. The anticipated effective dose of each scan will be 6.4 mSv, including radiation from the associated attenuation CT 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.

Participants who consent at screening/baseline are eligible for 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 Schedule of Assessments in Table 9. Refer to the Study Design (Section 3.1) for details regarding the circumstances when Tau PET scans will be performed. The Schedule of Assessments (Table 9) 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 and/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 and/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.

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 the ICF until the EOS, regardless of clinical significance or of the AEs suspected relationship to study drug and/or radiotracer.

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. 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. AESIs 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
- [redacted]

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 are described in Section 7.11. [redacted] should be managed by an ophthalmologist and the Medical Monitor.

The reporting of an AESI will trigger an auto notification email alert from electronic data capture (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.

7.3. 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 6.

Table 6: 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.

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 7.2 and Section 7.6.4 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 7.6.4.

7.6.2. Recording the Action Taken with Study Drug in Response to AE/SAE

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

7.6.4. 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 6.3.12 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.

7.6.5. Recording of [redacted] as Adverse Events of Special Interest

Findings of [redacted] (eg, [redacted]) are determined by local ophthalmologists and will be captured as such on the AE eCRF and marked as AESI.

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 ICF until the EOS 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 and descriptions of AE grading criteria are provided in Table 6.

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 2 additional scenarios requiring 24-hour reporting to the Sponsor:

1. AEs assessed as *related* to the *radiopharmaceutical*, Neuraceq® (florbetaben F18 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*.
2. 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 drugsafety@alector.com 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 Investigational New Drug (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 7.7.1) 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 Medical Dictionary for Regulatory Activities (MedDRA) Version [redacted] 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:

[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 AESIs 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, AESIs, 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

Among 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, 4 categories of ARIA will be tracked (see Section 7.6.4 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 6.3.12). 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), 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). Radiographic severity of ARIA-H findings (“mild”, “moderate”, “severe”) is defined as follows for the 3 categories of ARIA-H (Table 7):

Table 7: 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.

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”).

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. Schedule of MRI Surveillance for ARIA

Surveillance for treatment-emergent ARIA will be accomplished with MRI scans as described in the Schedule of Assessments (Table 9).

If new or worsening ARIA is observed on any of the MRIs conducted, dosing should be managed as prescribed in the Dosing Guidelines for ARIA (see Table 8).

7.11.2. 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. An evaluation of neurologic signs or symptoms may be assessed during an unscheduled visit.

Participants with asymptomatic ARIA-E should be observed; for participants with mild or moderate symptomatic ARIA-E, the use of oral or IV steroids may be considered (see Table 8 below). 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 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 with MRI evidence of ARIA at any visit will be managed according to the guidelines in Table 8.

Table 8: 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. 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. Participants who are undergoing dose titration when the ARIA occurs may continue up-titrating at the second post-resumption dose. 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

Table 8: Dosing Guidelines for ARIA (Continued)

Finding	Asymptomatic/Symptomatic	Action
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. 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. Participants who are undergoing dose titration when the ARIA occurs may continue up-titrating at the second post-resumption dose.
A second occurrence of ARIA-E after full resolution of a prior occurrence of ARIA-E	Asymptomatic or Symptomatic	Permanently discontinue treatment

ARIA=amyloid-related imaging abnormality; 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. [redacted]

Ophthalmological examinations will be conducted at baseline and approximately every 4 months to monitor for [redacted]. These will include [redacted] examination, [redacted], [redacted], and [redacted]. If evidence suggestive of [redacted]) is reported, the frequency of ophthalmologic examination should be increased to at least every 2 months until [redacted] is either ruled out or resolved.

7.13. General Safety Monitoring

7.13.1. Special Situations

Special situations are nonstandard 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 associated with SAEs must be reported within 24 hours of becoming aware. Special situations associated with AEs should be reported promptly.

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 AL002 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 AL002, 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 AL002 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.

7.13.2. Pregnancy

If applicable, pregnancy tests are to be performed at screening/baseline and/or at Week 49 and/or at EOS/ET (see Schedule of Assessments Table 9). 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 drugsafety@alector.com, according to the instructions provided in the Study Specific Regulatory Binder.

The participant must be immediately discontinued from study drug and/or 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 final study 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 fetus 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.

7.13.3. Breastfeeding

All AEs that occur in infants following exposure to a study drug from breastmilk should be reported.

8. STATISTICAL METHODS AND ANALYSIS PLAN

All data for participants will be [redacted]. Analyses may [redacted] of this AL002-LTE study. Missing data will not be imputed, unless otherwise specified in the statistical analysis plan (SAP). The SAP will provide further details regarding the analysis sets and planned analysis methodologies to address all study objectives. Statistical analyses will be performed using [redacted].

Continuous data will be summarized using an [redacted], unless otherwise specified in the SAP. Categorical data will be summarized using [redacted], unless otherwise specified 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

It is expected that [redacted] of the participants who completed the planned treatment period in the parent study AL002-2 ([redacted], approximately) will roll over into this AL002-LTE study, corresponding to a sample size between approximately [redacted] and [redacted] participants.

Slower dose titration has the potential to substantially decrease the incidence of ARIA (Retout 2022). Assuming that [redacted]% of [redacted] participants in the Titration Cohort would experience ARIA-E using a slower titration in this LTE study and [redacted]% of [redacted] participants in the AL002 [redacted] mg/kg treatment group would experience ARIA-E using a faster titration in the parent study AL002-2, the study has approximately [redacted]% power to detect the difference in the 2 proportions aforementioned based on the [redacted]

8.2. Analysis Sets

The LTE Safety Analysis Set will include [redacted].

Details of other analysis sets will be documented in the SAP.

8.3. Statistical Analysis Methodology

8.3.1. General Analyses

8.3.1.1. Disposition of Participants

Disposition will be summarized, presenting the [redacted]

8.3.1.2. Protocol Deviations

A protocol deviation occurs when [redacted].

8.3.1.3. Demographics and Other Baseline Characteristics

Summary statistics will be provided for demographics [redacted].

8.3.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO DD, September 2022 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/Week 1, either in the parent study or the LTE study. 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 study treatment, and compliance with treatment will be summarized.

8.3.2. Efficacy Analyses

All efficacy data will be summarized using [redacted]. Details of efficacy analyses will be specified in the SAP.

8.3.3. Safety Analyses

Safety analyses will be based on the LTE Safety Analysis Set.

AEs will be coded using the MedDRA Version [redacted] or later. They will be summarized by [redacted] will be summarized similarly.

Safety endpoints will be [redacted].

To evaluate the effect of dose titration on ARIA, the proportion of participants in the Titration Cohort who experienced ARIA-E using a slower titration in this LTE study will be tested against the proportion of participants in the AL002 [redacted] mg/kg treatment group who experienced ARIA-E using a faster titration in the parent study AL002-2. Details of the statistical test for 2 proportions will be specified in the SAP.

8.3.4. Pharmacokinetic Analyses

Individual and mean serum AL002 concentration-time data will be [redacted]. When available, the individual and mean CSF AL002 concentration-time data will be [redacted].

Potential [redacted] may be explored, as data allow. Additional [redacted]

[redacted] may be performed. The results of such additional analyses may be reported separately from the CSR.

8.3.5. Exploratory Biomarker Analyses

The exploratory biomarkers (including, but not limited to, [redacted]) will be summarized over time using descriptive statistics.

Details of biomarker analyses will be specified in the SAP.

8.3.6. Immunogenicity Analyses

Immunogenicity as assessed by incidence of ADAs will be summarized descriptively.

8.3.7. [redacted]

[redacted] may be performed. Details of the [redacted] will be provided in a separate SAP.

9. DATA QUALITY ASSURANCE AND PROTECTION

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.

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 [redacted] or later, an internal validated medical dictionary, and concomitant medications will be coded using the WHO DD, September 2022 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.

9.2. Data Protection

Alector will ensure that any collection and processing of personal data within the scope of and for purposes of this study will be carried out in compliance with applicable data protection laws, including the European General Data Protection Regulation 679/2016.

Alector implements and maintains organizational and technical measures designed to protect personal data and avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data. Such organizational and technical measures include,

but are not limited to, physical access controls including monitoring of physical access, security locks, security guards, automated access controls, such as badges, visitor approval; encryption and pseudonymization of data (where appropriate); restricted user access relevant to the function and type of activity performed in relation to the clinical trial; audit controls and procedures to maintain integrity and protection of personal data; ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services; network, system, and application security by means of access rights management, logging of access, antivirus/anti-malware protection and firewalls, and other security measures; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures, and response to such attacks; transfer and disclosure controls and protections; means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident; logging of security events/incidents in information systems; procedures to detect within timely manner if a personal data breach has occurred and incident response plan and procedures for investigation, containment, reporting and resolution of incidents; backup procedures and business continuity plans and procedures; a process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing; and security and training awareness for employees and personnel managing clinical studies.

All locations, personnel, and information systems that are used to perform services for the study will be covered. In addition, Alector will ensure the technical and organizational security measures described above, are regularly reviewed and updated to consider technological developments.

Alector and its selected vendors working on behalf of Alector or institutions working with Alector for purposes of the study are contractually bound to protect confidentiality of records and coded personal data of the clinical participants, and Alector has implemented appropriate internal safeguards and controls to protect the confidentiality of records and personal data of study participants, including by appropriate access rights management on a need-to-know basis and confidentiality undertakings for personnel involved in the handling of study participant data. Alector will only receive coded (pseudonymized) personal data of clinical participants with the code being allocated and held by the sites for each study participant. The relevant codes and attribution tables will be kept confidential, and coded (pseudonymized) data will be used instead of direct identifiers in all materials associated with the study participant. Alector will neither receive nor request any information to attribute any coded data to any individual study participants, except as necessary in the context of activities required to comply with applicable laws and/or the regulatory clinical trial framework, including for purposes of (on-site) monitoring, inspections and/or regulatory audits. Alector will only share participant coded data as described in the ICF.

Alector has implemented operational data breach response processes for responding to any data breach occurring at facilities and premises of Alector, its vendors, or institutions working with Alector, as required under applicable data protection laws. In case of the occurrence of any data breach, Alector will apply relevant measures to mitigate the risks to participant data as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data participants will be reported to data protection authorities and/or data

participants in accordance with the requirements and timelines set forth under applicable data protection laws.

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. As AD is a progressive neurodegenerative disease, some participants may become incompetent during the course of the study, and it is important to understand if AL002 is safe and effective in these participants. 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.

11. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject 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/baseline 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.

The iDMC will perform the safety review of all available safety and tolerability data (including from the MRI, neurological, and ophthalmological examinations) from all participants in an unblinded manner 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 ICF, 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 (including the EOS/ET 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: Schedule of Assessments

Table 9: Schedule of Assessments

Study Week[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window		**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	
Informed consent	x															
Social history[b]	x															
Demographic data	x															
Viral serology[c, e]	x															
Height and weight[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs[c, h, i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete PE[k]	x														x	x
Limited PE[c, m]					x				x							
Neurological examination[l]	x			x		x		x		x		x		x	x	x
Ophthalmological examination[c, d]	x					x				x				x	x	x
Concomitant medications[n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration		x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events[c, i, o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG (single)[c, p]	x	x	x		x			x						x	x	x
Pregnancy test (if applicable)[j]	x													x	x	x
Thyroid function[c]	x															

Table 9: Schedule of Assessments (Continued)

Study Week[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window		±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	
Folic acid and vitamin B12 levels[c]	x															
Hematology and chemistry[c, q, r]	x	x			x				x			x			x	x
Coagulation[c, s]	x														x	x
Urinalysis[c, t]	x	x							x						x	x
C-SSRS[c]	[redacted]															
MRI (safety, PD)[c, g, u]																
CDR[c, v, z]																
MMSE[c, v, z]																
ADAS-Cog13[c, v, z]																
RBANS-Update[c, v, z]																
ADCS-ADL-MCI[c, v, z]																
Serum PK sample(s)[i]																
Serum sample for ADA[c, w]																
Plasma sample for biomarkers[c]																
LP for CSF (optional)[c, y, z, aa, cc]																
Tau PET (optional)[c, x, bb, cc, dd]																
Longitudinal Amyloid PET (optional)[c, x, cc, dd]																

[^{18}F]MK-6240=fluorine-18 MK-6240; ADA=anti-drug antibody (-ies); ADAS-Cog13=Alzheimer's Disease Assessment Scale-Cognitive Subscale; 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; ARIA=amyloid-related imaging abnormality; BMW=Brain MRI Worksheet; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CDR®=Clinical Dementia Rating; COA=clinical outcome assessments; CSF=cerebrospinal fluid; d or D=day; ECG=electrocardiogram; eCRF=electronic case report form; EOS=End of Study; ET=early termination; ICF=informed consent form; LP=lumbar puncture; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PE=physical examination; PET=positron emission tomography; PK=pharmacokinetic(s); RBANS-Update=Repeatable Battery for the Assessment of Neuropsychological Status-Update; RNA=ribonucleic acid; SCR=screening (ie, initial study visit); SAE=serious adverse event; 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] Only new events or changes in the participant's social history prior to the initial dosing on Day 1/Week 1 are to be reported in the relevant social history section of the participant's eCRF.
[c] The screening/baseline period will begin on or at the final dosing visit of the parent study AL002-2 and upon signing of the ICF. This period will be used to schedule and perform required safety and/or efficacy assessments not captured during the final dosing visit in the parent study AL002-2. It can also be utilized to schedule and perform optional biomarker assessments prior to dosing on Day 1/Week 1. If the COAs or LP were collected in the last 12 weeks prior to Day 1/Week 1 or if the PET scans were done in the last 24 weeks prior to Day 1/Week 1, these will not have to be collected during the screening/baseline period. If the COAs or LP were collected in the 12 weeks preceding the ET Visit, these will not have to be collected at the ET Visit. If the PET scans were done in the 24 weeks preceding the ET Visit, these will not have to be collected at the ET Visit. The C-SSRS must always be collected during the screening/baseline period and at the ET Visit regardless of the last collection date. If an ophthalmological examination was performed within the last 8 weeks, it will not be required at EOS/ET.
[d] Ophthalmologic examinations have a window of ±14 days (longer than the standard visit window). See Section 7.12 for additional examinations required for findings suggestive of [redacted].
[e] 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.
[f] Height and weight will be measured at screening/baseline; weight will also be measured at all other indicated timepoints.
[g] 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 8.
[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. On dosing visits, serum PK samples will be collected pre-dose. On non-dosing visits, serum PK samples may be collected at any time during the visit. Blood samples for assessment of ADA will be taken throughout the study.
[j] Urine pregnancy test (WOCBP only) and vital signs will be performed, and concomitant medications and AEs will start being collected at the screening/baseline visit and subsequent visits for those participants participating in a Tau PET scan.
[k] 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.
[l] Neurological examination includes an evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes.
[m] Perform a limited, symptom-directed PE at specified timepoints or as clinically indicated.
[n] 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.

[o.] AEs, AESIs, and SAEs will be assessed after the participant signs the informed consent until the EOS participation. Any unresolved AEs, AESIs, and SAEs will be followed up through resolution or return to baseline. Additionally, SAEs considered related to study drug or [^{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.

[p.] A single 12-lead ECG will be obtained before blood draws (pre-dose) on appropriate days. A single 12-lead ECG will be performed pre-dose and 60 to 90 minutes after the end of infusion on Day 1/Week 1, Weeks 5, 13, 25, and 49. The ECG must be performed after the participant has been resting (supine) for 10 minutes.

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

[t.] 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).

[u.] Screening/baseline MRI is to occur as close to the beginning (Day -28) of the window as possible and at least 10 days prior to enrollment, for those who have not had a brain MRI in the 90 days preceding the first dose on Day 1/Week 1.

[v.] Perform COAs prior to any potentially stressful procedure (eg, LPs, imaging).

[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.] Informed consent and confirmation of eligibility must be received prior to performing PET scans.

[y.] Participants who discontinue due to ARIA may be requested to have an LP per Investigator discretion.

[z.] Per footnote v, COAs should be performed prior to LP, If possible, 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. LPs performed during the screening/baseline period will be performed at least 5 days prior to the expected Day 1/Week 1 dosing visit. LP should not be performed unless results from coagulation laboratory assessments were within clinically acceptable limits within 4 weeks ±5 days.

[aa.] If an ET Visit is initiated, the final optional CSF sampling should be performed at that visit. If an ET is not initiated, optional CSF sampling should be performed at [redacted]

[bb.] For participants in countries where local regulations allow, baseline (optional) Tau PET imaging should be performed prior to dosing on Day1/Week1 unless obtained within 24 weeks before Day 1/Week 1 in study AL002-2. In some cases, the initial (baseline) Tau PET scan may be performed after dosing with 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. PET imaging has a window of ±28 days (longer than the standard visit window).

[cc.] 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.

[dd] New longitudinal Amyloid and Tau PET imaging are required as the baseline scan for longitudinal Amyloid and Tau PET imaging if the participant opts in to the optional procedures unless already obtained within 24 weeks before Day 1/Week 1 in study AL002-2. PET imaging has a window of ±28 days (longer than the standard visit window). 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 scans.

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 toward memory (eg, Global CDR® Score). The sum of boxes (ie, CDR®-SB) score is a quantitative general index that provides more precision than the Global CDR® Score 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 Global CDR® Score, can be found at the Knight Alzheimer Disease Research Center's website.

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 for this study uses the updated version and is referred to as the RBANS-Update (Randolph 2013); it 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 (ADCOMS)

The 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 have been published (Wang 2016).

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).

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

CTCAE Toxicity Grade	Treatment	Premedication at Subsequent Dosing
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; IRR=infusion-related reaction; IV=intravenous; MB=myocardial band; NSAIDs=non-steroidal anti-inflammatory drugs; po=orally.

14.4. Appendix 4: Adaptation of Trial Protocol During COVID-19 Pandemic

Due to the COVID-19 pandemic, the parent study included certain adaptations outlined below that may continue to be applied as appropriate during the extension study.

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 conduct the AL002-LTE 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 all participants and site staff continues to be of paramount importance with regard to 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 AEs reported.

14.4.2. Implementation of COVID-19

The implementation of adaptations to visits and procedures detailed within this appendix only applies 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/Baseline Period

Every effort should be made to complete the screening/baseline assessment per the Schedule of Assessments detailed in Table 9. At the discretion of the Sponsor, the screening/baseline period may be extended up to an additional 4 weeks to accommodate COVID-related delays in reporting screening/baseline results. Extension of the screening/baseline period will be on a case-by-case basis, and Sponsor approval must be obtained prior to extending the screening/baseline window beyond 8 weeks. Extension of the screening/baseline window may necessitate repetition of some screening/baseline tests.

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 Schedule of Assessments detailed in Table 9. 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 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
- The following COAs listed below can be completed remotely via telephone by qualified raters:

1. **Clinical Dementia Rating – Sum of Boxes (CDR®)**

   While it is strongly preferred that participants and caregivers receive administration of the CDR® in person, it is understood that remote administration might be required due to extenuating circumstances. The CDR® 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® (Randolf 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® 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 biomarker (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 associate (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 source data verification will only be completed for participants who have consented to allow access to their health records remotely.

14.4.9. Home Visits

Study drug must be administered at an investigational site. Study drug administration at a participant's home is not permitted.

To allow for collection of safety and protocol assessment data, a home health service may be employed. A home visit for the purposes of this appendix is a visit to a participant's home or an alternative convenient location such as an alternate site. These home visits are separate from the remote assessments defined above and may be conducted by trained staff of the employed home health service.

In event of home visits being employed, appropriate regulatory and ethics approval will be obtained prior to implementation as applicable per local regulations.

14.5. Appendix 5: Country-Specific Requirements

14.5.1. Germany-Specific Protocol Differences

This Germany-specific protocol difference was approved by the Paul Ehrlich Institute as Protocol Addendum #1 (Germany) to AL002-LTE Version 1.0 on 25 April 2023:

Section 4.1 Inclusion Criteria

Inclusion criterion #2 is updated as follows (strikethrough text is removed):

"2. The participant is willing and able to give informed consent. ~~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 or independent ethics committee.~~"

Document Approvals

Approval Task Verdict: Approve	Jingjing Gao ([redacted]) SME Approval 12-Jan-2024 16:27:52 GMT+0000

Approval Task Verdict: Approve	Gary Romano, ([redacted]) Management Approval 16-Jan-2024 16:57:29 GMT+0000