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

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Background

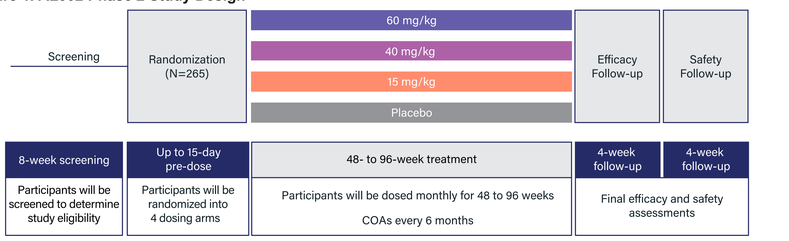
- Alzheimer's disease (AD) is the leading cause of dementia worldwide.[1] Only one medication (aducanumab) that targets the underlying pathology of AD has been recently approved in the United States under Accelerated Approval based on the reduction of amyloid and the reasonable possibility for cognitive benefit associated with a lower amyloid burden
- Triggering receptor expressed on myeloid cells-2 (TREM2) is a lipid receptor of the innate immune system expressed in the brain by microglia[2]
- Variants in the TREM2 gene increase the risk of developing AD by up to 3-fold, supporting the role of microglia in AD pathogenesis[3,4]
- AL002 is an investigational humanized monoclonal Immunoglobulin G1 (IgG1) antibody that targets TREM2
  - *In vitro*, AL002 activates human TREM2 expressed in cell lines or primary myeloid cells and enhances survival of multiple myeloid cell populations[5]
  - Mouse models demonstrated that a derivative of AL002 induced microglial proliferation and reduced amyloid β pathology[5]
  - The phase 1 first-in-human clinical trial (INVOKE) of AL002 showed that AL002 dose-dependently reduced soluble TREM2 (sTREM2) in the cerebrospinal fluid (CSF) of healthy volunteers and patients with AD, corroborating specific brain target engagement of TREM2[6]
  - AL002 was safe and well-tolerated, supporting its progression to the phase 2 study in patients with early AD[5]
- Here, we describe the study design of INVOKE-2, the ongoing phase 2 trial to assess the efficacy and safety of AL002 in participants with early AD

Methods

Study design

- INVOKE-2 (NCT04592874) is a multicenter, global, randomized, double-blind, parallel-group, dose-ranging, placebo-controlled, phase 2 trial to evaluate the efficacy and safety of AL002 in participants with early AD
  - This 2-part study will assess multiple dose levels of AL002 against placebo; Part 1 will have augmented safety and biomarker assessments for the first 40 participants enrolled in the study
- This trial will enroll an estimated 265 participants across approximately 90 sites in North America, Australia, New Zealand, Europe, and South America
- Participants will be randomized to receive AL002 15 mg/kg, 40 mg/kg, 60 mg/kg, or placebo via intravenous (IV) infusion every 4 weeks for a minimum of 48 weeks and a maximum of 96 weeks (**Figure 1**)
- CSF collection will be mandatory for participants enrolled in Part 1 and optional for those enrolled in Part 2
- Randomization will be stratified based on apolipoprotein E epsilon4 (APOE e4) status (carrier vs noncarrier)
- All participants will be asked to return for an efficacy follow-up (EFU) visit 4 weeks after, and a safety follow-up (SFU) visit 8 weeks after, their last dose of study treatment

Figure 1. AL002 Phase 2 Study Design



COAs=clinical outcome assessments.

Key inclusion criteria

- Participants (aged 50–85 years; weight range 45–120 kg) must be in the Alzheimer's continuum as defined by the 2018 National Institute on Aging and the Alzheimer's Association (NIA-AA) Research Framework, which requires evidence of cerebral amyloidosis[7]
  - Participants must demonstrate amyloid positivity based on the PrecivityAD™ blood test prior to having amyloid status confirmed via positron emission tomography (PET) or CSF
- Participants must demonstrate clinical severity consistent with Stages 2 through early Stage 4 as defined by the 2018 NIA-AA Research Framework,[7] and have:
  - Mild symptomology as defined by a Clinical Dementia Rating-Global Score (CDR-GS) = 0.5 or 1.0
  - Mini-Mental State Examination (MMSE) score ≥22
  - Episodic memory impairment as defined by a Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index (RBANS DMI) score ≤85
- Participants receiving symptomatic AD medications must have a stable dosing regimen for ≥3 months prior to screening
- Participants must have the availability of a study partner who has frequent contact (ie, ≥10 hours per week of in-person contact), consents to study participation, and agrees to provide information at clinic visits
- All participants and/or their study partners must provide written informed consent

Key exclusion criteria

- Participants meeting the following criteria based on magnetic resonance imaging (MRI) evidence will be excluded:
  - Evidence of >2 lacunar infarcts, any territorial infarct >1 cm^3, or white matter hyperintense lesions on the FLAIR sequence that correspond to an overall Fazekas score of 3
  - Presence of >5 microbleeds and/or areas of leptomeningeal hemosiderosis
  - Presence of cerebral vascular pathology or cortical stroke
- Contraindication to MRI or inability to tolerate MRI
- Contraindication for lumbar puncture
- History or presence of central nervous system, cardiovascular, hepatic/renal, immune, or metabolic/endocrine disorders
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Residence in a skilled nursing facility, convalescent home, or long-term care facility at enrollment
- Any continuous use of medications known to impair consciousness or cognition, or any investigational immunotherapy under evaluation to prevent or postpone cognitive decline, for a prespecified duration prior to study start and during the entire period of study participation

Endpoints

Outcome assessments

- Efficacy assessments, including clinical outcomes assessments (COAs) and fluid and imaging biomarker assessments, will be made at baseline (Screening or the Predose Baseline Visit), Weeks 24, 48, 72 and 96 and, when applicable, at an efficacy follow-up visit 4 weeks after the last treatment visit
- Safety assessments will be performed at every visit throughout the study treatment period, and at a safety follow-up visit 8 weeks after the last treatment visit
- Pharmacokinetic (PK), pharmacodynamic (PD), and anti-drug antibody (ADA) measurements will be made from blood samples (all participants) and from CSF samples in a subset of participants
- Imaging PD biomarkers include MRI (all participants) and optional tau and amyloid PET scans (tau-tracer fluorine-18 [^{18}F]-MK-6240; amyloid tracers ^{18}F-florbetaben, ^{18}F-florbetapir, and ^{18}F-flutametamol; both in a subset of participants)

Primary endpoint

- Disease progression as measured by the Clinical Dementia Rating – Sum of Boxes[8] (CDR-SB) at baseline and every 6 months

Secondary endpoints

- MMSE
- RBANS
- 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)
- Alzheimer's Disease Composite Score (ADCOMS)

Safety endpoints

- Incidence of adverse events (AEs), adverse events of special interest (AESI), and serious adverse events (SAEs)
- Changes from baseline in vital signs
- Findings from physical, neurological, and ophthalmological examinations
- Clinical laboratory assessments (eg, hematology, chemistry, coagulation, urinalysis, viral serology)
- Electrocardiograms (ECGs)
- Suicidality assessments using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brain abnormalities, including amyloid-related imaging abnormalities-edema (ARIA-E) and amyloid-related imaging abnormalities-hemosiderin (ARIA-H)

Biomarker endpoints

- Changes from baseline in levels of the following biomarkers will be assessed in CSF[a] and/or plasma:
  - Soluble TREM2
  - Biomarkers related to microglia function (eg, CSF1R, IL1RN, SPP1)
  - Biomarkers related to AD pathology in CSF and/or plasma (eg, Aβ40, Aβ42, pTau, tTau)
  - Neurodegeneration biomarkers (eg, NfL)
- Changes from baseline in the following optional assessments:
  - Brain pathological tau burden as assessed by tau PET
  - Brain amyloid burden as assessed by amyloid PET
  - Auditory/linguistic assessment of speech using the Winterlight Labs Speech Assessment (WSLA)
- Changes from baseline in brain volume, assessed by volumetric MRI

Pharmacokinetic (PK) endpoints

- Serum concentrations of AL002 and relevant PK parameters
- CSF concentrations of AL002 (when available[a])
- Incidence of ADAs

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

Statistical Methods

- The primary analysis will use a proportional mixed effect model with repeated measurement (pMMRM) approach, which models the treatment effect as a single proportional difference at each post-baseline visit
  - The treatment effect is defined as a percentage reduction of the placebo group clinical decline (ie, increase in CDR-SB)

Conclusions

- INVOKE-2 is designed to investigate the efficacy and safety of AL002, which is believed to be the first monoclonal antibody targeting TREM2 in clinical development for the treatment of AD
- Enrollment is ongoing

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Disclosures

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